ETIOPATHOGENESIS AND TREATMENT OF PSYCHOSIS

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ABSTRACT

Psychotic illnesses (schizophrenia and schizoaffective and affective psychosis) have a lifetime prevalence of 2–3% and probably occur at a similar rate in all human societies. No etiologically significant environmental precipitants have been identified, and this suggests that these diseases are primarily genetic. Brain studies reveal that in schizophrenic patients, development of cerebral asymmetry is arrested, which may be associated with a small reduction in cortical mass. Episodes of illness can be ameliorated by dopamine (in particular D₂) antagonists, drugs that are antipsychotic rather than merely antischizophrenic. The discovery of at least five dopamine receptor subtypes and their genes paves the way for new approaches to treatment. However, whether psychotic patients undergo a primary disturbance of dopaminergic transmission remains unclear.
DEFINITION OF PSYCHOSIS

Psychoses (schizophrenic, schizoaffective, and affective illnesses) are common (with a lifetime prevalence of 2–3%) and account for a high percentage of the serious morbidity associated with psychiatric disease. The magnitude of their social impact stems from their onset in early adult life coupled with a strong tendency to recur, or in some cases, to persist and even progress. The defining characteristics of psychoses are psychotic symptoms such as a delusion (a belief held despite evidence to the contrary), a hallucination (sensory experience without adequate external stimulus), or thought disorder. Without a clear understanding of pathogenesis, or a laboratory diagnostic test, such symptoms serve as the clinician’s principal guide to prognosis and treatment. This review examines advances in our understanding of pathogenesis, with a particular focus on brain morphology and neurochemistry studies, and explores innovations in treatment in the context of our current knowledge of etiology and outcome.

ORIGINS AND LIMITS OF THE CONCEPT OF SCHIZOPHRENIA

The term schizophrenia covers diverse conditions, [the “group of schizophrenias,” according to Eugen Bleuler (1)] but their subdivision has sparked heated controversy, and the distinction between schizophrenia and manic-depressive psychoses, the other major category of recurrent adult illnesses, has come under increasing scrutiny. Both of these types of disorders are still classified as functional psychoses, which implies that no change in brain structure occurs. This view is supported in textbooks stating that whereas structural brain changes related to cognitive and intellectual impairments occur in the dementias (chronic organic psychosis), such neural and psychological changes are absent in schizophrenia. However, schizophrenic patients sometimes exhibit severe intellectual impairments, and structural changes in the brain can also occur (2, 3).

Although such cases represent one extreme of the spectrum of severity of schizophrenic illnesses, the boundary between schizophrenia and affective disorder at the other end has given rise to considerable doubt as well. Recent studies reveal that these two diseases overlap, thereby refuting the Kraepelinian binary system, which purports that schizophrenia and manic-depressive illness are distinct entities and thus implies that they have different etiologies. Even Kraepelin himself began to question his original findings, and in 1920 (4) he wrote of

…the difficulties which still prevent us from distinguishing reliably between manic-depressive insanity and dementia praecox. No experienced psychiatrist
will deny that there is an alarmingly large number of cases in which it seems impossible, in spite of the most careful observation, to make a firm diagnosis. Nevertheless it is becoming increasingly clear that we cannot distinguish satisfactorily between these two illnesses and this brings home the suspicion that our formulation of the problem may be incorrect.

Two paragraphs later he added,

It is common to find cases of undeniable schizophrenia which show transitory or at times longer-lasting manic-depressive symptoms, and it may be quite impossible to distinguish them from the circular forms of insanity.

The alternative to the Kraepelinian concept is the idea of a continuum of psychotic illness that extends from unipolar depression through bipolar (manic-depressive) and schizoaffective psychosis to schizophrenia, with increasing severities of defect state (5). The most compelling evidence for this hypothesis is genetic in nature. Several studies have examined whether the psychoses breed true within families. For example, Angst et al (6) concluded that the dichotomy between schizophrenia and affective disorder was highly questionable and found a continuum of psychopathology between the two disorders. However, these authors did not support the hypothesis of a “unitary psychosis”. The psychoses exhibit significant differences, and as Kraepelin emphasized, the form of a psychosis relates to its outcome. In general, psychoses with a substantial affective element have a better outcome than those that are more typically schizophrenic in form. Nevertheless, no etiologically meaningful dividing line can be drawn between the different types of psychoses. The existence of the continuum and the variations in form of psychosis within it provide important clues to the origin of psychosis.

The most recent contribution to research on families with psychosis was made by Maier & Lichtermann (7), who studied 525 consecutive hospital admissions with unipolar and bipolar affective, schizoaffective, and schizophrenic psychoses, comparing them with 109 randomly selected controls. The Schedule for Affective Disorders and Schizophrenia-Lifetime version (SADS-L) was used to interview 1250 first-degree relatives. The information obtained was supplemented with interviews to determine polydiagnostic classification (Table 1).

Because the study included a group of control probands, one can assess whether the incidence of the various disorders for first-degree relatives is higher than for the general population. The increase in risk of unipolar (UP) affective disorder for the relatives in all categories of psychotic proband is the salient feature of the study, precluding any simple interpretation of the findings. The prevalence of schizophrenia (SCHIZ) and schizoaffective (SA) disorder in the relatives of probands with bipolar (BP) illness and the excess of bipolar disorder in the relatives of patients with schizoaffective disorder refute
any suggestion that a classical Kraepelinian line of demarcation can be drawn between schizoaffective disorders (which thereby are allocated to the category of schizophrenia) and bipolar affective disorder.

The findings are more consistent with the concept of a psychotic continuum (5) than with the original Kraepelinian concept of two distinct diseases. The continuum can be represented graphically as in Figure 1.

In Figure 1, the continuum extends from unipolar depression through bipolar (manic-depressive) illness to schizoaffective disorder, to schizophrenia with and then without significant mood disturbance, and finally to schizophrenia with a defect state (the presence of negative symptoms such as affective flattening or poverty of speech). In such a scheme, one can define boundaries that act as markers for particular positions along the continuum. Such markers include the presence of elation, mood-incongruent delusions, nuclear (first rank or Schneiderian) symptoms, and negative symptoms, as well as the presence or absence of significant mood disturbance. Of these markers, nuclear symptoms delineate a group of illnesses that (as Schneider suggested) can be reliably identified and may be characterized by a distinctive pathophysiology. For example, Trimble suggested (8) that nuclear symptoms are pathognomonic of left temporal lobe disturbance.

EPIDEMIOLOGY OF SCHIZOPHRENIA

One of the most characteristic features of psychosis is its age of onset. Psychotic disorders rarely manifest themselves before puberty, but their incidence then rises sharply, earlier in males than females. This discrepancy between the sexes with respect to onset of schizophrenia (the mean age for males is approximately 25 years vs 28 years for females) is the best established but least understood epidemiological fact about the disease. Schizoaffective and affective disorders have a somewhat later age of onset. In general, earlier onset is associated with worse outcome, as illustrated in a recent comparison of case register findings by Eaton and colleagues (9).
Whether schizophrenia and manic-depression occur with equal incidence in all societies or whether incidence varies significantly remains an important question. The anthropoparity principle (the assumption of constancy across different societies and over time) has generally been taken for granted, but this assumption is based on limited evidence without thorough examination of its singularity. Lately, however, the principle has been challenged (10, 11). This controversy stimulated a cross-cultural study of incidence conducted under the auspices of the World Health Organization (WHO) (12). In 10 countries, teams in centers collaborated to ascertain incidence in defined catchment areas using standardized criteria. Using a broad definition, they observed significant differences, but as the criteria narrowed, the differences diminished. The teams concluded that schizophrenia, when restrictively diagnosed, occurs probably at approximately the same rate in societies with gross differences in climatic, physical, industrial, and cultural environments. The WHO studies are rendered credible by their attention to diagnostic reliability and comparability of methods of case identification. Within the limitations of what appear to have been the most careful epidemiological studies yet conducted, the incidence of schizophrenia seems to be a cross-cultural constant.

Figure 1  Markers of severity and form of illness according to a continuum concept. UP, unipolar; BP, bipolar; SA, schizoaffective; S + A, schizophrenia plus affective change; S – A, schizophrenia minus affective; S + D, schizophrenia plus defect.
GENETIC VS ENVIRONMENTAL CONTRIBUTIONS TO ETIOLOGY

Twin and adoption studies [reviewed by Gottesman (13)] confirm a genetic predisposition to etiology, and estimates of heritability in excess of 70% demonstrate the strength of its influence. The key question remaining is whether environmental contributions also play a role.

A number of arguments suggest that if environmental contributions do exist, they are minimal. For example, adoption of a child from a family in which schizophrenia is present does not reduce the adoptee’s risk of illness. Although the onset of schizophrenia in adult life might suggest the involvement of an environmental agent, in cases in which two siblings contract the illness, it strikes at the same age, not at the same time (14). Thus intrinsic rather than extrinsic factors determine onset. Moreover, if incidence of the disease is relatively constant across populations in widely differing geographic, climatic, industrial, and social environments, as the WHO studies suggest, possible pathogenic agents whose distribution would not be expected to vary as widely across such conditions cannot be easily identified.

The recent literature has proposed two specific pathogens: birth injury and in utero exposure to influenza. However, a prospectively studied cohort of the UK population [the Perinatal Mortality survey and National Child Development study sample (15)], which included approximately 17,000 individuals born in a single week in March 1958, showed no evidence that those subsequently admitted to psychiatric hospitals with a diagnosis of schizophrenia were more at risk of perinatal complications than the rest of the sample. Moreover, some of these individuals were exposed to the 1957 epidemic of Asian influenza. The study found that those exposed in the second trimester were at no greater risk for subsequent schizophrenia than those who were not exposed at all (16).

BRAIN CHANGES

Structure—Brain Size and Asymmetry

Recent morphological studies have cast light on the nature of schizophrenia. Computed tomography (CT) scan and magnetic resonance imaging (MRI) studies have clearly shown that patients with schizophrenia exhibit a degree of ventricular enlargement. Recent findings indicate that this enlargement is not confined to a subgroup, but rather is characteristic of all schizophrenic patients (17, 18). A second group of studies [including some on postmortem brain by Pakkenberg (19) and Bruton et al (20)] suggests that the brains of patients with schizophrenia (perhaps particularly those with an early onset) are slightly smaller than those of controls, which may result from a reduction in volume of
the cerebral cortex (21). Such changes manifest themselves early and may reflect an arrest of development.

While the changes in the cortex are generalized, a localizing feature—deviant asymmetry—is present as well. Enlargement is greater in the temporal horns than elsewhere in the ventricular system and is more prominent on the left side of the brain than the right (22, 23). No such asymmetry has been found in the enlargement associated with Alzheimer-type dementia (22). One may therefore conclude that schizophrenia is a disease of the left brain, but an alternative interpretation is that a loss of asymmetry occurs. The left temporal horn is usually smaller than the right, presumably because the planum temporale (which corresponds approximately to Wernicke’s area) is larger on the left in most individuals (24). This asymmetry (together with brain size) distinguishes humans from other primates.

A number of studies support the loss of asymmetry interpretation. The Sylvian fissure (the lower boundary of which is defined posteriorly by the planum temporale) is longer on the left side of the brain than on the right (25). In schizophrenia, however, this asymmetry is diminished or lost entirely (26, 27). MRI assessments of the planum in schizophrenic patients show that the normal bias to the left is reduced or even reversed (28, 29). Most healthy individuals do not have uniform brain width—the frontal lobe is slightly wider on the right and the occipital lobe is wider on the left (the Yakovlevian torque). In schizophrenic patients, however, the torque is diminished or absent (30). This loss can be detected in groups with an early onset (31) and in patients experiencing the first episode of illness (32).

What do these changes signify? If the human brain evolved by a process of increasing hemispheric specialization, one would expect brain size and asymmetry to be closely related and functions such as language that are most central to the process to display the greatest degree of lateralization (33). Such functions might also vary considerably among individuals. The age at which brain size reaches a plateau represents a critical parameter. The plateau level and the time at which it is reached are influenced by genetic factors, which must have been subject to recent evolutionary pressures. In this context, the brain changes in psychosis can be viewed as an arrest of development (34), resulting in a less lateralized brain and a smaller cortical mass.

According to this view, the variation in brain structure in psychosis lies along the trajectory of recent evolution and represents an aspect of diversity in the general population. One can assume that individuals with psychosis constitute one extreme of a dimension of variation on which brain size and the development of asymmetry reach a plateau relatively early.

The above discussion suggests that psychosis is a developmental anomaly associated with a structural, and therefore presumably fixed, brain deficit. However, psychoses are characteristically episodic illnesses, particularly with
respect to positive symptoms (delusions, hallucinations, thought disorder). Such symptoms may remit, and they often respond to neuroleptic medication. These observations imply that the disease process involves not only structural components, but variable, presumably neurochemical, ones as well.

**Neurochemistry—Dopamine Hypothesis of Schizophrenia and Recent Developments in Dopamine Receptor Research**

The prevailing neurochemical hypothesis posits that overactivity of dopamine pathways is central to the disease. The dopamine hypothesis of schizophrenia is based on two sets of observations: (a) evidence that the efficacy of neuroleptics correlates with their binding to dopamine D₂ receptors (35–37), and (b) the observation that chronically administered stimulants such as amphetamine and cocaine, which increase activity of central catecholaminergic pathways, can induce psychotic episodes (38, 39). Nonetheless, direct evidence that dopaminergic systems are perturbed in schizophrenia has not been forthcoming, although the structural changes in brain morphology described above are associated with some dopamine projection areas such as the amygdalohippocampal formation (40). The possibility that dopamine receptors are elevated in neuroleptic-naive schizophrenics, thus providing a mechanism for overactive dopamine synapses, has been examined. Studies using in vivo positron emission tomography (PET) and receptor binding in postmortem brains to measure differences in D₂ receptor levels in schizophrenics vs controls have produced conflicting results. At present, therefore, the question of raised D₂ levels in the etiology of schizophrenia remains unresolved (41–43).

The molecular cloning of a family of genes encoding the dopamine receptors [reviewed in (44–46)] has greatly increased our knowledge of these receptors over the last several years. To date, five dopamine receptor genes have been identified. These are divided into two subfamilies corresponding to the D₁ and D₂ receptor classes defined by Kebabian & Calne (47). The D₁-like receptor genes, designated D₁ and D₅ in humans, encode similar proteins with a pharmacology consistent with that of a D₁ receptor. The three genes that encode D₂-like receptor subtypes have been designated D₂, D₃, and D₄. (A simplified nomenclature for dopamine receptor subtypes has been proposed (48), with the D₁-like subtypes designated D₁ₐ and D₁₉ and the D₂-like subtypes designated D₂ₐ, D₂₉, and D₂₉, but this terminology is currently not in general use). Alternative processing of the D₂ gene transcript produces two functional receptor isoforms that differ in size by 29 amino acids [D₂(Long) and D₂(Short)], giving a minimum of four D₂-like receptor subtypes (49). The receptor proteins encoded by the D₂, D₃, and D₄ genes display ligand binding profiles generally representative of a D₂ receptor; however, potentially important differences in their pharmacology have been observed. Significantly, the
D$_4$ receptor has an affinity for the atypical neuroleptic clozapine 10 times higher than that of the D$_2$ receptor (50).

Distribution studies of specific RNA transcripts for each of the dopamine receptor subtypes in rat, primate, and human brains have revealed that each subtype has a distinct expression pattern. D$_1$ and D$_2$ subtypes are expressed at the highest levels overall, whereas the D$_3$ and D$_4$ subtypes are expressed at lower levels, but with a higher proportion of expression in limbic regions and frontal cortex. Biochemical and behavioral studies in humans and animals have led to the proposal that abnormalities in these latter regions may be responsible for the psychotic symptoms of schizophrenia (51, 52). Therefore, the therapeutic effectiveness of clozapine treatment and its lack of extrapyramidal side effects may reflect D$_4$ receptor localization in the central nervous system (CNS), which is low in motor control areas such as the nigrostriatal system but relatively high in regions associated with mood and cognition. The D$_4$ receptor shows a more restricted pattern, with expression largely limited to the hippocampus, hypothalamus, and parafascicular thalamic nucleus. A recent report suggests that D$_3$ transcripts are also present in primate motor cortex (53).

Anatomical distribution studies in rats (54) have also demonstrated the presence of D$_2$ and D$_1$ transcripts in the substantia nigra, indicating that these receptor subtypes may function as dopamine autoreceptors (receptors involved in regulating dopamine synthesis and release and impulse flow in dopamin-
ergic neurons). Several compounds known to preferentially bind dopamine autoreceptors show selectivity for the D₃ receptor (46). However, a recent report by Landwehrmeyer et al (55) questions whether D₃ expression in the substantia nigra actually occurs in the human brain. In general, it should also be recognized that distribution patterns based on RNA expression profiles may not directly reflect receptor protein levels. The recent and continuing development of subtype-specific antibodies and binding assays that distinguish receptor subtypes will allow for more direct measurement of receptor protein distribution patterns in the future.

As discussed above, genetic factors likely contribute to the development of psychotic illness. The identification and human chromosomal mapping of the dopamine receptor subtypes has enabled investigators to search for linkage between these genes and psychotic illness in schizophrenic pedigrees. To date, however, researchers have observed no such linkage and have, in fact, strongly excluded linkage for the D₂ gene in many of the families studied (56–59). One report suggested an association between schizophrenia and homozygosity at the D₃ locus (60), but another study (61) found no evidence of a D₃ linkage in their schizophrenic families. Interestingly, although widespread polymorphism occurs in the coding region of the human D₄ gene (62), no linkage to psychotic illness has been observed (57, 63). The receptors expressed by the D₄ allelic variants differ with respect to clozapine and spiperone binding. Attempts have been made to directly correlate D₄ alleles with susceptibility to schizophrenia and response to drug treatment (64, 65), but these have proven unsuccessful thus far.

INNOVATIONS IN TREATMENT

Clozapine, Remoxipride, and Risperidone

Three compounds (clozapine, remoxipride, and risperidone) have attracted recent interest because of their potential advantages over established neuroleptics either in terms of their range of efficacy or the relative absence of undesirable side effects.

Clozapine, a dibenzodiazepine first introduced in the 1970s, was subsequently withdrawn from use in some countries after several cases of agranulocytosis were reported. Nevertheless, clozapine was reportedly more effective than standard neuroleptic agents (e.g. chlorpromazine), particularly in severely ill and refractory patients. This claim was reinforced in a landmark trial (66) in which 268 inpatients who had proven refractory to at least three different neuroleptics were randomly allocated to clozapine (up to 900 mg/day) or chlorpromazine (up to 1800 mg/day). Thirty percent of the clozapine-treated patients were classified as responders, compared with only 4% of chlorproma-
zine-treated patients. Clozapine’s apparent superiority among this group of patients may be explained by its relatively high affinity for 5HT2, histamine, and muscarinic acetylcholine as well as for D1 receptor sites. Of particular interest is clozapine’s relatively lower occupancy (as demonstrated in PET studies) of D2 receptor sites and its high affinity for the D4 receptor.

Remoxipride is a substituted benzamide that provides better access to the CNS than the previously available sulpiride. Remoxipride has displayed higher affinities for [3H]raclopride than for [3H]spiperone–labeled D2 receptors and for extrastriatal rather than striatal receptors. Remoxipride has an antipsychotic potency comparable to that of standard neuroleptics (67) but induces fewer extrapyramidal symptoms.

Risperidone is a potent antagonist of the dopamine D2 and serotonin S2 receptors. In a clinical trial comparison (68), 6 mg/day of risperidone proved more effective than 20 mg/day of haloperidol in reducing psychotic symptoms. It also induced fewer extrapyramidal effects. As in the case of clozapine, investigators have suggested that risperidone is more effective than existing neuroleptics in ameliorating negative symptoms such as affective flattening and social withdrawal. Such claims are potentially important but difficult to evaluate because negative symptoms can be assessed in a number of different ways. However, comparative studies between these three compounds and existing neuroleptics may clarify the mechanism and scope of the antipsychotic effect.

Figure 2  Response of psychotic symptoms to pimozide (solid line) and placebo (dashed line) in patients with elevated and depressed mood and no significant mood change. Taken from Ref. 69.
Form of Illness and Response to Treatment

It is generally assumed that the efficacy of neuroleptic medication is confined to schizophrenic illnesses. For example, affective psychoses, though sometimes treated with neuroleptics, respond more specifically to lithium. This assumption is challenged by the findings of the Northwick Park functional psychosis trial (69, 70). This trial included patients with psychotic symptoms with no identifiable organic cause. The patients were not otherwise allocated to a diagnostic category, although they were divided into three groups: predominately elevated mood, predominately depressed mood, and no consistent mood change. Pimozide (a dopamine D2 antagonist), lithium, a combination of the two medications, or placebo were then randomly administered to the 120 patients entered into the trial. Pimozide consistently reduced psychotic symptoms, proving equally effective for patients in all three groups (Figure 2).

In contrast, the only significant effect of lithium was to reduce elevated mood. Thus, the effects of neuroleptic medication (as exemplified by pimozide) seem relevant to the resolution of psychotic symptoms in all types of functional psychotic illness. These compounds are antipsychotic rather than antischizophrenic, whereas lithium may only be helpful in cases of mood disturbance.

The benefits of pimozide extended into the follow-up phase of the trial (70). Of the patients who had recovered on trial medication, those who continued on pimozide fared significantly better ($p = 0.01$) than those who continued on placebo. The benefits of lithium continuation, on the other hand, were insignificant. These findings do not support the view of the diagnostic distinction between the affective and schizophrenic psychoses as a critical predictor of response to neuroleptic treatment, and they raise the question of whether such medication can play a broader role in prophylaxis of affective illnesses than current practice implies.

Can antipsychotic medication prevent deterioration? Two studies have revealed a strong relationship between duration of symptoms before first admission and risk of relapse thereafter (71, 72). One could attribute this relationship to the fact that illnesses with a poor outcome are generally associated with a delay in admission, but it could also signify that early treatment prevents the development of an element of chronicity (73).

CONCLUSIONS

The etiology of psychotic (schizophrenic, schizoaffective, and affective) illness remains obscure. These illnesses have an impact throughout the reproductive phase of life and, particularly in the case of schizophrenia, substantially decrease fertility. No environmental factors have proven relevant, and the
unvarying incidence (as demonstrated in the WHO studies) in societies with gross differences in climatic, social, and industrial environments suggests that psychotic illness is intrinsic to the human condition, i.e. that it is a part of genetic variation maintained by selective factors. Studies of brain structure provide insight into the nature of these factors, indicating that schizophrenic illnesses involve an arrest of development of cerebral asymmetry. This finding is consistent with the hypothesis that the psychoses form a part of the spectrum of variability generated in the course of the evolution of hemispheric specialization and language.

Although morphological studies suggest that psychosis is an arrest of development, why these diseases have a defined onset, are often episodic in course, and respond to neuroleptic medication still awaits explanation. These characteristics are consistent with the concept of a reversible neurochemical element. The efficacy of dopamine (particularly D2) antagonists in treatment and of some dopamine agonists as psychotomimetics confirms the dopamine hypothesis as the prevailing heuristic model of psychotic symptoms. Despite these findings, genetic linkage, isotope imaging, and biochemical studies provide no direct support for primary aberrations in dopaminergic systems in schizophrenia; whether dopamine receptor numbers are increased remains a controversial subject. The recent discovery of multiple dopamine receptor subtypes with distinct distribution and drug binding profiles opens up new avenues of exploration for disease mechanisms and for the development of new, more selective drugs.

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