Abstract

The main achievements in the field of genetics, biochemistry, and immunology of schizophrenia in the laboratories of European research centers are surveyed. Despite the rapid development of scientific research techniques and methodology, the abundant hypotheses on the pathogenesis of schizophrenia are riddled with so many contradictory facts that it is impossible to formulate any concrete model of the disease. One factor impeding the progress of biological research in schizophrenia is the inadequate development of standardized clinical descriptions. This is an obstacle to the study of clinical-biological correlates, which are among the principal criteria used to verify the importance of biological parameters chosen for study in the pathogenesis of the disease. A current strategy in the biology of schizophrenia, which may obviate some of those problems, is the discovery and study of biological markers.

Throughout the history of biological studies of schizophrenia, the appearance of new lines of research in this field has been determined by progress in the basic sciences. Every stage in the development of science that has been accompanied by the appearance of more precise techniques, the discovery of new phenomena, or the birth of ideas has led to a reexamination of the accumulated facts in biological psychiatry and to the formulation of new hypotheses.

At present, the study of schizophrenia is marked by a steady broadening of biological research into the nature of the disease and attempts to understand the material processes that determine its origin and development. A distinguishing feature of the biology of schizophrenia was, and still is, the problem created by the diversity of the clinical picture, course, and outcome of the disease. This creates exceptional difficulties in the definition of its nosological entity and the recognition of clinically homogeneous groups of patients—steps that are essential if adequate biological research is to be undertaken.

Nowadays, the biology of schizophrenia is a widely ramified field of psychiatry that has developed on the basis of progress in modern molecular biology, biochemistry, immunology, neuroanatomy, genetics, endocrinology, neurophysiology, and other basic sciences that determine the principal lines of research in this field of science.

The present review is limited chiefly to an examination of the principal achievements in the field of genetics, biochemistry, and immunology of schizophrenia from European research centers.

Genetic Aspects of Research in Schizophrenia

Proof of the role of hereditary factors in the genesis of schizophrenia is one of the principal arguments for the biological nature of this disease. Studies of the genetics of schizophrenia must therefore be classed without reservation as being among the most important trends in biological psychiatry.

The first 60 years of the history of the genetic study of schizophrenia in Europe (1911–73) have been a long
period of accumulation of family histories and data on twins, and also of constant disputes over contradictory views on the general principles governing the inheritance of this disease. In the modern view, the advances made during this period, despite the extensive accumulation of empirical facts, may be regarded as relatively modest: from the point of view of techniques, the investigations carried out were imperfect and were bound to lead to disputed conclusions. The methodology of classical genetic analysis proved completely inadequate for the study of such complex phenotypical manifestations as the endogenous functional psychoses. This state of affairs was aggravated by some aspects of psychiatry itself, and in particular, the inadequate development of the tradition of studying strictly defined phenomena and using standardized clinical descriptions. Even today, these demands cannot be met sufficiently reliably, but they were, and still are, the basis for successful genetic analysis.

The imperfection and ambiguity of generalizations on the genetics of schizophrenia led a number of investigators in the 1960s to reevaluate the role of genetic and environmental factors in the development of mental disturbances. The basis for this reevaluation was provided by two original approaches to the comparative analysis of prevalence of the disease in families: (1) among blood relatives and foster relatives of adopted probands (Rosenthal et al. 1968) and (2) among half-siblings who are children of monozygotic twins, discordant for schizophrenia (Fischer 1973). In both cases conclusive proof was obtained of the important role of heredity in the development of disturbances associated with schizophrenia.

The modern period of genetic study of schizophrenia, which began in Europe in the 1970s, was thus preceded by real advances both in psychiatric genetics itself and in the field of the general theory of genetic-mathematical analysis of complex phenotypical manifestations. Modern requirements for the planning of genetic research in schizophrenia can be stated briefly as follows: (1) standardization of clinical descriptions based on criteria reproducible in different psychiatric settings and allowing elements of quantification of clinical manifestations; (2) epidemiological orientation toward the accumulation of data on families and populations, ensuring the genetic representativeness and statistical stability of the characteristics that are being looked for in genetic models; (3) a multidisciplinary type of study of the pathogenesis of the disease, with a view toward discovering pathogenetically important markers of the hereditary predisposition; and (4) the widespread use of modern methods of human analytical genetics, aided by computers (Gindilis and Vartanian 1979).

Two major investigations into the genetics of endogenous functional psychoses, based on different clinical material and using different analytical genetic methods, have been undertaken. A group of Soviet investigators (Gindilis and Shahmatova-Pavlova 1979; Moskalenko and Gindilis 1981) studied the extensive familial and epidemiological data gathered in the clinics and laboratories of the Research Institute of Clinical Psychiatry, All-Union Mental Health Research Center, Academy of Medical Sciences of the U.S.S.R.; using genetic dispersion and multiparametric segregation analysis. A second group of investigators (Rao et al. 1981) used Wright's method of path analysis in a study of pooled empirical data gathered in countries of Western Europe and the United States. The major results of these two investigations were in essential agreement. It was found, for instance, that the genetic component of liability to exhibit mental disturbances within the schizophrenia spectrum extends to 60-70 percent of all the etiopathogenetic factors of this pathology. Meanwhile, systematic environmental factors common to all members of the family (the so-called "cultural inheritance"), accounting for 13-20 percent of the total, also were found to be significant. It was also demonstrated that there is a specific twin component of liability to the disease (about 10 percent of all factors), and this is a clear indication of the limitations of the twin method in its traditional interpretation.

Finally, an important characteristic of the overall system of liability to schizophrenia was the significant influence of positive phenotypical assortativeness of mating.

In the past, the phenomenon of "anticipation," i.e., the earlier and more severe manifestation of a disease in a series of generations, was viewed as a "statistical artifact" or the simple result of differences in the way that families of an affected offspring are recorded. Recently, this interpretation has been revised. Relative to schizophrenia, the reality of the phenomenon has been tested on the basis of extensive factual material and stricter methods of analysis. It has been shown that the traditional view is valid only in relation to features with a simple dominant inheritance. In the case of multifactorial diseases with the trait present in both families, anticipation is an essential result of phenotypical assortativeness of mating (Trubnikov, Gindilis, and Shahmatova-Pavlova 1978).
Nonrandom choice of partners leads to an increase in the mean level of liability in the progeny because of an increase in homozygosity for genes involved in the general system of inherited predisposition in endogenous psychoses. A similar process, known as “oriented homozygotization,” extends over three or four generations and then becomes exhausted for two reasons: (1) Persons with severe progressive forms of endogenous psychoses are usually unable to produce offspring and therefore do not fall into the next sample of parents. (2) Healthy siblings of such patients marry with a tendency toward negative phenotypical assortativeness, as a result of which the level of homozygosity for the corresponding genes is higher in the offspring, and the mean index of liability to manifestation of the disease is consequently lowered. This concept provides an explanation for the genetic-population mechanisms of spread of endogenous psychoses as a whole and of schizophrenia in particular.

Another important branch of modern genetics of schizophrenia is the use of genetic-correlation analysis to establish the basis for pathogenetic systematics of clinical forms of this disease. The three widely adopted classifications of endogenous psychoses (those of Kraepelin, Leonhard, and Snezhnevsky) were subjected to comparative analysis on the basis of genetic criteria independent of any a priori clinical concept. It was shown (Ungvari 1982, 1983) that as a first approximation the best agreement between real groupings of patients by genotypical similarity is obtained with Snezhnevsky's clinical classification, based on assessment of the character of the course and progressiveness of the psychopathic process.

The syndromal principle of differentiation between clinically homogeneous groups of patients may prove constructive, under these circumstances, only within the limits of forms already differentiated and, moreover, allowing for the stereotype of development of the psychosis.

Jakimov-Venulet (1981) reports a similar investigation, the aim of which was to study genetic differences between bipolar and unipolar affective disorders. The investigation showed that liability to the development of both forms includes an important hereditary component, described most adequately by a multifactorial threshold model. The results do not allow bipolar and unipolar affective psychoses to be regarded as independent genetic entities. On the basis of the family records he studied, Jakimov-Venulet established a weak but significant genetic correlation between liability to develop bipolar and liability to develop unipolar affective disorders. Similar results regarding the heterogeneity of affective psychoses were obtained by Angst, Frey, and Zerbin-Rudin (1980).

The results of a collaborative study conducted under the aegis of the World Health Organization, in which four international centers took part (three of them in European countries), should be discussed in connection with the problem of genetic heterogeneity of affective psychoses (Gershon et al. 1980). In this investigation the hypothesis of possible genetic linking of the principal gene of the bipolar form of manic-depressive psychosis with the X chromosome was tested. However, the results did not confirm this hypothesis unequivocally, for it was impossible to demonstrate a close linking between the parameters studied. At the same time, these workers did not rule out the possibility of genetic heterogeneity of the bipolar form itself, and they suggested that some of its clinical variants may be genetically linked with the X chromosome, in particular, in the region of the color blindness locus.

The results mentioned above illustrate a well-known fact—namely, that many difficulties in the use of formal genetic analysis in mental diseases stem not only from the considerable difficulties in clinical diagnosis, but also from the small number of informative families in real genealogical samples. Further evidence of this is given by the work of Debray, Caillard, and Stewart (1978, 1979), who analyzed a large number of simple and complex genetic models of inheritance of schizophrenia. However, these workers were unable to make an unambiguous choice among the models they studied, mainly because of the insufficient volume of available genealogical material.

One other main trend in the study of the role of inheritance in the development of endogenous psychoses is the search for their genetic markers. This line of research is closely linked with other sections of biological psychiatry (e.g., biochemistry and immunology) and is currently in a state of active development. Discovery of genetic markers in endogenous psychoses must be the scientific basis for medical genetic counseling and the identification of increased risk groups—an extremely important development for the successful solution of such difficult problems (for this particular group of diseases) as those involved in prevention (Vartanian 1983).

In conclusion, it should be emphasized that this short survey of European investigations of the role of
Genetic research in Europe is currently devoted to a wide range of aspects of the role of hereditary factors in mental diseases. However, there is insufficient consolidation of these investigations with modern problems in clinical psychiatry. At the same time, many difficult problems in psychiatry—especially problems in the diagnosis and clinical standardization of nosological forms—which clinical psychiatry continues to tackle with its own resources, could probably be solved more quickly and more effectively on the basis of clinical-genetic investigations. The situation that has arisen in these fields of science appears to justify an attempt to combine the efforts of research workers within the framework of a major project, whose aim could be a goal-directed approach to the fundamental problem of genetics of endogenous psychoses on the basis of a unified methodology.

### Biochemical Hypotheses of Schizophrenia

Modern biochemical hypotheses of schizophrenia were preceded by many years of research during the period from the 1940s to the 1960s. The aim of this research was to discover and identify abnormal products of metabolism in patients with schizophrenia. Investigators confined their attention to the study of the toxic action of biological fluids and tissue extracts on the behavior and physiological functions of animals, and also of various biological objects. The efforts directed toward isolation and identification of these "toxic factors" from schizophrenic patients led to very contradictory conclusions, and this state of affairs is reflected in a number of general reviews (Vartanian 1966; Lozovsky 1968). Nevertheless, the stage of searching for the biochemical basis of schizophrenia was in many respects highly instructive, and played an important role in the development of modern views on the nature of the pathogenesis of this disease.

In particular, it became evident that the study of the biochemical basis of psychoses without regard to clinical features of their development (the type of course, relations between positive and negative symptoms, the existence of hereditary traits, and so on) is unpromising. Interaction between psychotropic drugs and the chemical systems of the body (catecholamines, indoleamines, and certain enzyme and receptor proteins of nerve and other tissue membranes) considerably modifies the state of these systems, making it difficult to evaluate any biochemical disturbances discovered, or their link with the true mechanisms of the disease. Consequently, in the course of biochemical research, a complex problem of selection of groups of patients suitable for biochemical study has arisen.

Besides the factors mentioned above, which may possibly affect the end result of the investigation, such characteristics of samples of patients and control groups as, for example, sex, age, diet, time of year, and time of day must be taken into account. These methodological precautions make modern biochemical investigations much more difficult to undertake, and even slight deviations from these conditions may introduce an element of contradiction into the results. However, despite all the difficulties, intensive biochemical searches for a biological substrate in schizophrenia have continued and have led to the formulation of several hypotheses.

One of these is the dopamine hypothesis of schizophrenia, which has stimulated a wide range of investigations in Europe as in the rest of the world. This hypothesis is based on the view that the dopamine system in schizophrenic patients is hyperactive (Randrup and Munkvad 1972), a view based on findings indicating that chemical compounds (amphetamine, apomorphine, methylphenidate, and L-dopa) which elevate concentrations of dopamine in the brain, at the same time, induce mental states analogous to acute paranoid schizophrenia. At the same time, it has been observed that most antipsychotic drugs (e.g., phenothiazines and butyrophenones) appreciably reduce the activity of dopamine-dependent systems in the body (Van Pragg 1977; Fredrickson and Richelson 1979). One result of these observations has been a large series of studies attempting to estimate the concentration of dopamine and its metabolites in the cerebrospinal fluid (CSF) of patients and in brain tissues post-mortem.
However, most investigators have been unable to find significant, still less specific, changes in the concentrations of dopamine and its metabolites in schizophrenia (Crow et al. 1979a; Rodnight 1983). The results of an investigation in which an elevated dopamine level was found in post-mortem brain tissues of schizophrenic patients (Bird, Spokes, and Iversen 1979; Mackay et al. 1982), or in which hyperactivity of the sympathoadrenal system in the phase of exacerbation of the disease was discovered in the course of clinical-biochemical tests (Vasiliev 1980), must be regarded with caution. The extensive material available, providing evidence of a wide variety of changes in neurotransmitter metabolism arising under the influence of neuroleptics, must also be taken into account under these circumstances (Le Fur et al. 1979; Mitchell and Doggett 1980; Tissari 1982).

The subsequent development of research exploring the dopamine hypothesis is reflected in a study of activity of dopamine-β-hydroxylase, an enzyme converting dopamine into noradrenalin. Comparative analysis of the activity of this enzyme in six different parts of brains from schizophrenic patients revealed no abnormality (Crow 1979). At the same time, however, there is evidence of reduced activity of dopamine-β-hydroxylase in the peripheral blood of schizophrenic patients (Arató et al. 1982).

Recent years have seen a sharp increase of interest in the study of dopamine receptors in the limbic region and corpus striatum. For instance, an increase in the density of dopamine receptors in the striatum and nucleus accumbens, correlating mainly with positive symptoms of schizophrenia (Mackay et al. 1982), was demonstrated in post-mortem material from schizophrenic patients (Owen et al. 1978, 1981b). A more detailed analysis of this finding led to the discovery of an increased density of D₂ receptors in tissues of the striatum isolated after death from the brains of untreated patients, and absence of any such changes in the properties of D₁ receptors. From this, Cross, Crow, and Owen (1981) concluded that the increase in number of D₂ receptors is linked with the pathogenesis of schizophrenia. However, this conclusion requires rigorous testing, for there is much evidence of significant changes in the properties of different neuronal receptors (including receptors for dopamine) under the influence of psychotrophic drugs (Clow et al. 1980; Hall and Ögren 1981; Murugaiah et al. 1982).

Another approach that may be used to evaluate dopamine-dependent systems in schizophrenic patients is the study of prolactin levels in patients' plasma and CSF (Cotes, Crow, and Johnstone 1978; Pusmurova et al. 1979; Naber et al. 1980). Secretion of prolactin from the pituitary is controlled by the brain dopamine system, so that any hyperactivity of that system ought to lead to an increase in the blood level of the hormone. However, no appreciable changes in prolactin levels were found in untreated patients. In the course of these investigations, correlation between changes in the psychotic state of the patients and the prolactin level in the body could be detected only during treatment with neuroleptics.

It should also be pointed out that interpretations of the effect of dopamine agonists on the mental state of schizophrenic patients are currently being revised. For example, it has been shown that in some cases apomorphine does not induce a psychosis, but causes an improvement in the patient's psychotic state (Corsini et al. 1981). This effect, according to these investigators, is evidence of predominant stimulation of presynaptic receptors, leading to a fall in the level of dopamine secreted and, correspondingly, reduced stimulation of dopamine receptors on the postsynaptic membrane.

Hence, with all the experimental data now available, it can be confidently asserted that deviations in the function of the dopamine system exist in schizophrenia. It must be recognized, however, that the dopamine hypothesis, in its present form, is still an example of a highly simplified, although productive, biological model of the pathogenesis of schizophrenia. Substantial progress apparently will only be achieved after an awareness is gained of the principles of interaction between different biochemical systems of the human brain.

Attempts have already been made to use an integral approach to explain disturbances of the biochemical homeostasis of the brain discovered in schizophrenia (Heimann 1983). For instance, the author of a critical survey (Horneykiewicz 1978) suggests that at least three basic systems of the brain are involved in the development of the schizophrenic process: the reticular formation of the forebrain and the midbrain, the limbic system of the forebrain, and the corpus striatum. In Horneykiewicz' opinion, this is manifested as a complex combination of disturbances of the noradrenergic and dopaminergic systems of the brain, and it accordingly suggests that other neurotransmitters in addition to dopamine are also involved in the pathophysiological process: serotonin, acetylcholine, γ-aminobutyric acid, and noradrenalin.
In recent years interest has been renewed in the study of the noradrenergic system, whose hyperactive state in schizophrenia is supported by several facts. For example, an increase in the noradrenalin concentration in the limbic region and putamen has been demonstrated in post-mortem material from patients with schizophrenia (Farley et al. 1978; Crow et al. 1979a). The study of the CSF revealed a significant elevation in the level of this neurotransmitter in patients in the acute phase of illness (Kemali, Del Vecchio, and Maj 1982). Similar results were obtained in an investigation of untreated patients with chronic schizophrenia (Gomes et al. 1980). Elevation of the noradrenalin level also was demonstrated in peripheral blood plasma (Kemali, Del Vecchio, and Maj 1982). In the last case, however, the authors express doubts about the etiological significance of the results. Some particularly interesting results were obtained in a study (Kemali et al. 1984) in which a significant correlation was demonstrated between the increase in the noradrenalin concentration in the CSF and computerized electroencephalographic findings, indicating an excited state of the patients. The correlation thus revealed confirms a connection between the hyperactive state of the noradrenergic system of patients with schizophrenia and factors inducing an anxiety state. However, any conclusions about the role of these factors in the pathophysiological process in schizophrenia must await further study.

In the mid-1970s the development of modern biochemical methods, in particular, acted as a stimulus to the intensive study of the role of serotonin in the pathogenesis of schizophrenia. The development of this line of research was a corollary to the now traditional methodology of biochemical research in the field of biological psychiatry. The principal approaches were: (1) determination of concentrations of serotonin and its metabolites in the body fluids of patients with schizophrenia (urine, blood, and CSF); (2) use of post-mortem material for direct evaluation of the state of the serotonin system of the brain (determination of metabolite levels and studies of receptors); (3) the study of platelets as an extracerebral model in order to analyze the rate of metabolism of serotonin and the mechanisms of its uptake and release, and also to determine the changes in the properties of serotonin receptors with time during the development of the disease.

With the accumulation of often contradictory experimental results, the problems of interpretation intensified. First and foremost, this applies to the figures reflecting the level of 5-hydroxyindoleacetic acid (5-HIAA), the principal metabolite of serotonin, in the peripheral blood and urine of schizophrenic patients. The problems of interpretation are not particularly surprising, for the concentrations of serotonin and its metabolites that reflect their metabolism in the brain do not account for more than 1-2 percent of the main pool of these compounds at the periphery.

Contradictory results also were obtained in CSF studies of patients with schizophrenia. Wode-Helgodt et al. (1977) and Gomes et al. (1980) found a very slightly increased concentration of 5-HIAA in CSF, whereas Ashcroft et al. (1966) and Gattaz, Waldmeir, and Beckmann (1982) demonstrated a significant decrease. In the Gattaz study, it was shown that the fall in the 5-HIAA level is not connected with treatment. In this connection, attention is drawn to data obtained in several laboratories in the U.S.A., which showed a fall in the 5-HIAA concentration in the CSF and an increase in the serotonin concentration in the blood and platelets of patients with chronic schizophrenia, with abnormalities detectable by computed tomography (DeLisi et al. 1981; Potkin et al. 1983; Stahl et al. 1983).

No less contradictory results were obtained by the study of post-mortem material. Winblad et al. (1979), investigating serotonin and 5-HIAA concentrations in different parts of the brain, found a decreased level of these compounds in schizophrenics. Meanwhile Crow et al. (1979a) found an elevated serotonin concentration in the putamen. Still another conclusion was reached by Joseph et al. (1979), who found no abnormalities in the levels of tryptophan, 5-HIAA, and kinurenin in the brain tissues of schizophrenics. Negative results were obtained in an attempt to find differences in the properties of serotonin receptors in tissues of the frontal cortex of schizophrenic patients (Whitaker, Crao, and Ferrier 1981). Fillon and Fillon (1981) demonstrated the ability of antidepressants to induce marked changes in the properties of serotonin receptors, a fact which makes special care necessary in the interpretation of results of receptor studies, both in brain tissues and in platelets, in patients with various mental diseases.

The studies reviewed above reflect the typical situation confronting investigators who have tried to evaluate the role of serotonin in the pathogenesis of schizophrenia. At present, therefore, we can only hope that the development of fresh approaches will lead to more productive research in this direction. As an example of the most promising of these approaches, the preliminary selection of patients on the basis of
computed tomography and the study of mechanisms of action of psychotropic drugs, modifying the state of the serotonin system in the human body selectively, may be mentioned.

Another promising trend in biological psychiatry is, as before, the study of enzymes participating in the metabolism of biogenic amines.

The properties of monoamine oxidase (MAO) in schizophrenia and other mental diseases have received the most detailed study in recent years. In the modern view (Gorkin 1981), two types of this enzyme can be distinguished: MAO of types A and B. Type A monoamine oxidases are called amine oxidases, and their activity is blocked by low concentrations of clorgyline; noradrenalin and serotonin are specific substrates for MAO A. The activity of type B MAO is inhibited only by much higher concentrations of clorgyline; deprenyl is a selective inhibitor of this type of MAO, and its specific substrates are benzylamine and the biogenic monoamines 2-phenethylamine and N-methylhistamine.

Interest in the study of MAO in mental diseases is based on two suppositions. The first is that reduction or alteration of the substrate specificity of MAO must lead to a disturbance of metabolism of vital neurotransmitters and may be accompanied by high body levels of amines such as, for example, N,N-dimethyltryptamine, a powerful psychotomimetic. The second supposition is based on the idea that parameters reflecting MAO activity in the body can be used as biological markers.

However, to date, all attempts to obtain proof of the validity of the first hypothesis, based on the study of post-mortem material, have ended in failure. For instance, Crow et al. (1979a) and Reveley et al. (1981) used biochemical methods to study MAO activity in various parts of the brain of schizophrenics and a control group. They used a broad spectrum of substrates for this purpose, suitable for estimation of activity of MAO of both type A and type B. However, these workers were unable to find any differences between the groups studied. These results are in good agreement with those of electron cytochemistry of the brain in schizophrenia (Anders and Orlovskaya 1982).

It must be pointed out, however, that these negative results were obtained during investigations of unpurified MAO preparations without separation of the numerous forms of this enzyme. The first positive results in this direction, obtained by the present writer jointly with the staff of Gorkin's laboratory (Moskvitina et al., in press), are therefore interesting. The concentration of SH-groups and substrate specificity of a purified MAO fraction from the cerebral cortex of 14 schizophrenic patients and 6 mentally healthy individuals were studied. Both in normal subjects and in schizophrenics, the enzyme was shown to be present in a partially oxidized form. The purified enzyme contains two SH-groups per 10^6 daltons of protein and, besides MAO substrates (serotonin and β-phenethylamine), it also deaminates the substrate of diamine oxidase (histamine). Reduction of partially oxidized SH-groups of MAO to 15 SH-groups per 10^6 daltons of protein in the fraction obtained from schizophrenics, unlike that from normal subjects, does not lead to disappearance of histamine-deaminase activity but, on the contrary, potentiates it considerably. These authors suggest the existence of structural changes in MAO in schizophrenia and discuss their findings in connection with activation of lipid peroxidation, discovered in such patients (Prilipko and Liedeman 1982b; Prilipko 1984). On the basis of these preliminary findings, a more detailed study of the properties of the many different forms of monoamine oxidase in various brain structures in endogenous psychoses appears indicated.

By contrast with the few studies of MAO conducted on post-mortem material, there is a very extensive literature mainly describing reduced activity of this enzyme in platelets of patients with chronic schizophrenia (see, for reference, Wyatt, Potkin, and Murphy 1979; Sandler et al. 1981). There is no doubt at the present time that MAO activity in the platelets is reduced in schizophrenia, but the view that this phenomenon plays a role in the pathogenesis of the disease is being drastically revised. For example, it has been shown that neuroleptics can significantly reduce MAO activity both in vivo and in vitro (Gattaz et al. 1981; Owen et al. 1981a; Del Vecchio et al. 1983). The presence of low-molecular-weight proteins inhibiting platelet MAO activity has been demonstrated in the plasma of schizophrenic patients and healthy blood donors (Becker and Giambalvo 1982). A correlation has been found between parameters characterizing MAO activity in the platelets and the sex of the individuals studied; this indicates the necessity for strict verification of results obtained for this parameter (Gattaz et al. 1981).

Evidence in support of the role of depressed platelet MAO activity in the pathogenesis of schizophrenia could be provided by the changes mentioned above in biogenic amine metabolism. However, no direct proof of the presence of correlation between parameters reflecting MAO activity and the neurotransmitter level in vivo has yet been obtained.
Some particularly interesting research in this direction was undertaken by Reveley et al. (1983), whose results prove convincingly that depression of MAO activity in schizophrenia can be explained by genetic factors and not by the influence of the disease or its treatment. As a result of twin investigations, these workers showed that platelet MAO activity is largely under genetic control, but at the same time environmental factors do exert some influence. No significant differences were found within pairs of monozygotic twins discordant for schizophrenia. On the whole, however, MAO activity in these twins with a schizophrenic genotype was 25-28 percent lower than that in a group of healthy monozygotic twins and of individuals born singly. The degree of genetic control over the activity of this enzyme is determined quantitatively at 70-80 percent. These observations are in agreement with the results obtained by Winter et al. (1978), who studied platelet MAO activity in healthy twins and also showed that the activity of this enzyme is under genetic control. The results of these investigations suggest that a parameter characterizing MAO activity in platelets may be used as a biological marker for schizophrenia.

Nevertheless, in the light of the data examined above, it must be recognized that the monoamine oxidase hypothesis of schizophrenia demands further analysis, taking many factors capable of influencing the end results of the investigations into consideration, including the role of the distinctive clinical features of the disease.

In the mid-1970s, a new and promising trend in biological psychiatry appeared, aimed chiefly at the study of neuropeptides, which are low-molecular-weight compounds with unusually high and diverse biological activity. In a short period, many investigations were reported, and in most of them special attention was paid to the study of endogenous morphines during the development of mental disorders, including those of schizophrenia. Typical representatives of the group of compounds are α-, β-, and γ- endorphins, methionine-endorphin, and leucine-endorphin, which from the structural point of view are fragments of the β-lipotropin molecule.

Two competing hypotheses linking endogenous opiates to the development of schizophrenia currently coexist. One of them postulates a decrease in the concentrations of endogenous opiates in the body; the other postulates the directly opposite state of affairs.

Recent research to test the validity of these hypotheses has developed along traditional lines (direct determination of these compounds in the patients' tissues and body fluids), and also in the form of psycho-pharmacological investigations based on the study of the effect of agonists and antagonists of opiate receptors on the patients' mental state.

It must be admitted that the results of determination of endorphin levels in the body fluids of schizophrenic patients are still highly contradictory. For example, it follows from the work of Hole et al. (1979) and of Drysdale et al. (1982) that a fraction of increased ability to activate opiate receptors can be isolated from the urine and blood of patients with schizophrenia. In the case of blood, it has been shown that a fraction isolated from the blood of schizophrenics induces a state of hyperactivity in animals, and in vitro it inhibits binding of [3H]-naloxone. On the basis of data such as these, an attempt was made to explain the therapeutic effect of hemodialysis in schizophrenia, which has been observed in a series of cases. In recent publications, however, the therapeutic effectiveness of this procedure was not confirmed (Vanherweghem, Linkowski, and Mendlewicz 1983). Meanwhile Emrich et al. (1979) found no difference between the plasma β-endorphin concentration in schizophrenic patients and in patients with other mental disorders.

A careful study of the CSF by a group of Swedish workers (Terenius et al. 1976; Rimon, Terenius, and Kampman 1980) revealed an increase in opioid activity in patients with schizophrenia. However, in another study carried out in the United States, directly opposite results were obtained (Naber et al. 1981). The authors cited found a decrease in opioid activity in the CSF of schizophrenic males.

It is still too early to attempt to explain these contradictions, for the research is still in a stage of development, and the existing data are clearly insufficient to allow valid analysis.

The results of studies of the pharmacological action of agonists and antagonists of the opiate receptors likewise do not yet permit any unambiguous conclusion to be drawn on the role of endogenous opiates in the pathogenesis of schizophrenia. Several detailed surveys, covering virtually all the principal results obtained in the last 6 years of research in this field, have recently been published (Davis, Buchsbaum, and Bunney 1979; Mueser and Dysken 1983). We can therefore be content here with a short comment on the present status of this research. Endogenous opiates undoubtedly play an important role in the formation of an individual's mental status, but the role of these compounds in the development of schizophrenia has not been defined.
This indeterminacy is due to the existence of directly opposite pharmacological effects of endorphins and other agonists of opiate receptors. The nonproportional dependence of the pharmacological effect of the preparation on its dose, differences in susceptibility of individuals due to previous treatment with psychotropic drugs, and, of course, clinical heterogeneity of the populations of patients studied are currently regarded as possible explanations for these opposite effects.

The same list of explanations may be equally applicable to the diversity of results obtained in studies using antagonists of opiate receptors as a probe to assess the role of the opiate system in the development of schizophrenia. An example of one of the most extensive investigations of the therapeutic effect of an opiate antagonist, namely naloxone, in schizophrenia is the combined study undertaken as part of an international program of the World Health Organization, in which seven research centers from different regions of the world participated (Pickar et al. 1982). The sample comprised 32 patients with schizophrenia and 26 patients with manic-depressive psychosis. The effect of naloxone proved most marked in a group of schizophrenics who continued to receive psychotropic drugs; in particular, their hallucinatory manifestations were appreciably diminished. In the group of untreated patients, the diminution of hallucinatory manifestations was substantially less marked and the patients’ condition as a whole actually worsened. A more detailed analysis of the section of this investigation conducted in the U.S.S.R. (Liedeman et al. 1980) showed that clinically homogeneous groups of patients with manic-depressive psychosis and schizophrenia were extremely heterogeneous in their response to naloxone. Some patients did not respond to naloxone at all, whereas administration of the drug to others led to a transient (for a few hours) improvement of their clinical state. Patients with mania became less manic, and patients with schizophrenia became less hallucinatory. Thus, the endorphin system is evidently involved in processes determining the clinical manifestations of the disease in some patients with endogenous psychoses.

Further evidence in support of the above hypothesis is found in the results obtained by a group of workers from The Netherlands (van Praag et al. 1982). In a series of investigations, this group of workers found a positive therapeutic effect of des-tyrosine-y-endorphin (DTyE) in the treatment of schizophrenia. This peptide belongs to the endogenous endorphin family but does not possess opiate-like activity. A few days after the beginning of treatment with DTyE, van Praag et al. (1982) observed an improvement in the clinical state in about 70 percent of schizophrenic patients. This effect was reproduced when the course of treatment was repeated. It must be pointed out, however, that other investigators were unable to confirm these results (Emrich et al. 1980). On the basis of analysis of the data so far available on the use of DTyE in schizophrenia, the authors of a critical survey (Manchanda and Hirsch 1982) concluded that the question of the therapeutic efficacy of this peptide still awaits an answer. Nevertheless, the results so far available indicate that further study of neuropeptides as part of biological research in schizophrenia may prove fruitful.

Only a few of the modern lines of investigation of schizophrenia have been examined in this survey. Other, no less intriguing, biochemical hypotheses exist, and they are attracting the attention of a large group of investigators. They include such topics as, for example, the study of methylation processes in endogenous psychoses, the role of y-aminobutyric acid in the regulation of the dopamine system in schizophrenia, and so on. This gap may perhaps be filled by the series of excellent reviews by Baldessarini, Stramentonoli, and Lipinski (1979), Berger (1981), and Rodnight (1983), among many others.

**Immunological Components of the Pathogenesis of Schizophrenia**

The immunological subdivision of biological psychiatry was developed in Europe at the beginning of the present century. The idea of a possible disturbance of the immune system in mental diseases was first put forward by the Russian investigator Horoshko (1912). The role of autoimmunization in the development of mental diseases also was postulated by Snesarev (1934).

The development of fundamentals of classical immunology also stimulated the formulation of various hypotheses linking immunopathology to schizophrenia. Among the first of these was the infectious theory of schizophrenia, which postulated an etiological and pathogenetic role in the development of schizophrenia for a change in the intestinal and coccal flora of the human body (Buscaino 1953). The infectious hypothesis was soon followed by that of the viral etiology of schizophrenia, based on the discovery of virus-like particles in the CSF and nasal secretions of a certain proportion of schizophrenic patients (M.A. Morozov 1954a;
V.M. Morozov 1954b). The virological study of the CSF in schizophrenia was further developed by Italian investigators from Buscaino's clinic (Scarlatto and Mastogiovanni 1956) and also in the U.S.S.R. (Malis 1959).

It must be pointed out, however, that in the 1950s and 1960s the results of these investigations aroused strong skepticism on the part of psychiatrists, and the low standard of the research techniques available at that time did not permit supporters of the viral hypothesis of schizophrenia to develop their ideas successfully, so that interest in this field of biological psychiatry waned appreciably.

The viral hypothesis of schizophrenia is currently experiencing its rebirth, and this was largely stimulated by the discovery of latent viruses (Gajdusek and Gibbs 1977). Interest in the role of viruses in the pathogenesis of endogenous psychoses has definitely increased in the last few years in the European region. Groups from Great Britain, Finland, Czechoslovakia, Sweden, and Belgium are pursuing active research in this direction. One result of their investigations has been the discovery of virus-like particles with a marked cytopathic effect in the CSF of schizophrenics (Crow et al. 1979b; Tyrrell et al. 1979). The interferon level and the titer of antibodies against herpes viruses have been shown to be elevated in patients with schizophrenia (Libikova et al. 1979a, 1979b). Epidemiological studies have yielded facts which, in Hare's (1983) opinion, support the viral theory of schizophrenia. Suggestions regarding the possible role of viral infection in changes in neurotransmitter metabolism in schizophrenia are now being discussed in the literature (Koos 1984). Attempts are being made to examine results of histopathological investigations as well as data from computed tomography of the brain of schizophrenic patients in the light of the viral hypothesis (Crow 1983; Rimón 1983; van Kammen and DeLisi 1984).

Despite definite experimental advances, it must be recognized that no unequivocal proof of the leading role of viruses in the genesis of schizophrenia has yet been obtained. Nevertheless, the prospects of viral research in the study of the etiology and pathogenesis of schizophrenia are now regarded with much less skepticism than previously.

More substantial progress has been achieved in the field of the autoimmune hypothesis of schizophrenia. The first positive results were obtained in Europe in 1937-39 by Lehmann-Facius, who found antibodies against brain antigens, extracted from brain tissues with organic solvents, in the blood serum and CSF of patients with schizophrenia (Lehmann-Facius 1937). The results acted as a stimulus for the systematic study of antibrain antibodies in this disease. In the 1960s, it was established that schizophrenia is accompanied by clearly defined autoimmune reactions with the appearance of brain antigens and antibodies against brain tissue in the blood stream (Vartanian 1963). Clinical-biological correlations have shown that autoimmune processes, manifested in schizophrenia by the appearance of brain antigens and antibodies against brain tissue in the blood stream (Vartanian 1963). Clinical-biological correlations have shown that autoimmune processes, manifested in schizophrenia by the appearance of brain antigens and antibodies against brain tissue in the peripheral blood reflect the acuteness of the disease, and the rate and severity of its course (Kolyaskina and Kusher 1969; Semenov and Glebov 1969). The appearance of antigens in the blood stream, moreover, usually precedes the appearance of antibrain antibodies (Glebov 1970). With the appearance of more sophisticated preparative immunochemical methods, many investigations attempted to evaluate the level of the main classes of immunoglobulins (IgG, IgM, IgA) in the CSF and blood serum of schizophrenic patients (Durell and Archer 1976). In the course of analysis of the results of these investigations, the first feature to draw attention was the contradictory nature of the results. Some workers found a marked increase in the levels of all three types of immunoglobulins in patients with both acute and chronic forms of schizophrenia (Amkraut, Solomon, and Allansmith 1973; Domino et al. 1975; Zarrabi, Zucker, and Miller 1979). Others discovered a significant increase in the IgM level (Pulkkinen 1977) and, finally, a series of experiments by Bock, Weeke, and Rafaelsen (1971) revealed a significant decrease in the IgM concentration and no change in the IgG and IgA levels.

Clearer results were obtained by the use of brain-specific proteins as antigens in immunochromic reactions. For instance, Vartanian et al. (1978) found a significant rise in the titer of antibodies against "fraction 10," containing several types of brain-specific proteins, the characteristics of which were described by Klyushnik and Burbaeva (1983) and Zayko et al. (1984). The use of neurospecific protein S-100 in skin tests revealed a positive reaction of delayed type in patients with schizophrenia, and in the opinion of the workers concerned (Jankovic, Jakulic, and Horvat 1980), this indicated participation of reactions of humoral and cellular immunity in the pathogenesis of schizophrenia.

A link between the characteristics of reactions in cellular immunity and the pathophysiological process in schizophrenia is supported by the results of an extensive systematic
study of peripheral blood lymphocytes (Kolyaskina 1983; Prilipko and Liedeman 1982b). The discovery of enhanced blast transformation of blood lymphocytes from patients with schizophrenia in response to the addition of brain antigen to the culture (Kolyaskina 1972) can be regarded as the beginning of research in this direction.

A subsequent study of T lymphocytes revealed a decrease in the relative percentage of these cells in the peripheral blood of patients with schizophrenia (Loseva 1977; Duorakova, Zulosky, and Herzog 1980), including a decrease in the proportion of T-suppressor cells (Maznina et al. 1984). A study of the functional state of these cells showed a decrease in proliferative activity of the T lymphocytes in response to phytohemagglutinin, due to biologically active factors in the blood serum of schizophrenic patients (Babayan, Sekoyan, and Prilipko 1976; Kerepcic, Bamburac, and Jurin 1979; Pivovarova and Kolyaskina 1980). Later investigations showed that antibodies against O-antigens, present on membranes both of nerve cells and T lymphocytes, may be one of the factors capable of changing the number of lymphocytes in patients with schizophrenia and their function both in vitro and in vivo (Luria and Domashneva 1974; Kushner and Maznina 1980). This fact was confirmed in a detailed study of antithymic immune factor in schizophrenia, as a part of the World Health Organization Collaborative Program. Seven international research centers in biological psychiatry, including six centers in the European region, took part in these studies (Kolyaskina et al. 1980).

In addition to the topics reviewed above, the morphology and physiological state of the lymphoid cells of schizophrenics have been analyzed. This approach revealed an increase in the subpopulation of activated lymphocytes with atypical morphology, due to the effect of membranotropic factors in the patients' blood serum (Prilipko and Liedeman 1982a). Data indicating the existence of a subpopulation of activated B lymphocytes in the peripheral blood of schizophrenic patients have been reported in recent years (Mach, Schutts, and Borner 1983).

The results as a whole indicate the existence of changes in the immune status of patients with schizophrenia. However, may difficulties still remain to be solved before we can understand the true causes of the change in the immune responses in this disease. For instance, one of them may be the effect of psychotropic drugs on the patient's immunological reactivity, including the function of his immunocompetent cells through the direct action of xenobiotics on receptors of the plasma membranes of the lymphocytes (Loseva 1981; Zozulja, Parsakova, and Kost 1982; Shaskan et al. 1983). It is thus too early to draw unequivocal conclusions on the autoimmune nature of schizophrenia, but an autoimmune component does appear to be implicated in the pathogenesis of this disease.

We may conclude this short survey of immunological research in schizophrenia by stating that many of these investigations in Europe are linked with the study of human leukocytic antigens of the HLA system, controlled by several loci: A, B, C, and D, which are closely interlinked and are located in the sixth human chromosome.

The association between antigens of the HLA system and various clinical parameters in schizophrenia has now been investigated in some detail, but experimental data in this field are still extremely contradictory (Goudeman et al. 1981). For instance, a positive association of the disease with HLA-A9 has been found in data for the Swedish and Czech populations (Eberhard, Franzen, and Low 1975; Ivanyi, Zemek, and Ivanya 1978). Italian workers (Cazzullo, Smeraldi, and Penati 1974; Cazzullo and Smeraldi 1979) found an increase in the frequency of HLA-A11 and a decrease in the frequency of A3 and A10. A decrease in the frequency of A10 and B5 was found in France in a group of 75 patients with chronic schizophrenia (Singer et al. 1982). In the German population, a statistically significant increase in the frequency of HLA-A27 has been demonstrated both in the total group of patients with schizophrenia and in certain subgroups (in patients with paranoid schizophrenia, in patients with a chronic type of disease with a poor prognosis, and in patients in whom the disease began before the age of 20 years). An increase in the frequency of HLA-A9 was discovered in these same subgroups (Gattaz and Beckmann 1982). In the U.S.S.R., on the basis of an investigation of 87 patients with different forms of schizophrenia and 130 normal blood donors, an increase in the frequency of HLA-A10 was found in patients with a continuous type of course, together with an association of HLA-B12 with an episodic type of schizophrenia (Mitkevich, 1981; Mitkevich and Eliava 1983).

These results encourage the hope that a more detailed analysis of the association of antigens of the HLA system with the clinical parameters of the disease will explain contradictions in the data reported to date.
Conclusion

This survey of recent progress in the field of biological psychiatry, although restricted to an examination of the main results obtained in the fields of genetics, biochemistry, and immunology of schizophrenia, nevertheless provides evidence of the rapid development of research methodology and techniques in this field. The scope of the biological problems has broadened dramatically in concert with the appearance of new and the development of traditional lines of research in biological psychiatry. Advances are due, in particular, to progress in basic research in the biochemistry of the central nervous system, in molecular genetics, and in modern immunology.

It must be recognized, however, that the many different hypotheses of the pathogenesis of schizophrenia are still riddled with gaps and contradictory experimental facts, so that a concrete model of the pathogenesis of this disease cannot yet be formulated. One explanation for the failure to overcome these difficulties, as already mentioned, is the polymorphism of schizophrenia. It is responsible for the inadequate development of standardized clinical descriptions—a serious difficulty impeding the study of clinical-biological correlates, since diagnosis is one of the principal criteria used to test the significance of biological parameters in the pathogenesis of the disease.

Another objective difficulty is the lack of adequate biological models of schizophrenia, and this is aggravated by the latent contradiction between the principles of experimental biology, which envisages in most cases active intervention on the test object, and the classical postulate of medicine, which prohibits any intervention that may harm the patient.

These circumstances determine the current strategy of research into the biology of schizophrenia, which is to discover and study biological markers, i.e., parameters whose changes in schizophrenia reflect the pathophysiological process or accompany its development.

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The Author

Leonid Leonidovich Prilipko, Dr. Biol. Sci., is Senior Scientific Assistant, Institute of Clinical Psychiatry, All-Union Mental Health Research Center, Academy of Medical Sciences of the U.S.S.R., Moscow.

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