Biology of Schizophrenia Subtypes: A Review and Proposal for Method of Study

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Abstract
This article describes two assumptions that are currently operative in biological research in schizophrenia. First, it is assumed that etiologic heterogeneity is present in this group of patients, even within patient cohorts diagnosed by precise, narrow research criteria. Secondly, it is assumed that overlap may exist with regard to specific biological abnormalities between schizophrenics and patients who satisfy research diagnostic criteria for other psychiatric disease entities. These assumptions suggest a need to relate putative biological abnormalities in schizophrenics to an array of historical, phenomenological, treatment response, long-term outcome, and family data in order to identify schizophrenic subtypes. Concern with biochemical abnormalities as "markers" for schizophrenia should be supplemented by efforts to demonstrate that the abnormality is relevant to the psychopathology of the perhaps small subgroup of patients in whom it is found. The following areas of research are reviewed for evidence of any usefulness in identifying schizophrenic subtypes: dopaminergic abnormalities; studies of other neurotransmitters or neuromodulators, including peptides; neuroendocrine studies; platelet monoamine oxidase (MAO) activity studies; autoimmune phenomena; and HLA antigens. The importance of genetic studies for biochemical research in schizophrenia is emphasized.

There is a general consensus that schizophrenia is a syndrome rather than a specific disease. According to this view, beneath the variegated clinical presentation of schizophrenia lie a host of separate disorders that we have not yet learned to differentiate. This is held to be most true of the broader definitions of schizophrenia but may even be true for the narrow definitions such as those of Feighner et al. (1972). Although I subscribe in general to this view, I also believe that there is biological overlap among the various subtypes of schizophrenia. The overlap could be based on the sharing of various combinations of genes that may produce the clinical picture of schizophrenia when a certain number of those genes plus appropriate environmental influences coexist. As different gene-environment combinations may lead to the same or similar phenotypes, it may be impossible from the phenotype alone to identify unique, biologically homogeneous groups.

How then should the biologist proceed in his efforts to develop a means of subtyping schizophrenia?

Biological investigations of schizophrenia have attempted to relate specific biological parameters to various dimensions or axes by which a defined group of psychiatric patients, usually with psychotic symptoms but without coarse organic brain disease, may be tested for homogeneity or divided into meaningful subtypes. The schema most frequently used for this purpose is based more or less exclusively on symptoms: for example, the presence, absence, duration, and severity of paranoia, catatonia, hallucinations, affective symptoms, or Schneider's first rank symptoms (Schneider 1959). In addition to classifications based on symptoms, biologists studying schizo-
phrenia have attempted to relate specific laboratory measures to pre-morbid functioning or clinical course. The most commonly studied dimensions include: acute/chronic, process/reactive, good/poor premorbid functioning, good/poor prognosis, and response to treatment with somatic therapies. Finally, there are biologic studies of schizophrenic subtypes based upon the presence or absence of schizophrenia in first degree relatives. A few studies use various combinations of symptoms, course, outcome, and familial pattern in an effort to characterize a homogeneous population.

It is my belief that specific biological parameters should be related to the types of dimensions cited above, regardless of the outcome of an initial data analysis relating a biological parameter to the particular means of making the diagnosis of schizophrenia used by a research group. If the initial analysis reveals a significant overall group difference between schizophrenics and normal controls, further analysis may reveal a particular group that provides the major contribution to the group differences and that will facilitate replication and extension of the findings. If the initial analysis revealed no difference between schizophrenics and psychiatric comparison groups, including normal controls, it is possible that a particular subtype, which may only be a small component of the total group, will nevertheless be significantly different not only from the comparison psychiatric groups and normal controls, but also from the rest of the schizophrenic group.

One of the best examples of this strategy is a recent series of studies by Rodnight and colleagues (Murray et al. 1979; Rodnight et al. 1976). The investigators sought to determine the relationship between schizophrenia and N,N-dimethyltryptamine (DMT), an indole hallucinogen that may be formed endogenously in man. In their initial work (Rodnight et al. 1976) a reliable method for qualitative identification of DMT was used to study 122 patients admitted over a 12-month period to three psychiatric hospitals. A single 24-hour urine specimen was collected shortly after admission. Each patient was evaluated with the Present State Examination (PSE) and classified by the Catego system (Wing, Cooper, and Sartorius 1974), a computer program that reduces the 150 PSE items to 38 syndromes such as “catatonia” or “delusions of reference”; these syndromes can in turn be used to form diagnostic groupings. Additional information was also obtained in interviews after discharge.

In the first of a sequence of analyses, the presence or absence of DMT in urine was found more frequently in all patients compared to normal controls. The incidence of DMT in all psychotic patients was not significantly greater than in non-psychotic patients, but the incidence in schizophrenics (by hospital diagnosis) and patients with nonaffective psychoses was comparable and significantly greater than that in normals, those with affective psychoses, and nonpsychotic patients. The incidence of DMT in schizophrenics as defined by the following nine different sets of criteria was considered next: hospital diagnosis, Catego, Schneider’s first rank symptoms, Feighner’s criteria (Feighner et al. 1972), Langfeldt’s criteria for poor prognosis (Langfeldt 1960), Carpenter’s flexible system criteria (Carpenter, Strauss, and Bartko 1973), New Haven Schizophrenia Index (Astrachan et al. 1972), two sets of Forrest and Hay’s criteria (Forrest and Hay 1973), and consensus diagnosis (meeting any four of the previous nine criteria). The kappa coefficient (Cohen 1968) was used to analyze the results. There was a significant association between DMT and the hospital diagnosis of schizophrenia, the New Haven Schizophrenia Index criteria, and a consensus diagnosis of schizophrenia. No major relationship between DMT excretion and schizoaffective psychosis, paranoid psychosis, mania, or psychotic depression was found.

DMT excretion was then related to the 38 PSE syndromes, which were examined in various specific combinations as well as individually. These analyses brought out the relationship between DMT excretion and psychotic symptoms in general, and hallucinations in particular. Finally, a discriminant function analysis identified a group of 21 patients from the group of 99, 15 of whom excreted DMT.

Many of the results were replicated when a more sensitive chemical means for determining DMT in urine was used with a different patient sample (Murray et al. 1979). A few slightly different analyses were used in the second study. DSM-III criteria added the dimension of course—acute, subacute, chronic, and subchronic. Instead of a discriminant function analysis, a stepwise linear function analysis was used. However, the results still indicated that DMT, to the extent that its metabolism is revealed by a 24-hour urine collection, is neither a necessary nor sufficient cause for psychosis in general or schizophrenia in particular.

Although the biological aspects of these studies do not constitute a definitive test of the DMT hypothesis of schizophrenia, the methodology may serve as a model, with some ad-
ditions to be described subsequently, for the approach that should be taken to relate biochemical parameters to subgroups of schizophrenics. Such an approach requires large samples and statistical assistance but may be necessary to prevent the rejection of valid linkages of biological abnormalities to relatively small subsets of psychotic patients. I wish particularly to call attention to the multiple approaches to the diagnosis of schizophrenia that were used in the study of Rodnight et al. (1976). The ability to do this was based upon a broad data base, only some of which is obtained through the PSE. Because of the current uncertainty about the history, symptom, sign, and outcome data that best subdivide a group of psychotic patients into those with a common etiology or pathophysiology, such a noncommittal approach to a particular diagnostic schema would seem the most prudent.

Some features of a model study that the Rodnight investigations lacked include: (1) the relationship of DMT to family history of psychosis with a parallel study of affected and nonaffected first degree relatives (to be discussed subsequently); (2) relationship to clinical response to neuroleptic or other somatic treatment; and (3) a study of DMT excretion over time—before treatment, after treatment, and off medication. Such an approach would reveal within and between subject variances, which might clarify whether the characteristic is a stable trait or is state dependent.

It is important to call specific attention to the current interest in whether schizoaffective illness is a subtype of schizophrenia or a variant of affective illness. There have been numerous investigations of this problem, and these have recently been reviewed by Pope and Lipinski (1978). Interestingly, they do not mention a single biological study—with the exception of trials of lithium responsiveness—that contributes to the clarification of this issue. Nevertheless, they believe there is sufficient evidence to conclude that schizoaffective illness is really manic-depressive illness and not a subtype of schizophrenia. From this, one might conclude that biological studies are not of crucial moment for diagnostic purposes—however useful they might be for determining etiologic factors, predicting drug response, understanding drug action, etc. In my view, the question of the relationship between schizoaffective illness and mania, depression, and schizophrenia is an area in which meaningful biological studies should be concentrated with the explicit purpose of comparing specific biological parameters in patients who fulfill predefined criteria for schizoaffective illness, manic-depressive illness, and schizophrenia.

It has, in fact, been argued that one of the major issues in subtyping schizophrenia is whether there are a variety of etiologies and pathophysiologies of the psychopathology of schizophrenia that may overlap to some extent with those of manic-depressive illness, schizoaffective illness, or any of the dichotomies cited above. As discussed by Blass, Milne, and Rodnight (1977), the various diagnostic classifications based on clinical criteria alone do not necessarily define discrete disease entities, and a diverse group of metabolic abnormalities may well be found in some schizophrenics that will overlap with abnormalities present in manic-depressive/schizoaffective illness. This type of overlapping biologic abnormality has been found in a number of studies: for example, a variety of abnormalities of the neuromuscular system (Meltzer 1976), decreased urinary 3-hydroxy-4-methoxy-phenylglycol (MHPG) (Joseph et al. 1976; Maas, Dekirmenjian, and Fawcett 1974; Taube et al. 1978); decreased platelet monoamine oxidase (MAO) activity (Murphy and Weiss 1972; Murphy and Wyatt 1972); decreased serum dopamine-beta-hydroxylase activity (Fujita et al. 1978; Meltzer et al. 1976); abnormalities on an aphasia-screening test (Taylor, Abrams, and Gaztanaga 1975), to name a few. Because of the problem of overlap, studies of groups of schizophrenic patients, or those with other psychoses as defined by clinical criteria, are often unlikely to lead to significant differences between comparison and control groups. Within the patient groups, however, there will be individuals with significantly deviant characteristics, which may be related to the etiology or pathophysiology of their psychopathology and probably found in any of their affected close relatives. The issue, then, is not whether the specific abnormality is a marker for schizophrenia or affective illness but to demonstrate that the abnormality in question is relevant to the psychopathology of the individuals in whom it is present. Some ways in which this may be done are:

- The abnormality may be shown to cause psychopathology when it is induced under research control—in the probands themselves, their first degree relatives, or normal subjects.
- The abnormality may be shown to be the consequence of some prior defect, which induces psychopathology—for example, the catabolite of an endogenous hallucinogen.
- The abnormality may predict an excellent or adverse response to a currently available psychothera-
Dopamine and Schizophrenia

The most widely advocated hypothesis of schizophrenia is that it is associated with increased activity of some dopaminergic neurons, most likely the mesolimbic and mesocortical dopaminergic pathways. The increase in dopaminergic activity may be relative to decreased activity of one or more other neurotransmitters or neuromodulators, such as acetylcholine, norepinephrine, gamma-aminobutyric acid (GABA), or serotonin, that are normally integrated with dopamine to regulate the input and output of central nervous system neurons. This hypothesis has been extensively reviewed in the Schizophrenia Bulletin (Meltzer and Stahl 1976) and elsewhere (Crow et al. 1976; Carlsson 1978; Luchins 1975; Meltzer, in press; Snyder, Greenberg, and Yamamura 1974; Van Praag 1977). We will focus here on selected studies that attempt to subtype schizophrenia on the basis of the dopamine hypothesis.

Spinal Fluid Metabolites. Central dopaminergic activity in schizophrenia has been extensively studied by examining the levels of the dopamine metabolite, homovanilllic acid (HVA), in the cerebrospinal fluid (CSF), even though the major source of HVA in the CSF is believed to be the caudate nucleus and other dopaminergic structures of the striatum that border on the lateral ventricles (Garelis et al. 1974; Papeschi et al. 1971; Sourske 1973). The contribution of HVA from the mesolimbic and limbic cortical dopaminergic neurons to CSF HVA may, in fact, be too small to influence the overall levels of HVA in CSF. This may explain why a number of studies have found no differences in either basal CSF HVA levels or HVA levels following probenecid, which inhibits the transport of HVA and other organic acids from the CSF (Bowers 1972, 1973; Chase, Schnur, and Gordon 1970; Persson and Roos 1969; Post et al. 1975; Rimon et al. 1971; Sedvall et al. 1974).

However, several studies have found interesting differences between subgroups of schizophrenia. Rimon et al. (1971) found that paranoid schizophrenics and those with paranoid states had significantly higher CSF HVA levels than non-paranoid schizophrenics. Bowers (1973) compared acutely psychotic patients who had at least one of the first rank symptoms of Schneider (1959) and had lower ratings on the Stephens, Astrup, and Mangrum (1966) prognosis scale to patients who were without such symptoms and had relatively higher prognosis ratings (but still in the poor prognosis range). Schneider-positive patients were characterized by decreased basal levels of HVA and increased basal levels of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of serotonin. The ratio of 5-HIAA to HVA was significantly elevated in the Schneider-positive, poor prognosis psychotics compared to Schneider-negative psychotics, depressed patients, and prison inmates. No difference between HVA or 5-HIAA/HVA was found in patients with relatively higher ratings of paranoia. In a subsequent study, Bowers (1974) found that probenecid-induced accumulation of HVA was also reduced in schizophrenic patients with a poor prognosis (based on the Stephens, Astrup, and Mangrum scale) compared to good prognosis patients. In this study, schizophrenics as a group had significantly lower HVA levels than a comparison group of patients with affective disorders, but the major contribution to this group difference was from the poor prognosis patients. Inspection of the raw data indicates, how-
ever, that three of eight good prognosis patients had HVA levels that were in the very low range (below the lowest level found in the affective patients) compared to eight of nine poor prognosis patients. CSF 5-HIAA differences between the good and poor prognosis patients were in the same direction as in Bowers’ (1973) earlier study. Bowers (1974) speculated that the decreased HVA levels might be indicative of a feedback-induced reduction in dopamine synthesis by supersensitive dopamine receptors. Recent studies of neuroleptic binding in postmortem tissue have partially supported the existence of such receptors in some schizophrenics (Lee et al. 1978; Owen et al. 1978) as will be discussed subsequently. The studies of Bowers provide considerable support for studying the relationship between biochemical parameters in a cohort of schizophrenics to dimensions such as prognosis and symptom pattern. Post et al. (1975) found the same relationship between Schneider-positive symptoms and probenecid-induced accumulation of HVA but not 5-HIAA in a group of acute unmedicated schizophrenics that Bowers did in more chronic schizophrenics (Bowers 1973). Van Praag and Korf (1976) reported that increased motor activity may be a critical factor characterizing schizophrenics with increased HVA levels, but Sedvall et al. (1974) found no relationship between motor activity and CSF HVA in manic patients.

Schizophrenics, particularly nonparanoid, withdrawn schizophrenics, have been reported to be "reducers" of neurophysiological stimuli rather than augmenters: That is, they show a lack of increase or even a decrease in amplitude of the visual evoked response with increasing stimulus intensity (Buchsbaum and Silverman 1968; Petrie 1967; Silverman 1964). In a miscellaneous group of 113 psychiatric patients containing schizophrenics, Von Knorring, Monakhov, and Perris (1978) reported that reducers have significantly greater CSF HVA and 5-HIAA levels than augmenters. Reducers tended to have lower platelet MAO activity and lower serum DBH activity as well. The relationship between these biochemical and neurophysiological parameters warrants further study. It points up the possibility of a confluence of biological factors (dopamine and serotonin turnover, MAO and DBH activities) relating to basic central nervous system characteristics (the augmenting/reducing dimension), which may contribute to psychopathology that is present in patients with a variety of clinical diagnoses.

3,4-Dihydroxyphenylacetic acid (DOPAC) is the major intraneuronal metabolite of dopamine. Markianos, Rüther, and Gluba (1976) have studied the levels of DOPAC and HVA in the CSF and serum of 13 unmedicated psychotic patients. Diagnosis was not specified. Marked variations in the absolute amounts of each metabolite and the ratio of the two metabolites were present in serum; the levels also varied in CSF but were less variable than in serum. This ratio may reflect the rate of extraneuronal metabolism, which may be more physiologically relevant. No data were presented for normal controls, so it is not possible to determine if any or all of the individuals have elevated (or reduced) intra- or extraneuronal dopamine metabolism. The marked variation found does suggest, however, that there is considerable heterogeneity in dopaminergic activity in psychotic patients. The major significance of this study is the introduction of blood and CSF DOPAC levels as a means of studying dopamine metabolism in man.

Bird et al. (1977) reported postmortem brain dopamine levels were 48 percent higher in the nucleus accumbens of 26 psychotic patients compared to 23 control subjects. No difference in dopamine levels in the putamen between the two groups was noted. Only two of the schizophrenic patients had nucleus accumbens dopamine levels that were higher than the levels found in the highest of control subjects. Crow et al. (1978b), on the other hand, found no difference in dopamine levels in the nucleus accumbens of 16 schizophrenics compared to 18 controls but did find increased dopamine levels in the caudate of the schizophrenics. Since these investigators found lower HVA levels in the caudate of the schizophrenics, they suggested the increased dopamine levels did not indicate increased dopaminergic activity. Although Crow et al. did not so indicate, the findings of increased dopamine and increased HVA would actually suggest decreased dopaminergic activity in the caudate. However, no difference in DOPAC levels was noted (Owen et al. 1978). In view of the long-term neuroleptic treatment of many of the patients and the many methodologic problems that plague post-mortem studies, it is difficult to assess the significance of these findings.

Biederman et al. (1977) reported that the variance in CSF cyclic adenosine monophosphate (AMP) levels in the CSF of 19 chronic schizophrenics was significantly greater than that of 10 normal controls. This is important because of the role of cyclic AMP as a second messenger for numerous neurotransmitters and hormones. Cyclic AMP has been linked to the
dopamine receptor (Iversen 1975), but there is great controversy over this (see Meltzer and Stahl 1976). Biederman et al. (1977) found 2 of 19 schizophrenics had CSF cyclic AMP levels higher than those of any of the control subjects. These two patients responded exceptionally poorly to neuroleptic treatment and differed clinically from the rest of the patients in having an illness with a more insidious onset and greater subsequent deterioration.

**Dopamine Receptors.** The ability of dopamine and neuroleptics to bind to brain tissue in a saturable, stereospecific, high-affinity manner has been used to define dopamine receptors (Burt, Creese, and Snyder 1976; Seeman et al. 1976). The antipsychotic effect of neuroleptics is believed to be initiated by binding to these receptors (Seeman et al. 1976; Snyder 1976). Whether there is more than one dopamine receptor—presynaptic as well as postsynaptic (Nagy et al. 1978; Titeler et al. 1978); or varieties of postsynaptic receptors (Cools and Van Rossum 1976)—is beyond the scope of this review. Two groups have reported increased binding of 3H-neuroleptics to caudate, putamen, or nucleus accumbens obtained at autopsy from some schizophrenics compared to normal controls (Lee et al. 1978; Owen et al. 1978). Owen et al. (1978) reported that the increase in 3H-spiroperidol binding was due to increased numbers of binding sites as well as increased affinity. Lee et al. (1978) found no difference in 3H-apomorphine binding between patients and controls. There was considerable overlap between patients and controls in both studies, indicating that this finding, if valid, may be characteristic of only some schizophrenics. The effects of neuroleptic drug treatment on this parameter could not be examined in depth. Only a few nonmedicated patients were studied. Increased 3H-spiroperidol binding in the striatum has been reported following neuroleptic treatment in animals (Burt, Creese, and Snyder 1976). These extremely important studies, which come from excellent laboratories, must await confirmation by studies that include, for example, larger numbers of unmedicated patients, more specific ligands, and shorter intervals between death and obtaining specimens.

**Pharmacologic Differentiation of Schizophrenic Subtypes.** Pharmacologic studies provide the essential data in support of the dopamine hypothesis. Specifically, drugs that reduce dopaminergic activity are frequently antipsychotic, regardless of the mechanism by which they achieve this reduction: (1) neuroleptics via receptor blockade; (2) reserpine via inhibition of dopamine storage in granules; and (3) alpha-methylparatyrosine via inhibition of dopamine synthesis. The clinical studies supporting these assertions have been reviewed in detail elsewhere (Meltzer and Stahl 1976). Here we wish to emphasize the heterogeneity of the effects of dopaminergic drugs on patients diagnosed as schizophrenic. While the majority of schizophrenic patients treated with neuroleptics experience remission of delusions and hallucinations, alleviation of agitation and sleep disturbance, and diminution in the variety and frequency of bizarre, inappropriate activities, it is common clinical experience, documented by clinical investigation, that partial or total nonresponders are encountered. Some of this may be due to pharmaco-availability (e.g., inadequate doses, poor absorption, and rapid metabolism), but this does not explain all such patients. It is possible that such nonresponders are patients who fit within the schizophrenic syndrome by virtue of phenomenology, clinical course, and social functioning but whose psychosis is not and has never been dependent upon dopamine. Alternatively, although dopamine may have, at some earlier time, been involved in the etiology of the psychosis in these patients, alteration of dopamine physiology no longer can affect the clinical course because of irreversible central nervous system changes.

**Decreased Dopaminergic Activity.** The dopamine hypothesis of schizophrenia has emphasized the possibility of increased dopaminergic activity as the probable basis of schizophrenia. We have proposed as alternatives that increased dopaminergic activity may be secondary to some other primary biological abnormalities that are the basis of schizophrenia (Meltzer and Stahl 1976) and that increased dopaminergic activity may be more relevant to the psychotic process, which is common to all forms of the major psychoses in man, than to the core abnormality in schizophrenia (Meltzer et al. 1978; Meltzer, in press).

If increased dopaminergic activity is an etiologic factor in acute psychoses, rather than schizophrenia, then the accumulating evidence that at least some schizophrenics may have decreased dopaminergic activity or that the long-term clinical effects of neuroleptics on schizophrenics may be due to their ability to increase dopaminergic activity is not so surprising. Thus, we have reported that the H-reflex recovery curve in approximately one third of unmedicated chronic schizophrenics is identical to that of patients with...
Parkinson's disease (Goode et al. 1977). The increased excitability of the alpha-motor neuron in parkinsonian patients and chronic schizophrenics revealed by this technique is most likely due to decreased dopaminergic activity. The fact that motor neuron excitability in parkinsonian patients is reduced by L-dopa, which increases dopaminergic activity, and is reduced in the chronic schizophrenics by chronic treatment with neuroleptics, suggests that the long-term effect of chlorpromazine may be to increase dopaminergic activity. The physiological basis for this increase in dopaminergic activity following treatment with dopamine receptor blockers could be the feedback activation of dopaminergic neurons following inhibition of dopamine receptors (Carlsson and Lindqvist 1963).

As previously discussed, increased levels of dopamine, decreased levels of HVA, or both have been found in the nucleus accumbens (Bird et al. 1977) and caudate (Crow et al. 1978b; Owen et al. 1978) of psychotic patients, without change in DOPAC levels, which is closer to what would be expected of decreased dopaminergic activity than increased activity. The CSF HVA studies previously reviewed are also consistent with decreased dopaminergic activity, suggesting that the only way to reconcile the dopamine hypothesis with the available neurochemical data is to postulate receptor supersensitivity (Bowers 1974).

The improvement in some schizophrenics following treatment with L-dopa (see Melzer and Stahl 1976 for review of the extensive literature; also Alpert et al. [1978b]) is consistent with the possibility that some schizophrenics have decreased dopaminergic activity. Other evidence consistent with this view is that some schizophrenics appear to improve clinically when given d-amphetamine, an indirect dopamine agonist (Van Kammen et al. 1977). This should be compared to the evidence that the majority of acutely disturbed schizophrenics worsen when given d-amphetamine or methylphenidate (Janowsky and Davis 1974) and that chronic schizophrenics may be less responsive to d-amphetamine than normals (Kornetsky 1976). Huey et al. (1978) found that a patient with chronic schizophrenic symptomatology who had a past history of probable minimal brain dysfunction (MBD) responded well to methylphenidate. They speculate that some apparent schizophrenics may have a variant of the MBD syndrome, particularly those who respond well to psychostimulants. Low-dose L-dopa exacerbated the psychotic symptoms of two of three chronic schizophrenics who were resistant to neuroleptic treatment (Calif, Yesavage, and Hollister 1977).

Alpert et al. (1978a) demonstrated that clinical response to neuroleptics is negatively correlated with their ability to produce a specific extrapyramidal side effect (tremor). Originally, they had hypothesized that increased dopaminergic blockade, as evidenced by severity of tremor, should predict good outcome. Since the reverse was found, they suggested that the therapeutic basis of neuroleptics may be their ultimate ability to increase dopaminergic activity. Their finding is also compatible, however, with the notion that there are subgroups of schizophrenics with normal (or reduced) as well as increased dopaminergic activity. Those with increased dopaminergic activity will have fewer extrapyramidal side effects (EPSE) when given neuroleptics because their relatively excessive dopamine antagonizes the neuroleptic-induced receptor blockade. Clinical response to neuroleptics would be better in these subjects because the increased dopaminergic activity would suggest that dopamine is indeed a primary factor in their psychosis. Dopamine would be relatively unimportant in those neuroleptic-treated schizophrenics who did develop more severe EPSE, because of lower striatal dopaminergic activity, which could be taken as an indication that limbic system dopaminergic activity is also not increased in these subjects and, hence, not of major importance to the etiology of their psychoses. If so, then neuroleptics would be expected to be less therapeutic for these subjects. If this hypothesis is supported by further investigation, it would mean that clinical response and EPSE associated with neuroleptic treatment could be used to subtype schizophrenics on the basis of the role of dopamine in the etiology of psychosis.

Neuroendocrine Studies

Secretion of hormones such as prolactin, growth hormone, adrenocorticotropic hormone (ACTH), and thyroid-stimulating hormone (TSH) from the anterior pituitary gland is regulated by hypothalamic releasing or release-inhibiting factors (Muller, Nistico, and Scapagnini 1977). The release of these hypothalamic factors is, in turn, regulated by neurotransmitters or neuromodulators, such as dopamine, serotonin, and norepinephrine. Prolactin-inhibiting factor is most likely dopamine itself, secreted into the pituitary portal circulation by tuberoinfundibular neurons. The secretion of prolactin and growth hormone has been used in
several studies to subtype schizophrenic patients. We reported that the effect of apomorphine, \(0.75\) mg/kg given subcutaneously, on serum prolactin and growth hormone in 10 chronic schizophrenics was not significantly different from that of 7 normal controls (Meltzer, Goode, and Fang 1978). Ettigi et al. (1976) studied the serum growth hormone and prolactin response to apomorphine in 17 unmedicated schizophrenic patients, 4 of whom had an oral dyskinesia, and 21 controls. Six of the schizophrenics, but none of the controls, had raised baseline levels of growth hormone. Eight of the patients had an inadequate growth hormone response to apomorphine. The peak growth hormone response was significantly less after apomorphine in patients withdrawn from neuroleptics compared with controls. Among patients withdrawn from neuroleptics, the growth hormone response to apomorphine was significantly greater in patients without oral dyskinesia than those with dyskinesia. The decrease in prolactin after apomorphine was not significantly different in patients and controls. The diminished growth hormone response was believed to result from prior treatment with neuroleptics. Rotrosen et al. (1976) also observed a diminished growth hormone response to apomorphine in seven chronic schizophrenic patients who responded to neuroleptics and an enhanced growth hormone response in three unmedicated schizophrenics who subsequently failed to respond to neuroleptics. The relationship between growth hormone response and clinical response was not maintained in a subsequent larger sample (Rotrosen et al. 1978b). In a later study, this group (Rotrosen et al. 1978a) found that the decrease in prolactin levels in schizophrenics given apomorphine was slightly less than in controls, but the decrease following L-dopa, a precursor of dopamine, was slightly greater.

Tamminga et al. (1977) also reported a nonsignificant tendency toward a decreased growth hormone response to apomorphine and a significantly smaller prolactin response in eight chronic schizophrenic patients with tardive dyskinesia. This group also reported similar results for chronic schizophrenics without tardive dyskinesia and an enhanced growth hormone response in acute schizophrenics (Pandey et al. 1977).

We have recently completed a study of the effect of apomorphine, \(0.75\) mg, on growth hormone and prolactin secretion in 13 chronic schizophrenics, 5 acute schizophrenics, and 19 normal controls. There was no significant difference in the areas under the curve (AUC) which reflects the fall in prolactin levels or the increase in growth hormone levels for the three groups. However, when the chronic schizophrenic patients had been separated on the basis of duration of illness into those who were ill for less than 4 years or more than 4 years, we found a significant difference: AUC for six patients ill less than 4 years was 38.8 ± SD 22.4 vs. 7.31 ± SD 5.1 for six patients ill equal to or greater than 4 years \((p < .05)\). We further found a significant negative correlation \((r = -0.47, p < .05)\) between growth hormone and discharge psychosis ratings (a global rating of psychosis on a scale of 1 to 5) for all 18 schizophrenics. Thus, we found good response to neuroleptics (low discharge psychosis ratings) to be related to a relatively high growth hormone response to apomorphine. This is opposite to the early, unreplicated finding of Rotrosen et al. (1976) but is in accord with the finding of Pandey et al. (1977) that acute schizophrenics tend to have high growth hormone secretion after apomorphine. Thus, our results indicate that chronic patients have a diminished response to dopamine agonists in the hypothalamus (as indicated by low growth hormone response) but not the pituitary (normal prolactin response). On the other hand, they have a normal response to neuroleptics in the pituitary (again signified by normal prolactin response). The negative correlation between growth hormone, AUC, and discharge psychosis ratings in all 18 schizophrenics indicates a tendency for poor clinical response to dopamine receptor blockers to be associated with a minimal response to a dopamine agonist in presumably another region of the brain (mesolimbic and mesocortical vs. hypothalamic dopamine receptors). The diminished growth hormone response to apomorphine suggests subsensitivity of dopamine receptors in these chronic schizophrenics. The implications of this finding for treatment depend upon whether the subsensitivity extends to dopamine receptors in other regions such as the mesolimbic and mesocortical areas and whether subsensitivity is a primary factor in these patients, an adaptation to chronic neuroleptic treatment, or an effect of chronic neuroleptic treatment. It is conceivable that subsensitivity of some dopamine receptors may explain why direct and indirect dopamine agonists are of clinical benefit to some schizophrenics.

These initial attempts to use the neuroendocrine system to identify biological abnormalities in schizophrenics have produced inconsistent results. However, the approach does permit the assessment of specific responses to neurotransmitter agon-
ists (or antagonists) in man, at specific receptors, which might lead to a biological means of identifying individuals with aberrant receptor dynamics.

Other Neurotransmitters and Schizophrenic Subtypes

Although the greatest attention has been paid to the role of dopamine in the etiology and pathophysiology of schizophrenia, for the reasons just described, there is also a considerable body of literature concerning the role of acetylcholine (Davis, Janowsky, and Casper 1977; Davis et al. 1978; Friedhoff and Alpert 1973), GABA (Roberts 1977; Tamminga, Crayton, and Chase 1978; Van Kammen 1977), serotonin (Bender 1976; Smythies 1976; Stevens 1973; Wyatt et al. 1972), norepinephrine (Farley et al. 1978; Hartmann 1976; Stein and Wise 1971), and more recently phenethylamine (Sandler et al. 1978; Wyatt et al. 1977) in the etiology of schizophrenia. In many instances, preclinical and clinical studies have been carried out because of the interactions between these neurotransmitters and dopamine: For example, GABAergic (Kim et al. 1971) and serotonergic (Dray et al. 1976) neurons are believed to inhibit dopaminergic neurons.

It is beyond the scope of this review to reassess this literature. There is as yet no convincing evidence for hypo- or hyperfunction of any of these neurotransmitters in any subgroup of schizophrenics. Nevertheless, it is premature to conclude that subtyping of schizophrenics could not be based upon abnormalities in one or more of these neuronal systems, either through their impact on the dopaminergic system, or through their primary roles in the control of cognitive, affective, and motoric function. An excellent early discussion of this hypothesis is found in Cools (1975).

Peptides and Schizophrenic Subtyping

Peptides that have a morphine-like action and that are produced endogenously have been implicated in schizophrenia on the basis of the ability of beta-endorphin to induce in rats an inhibition of motor activity, loss of righting reflex, and extreme muscular rigidity which Bloom et al. (1976) likened to catalepsy. Jacquet and Marks (1976) suggested the behavioral state produced by this agent was closer to a neuroleptic-induced catalepsy. Bloom et al. (1976) proposed that an excess of beta-endorphin-like substances in the central nervous system might have an etiological role in mental illness and that "anti-endorphins" such as the available opiate antagonists might be therapeutic. Conversely, Jacquet and Marks (1976) proposed that a deficiency of beta-endorphin-like substances in the central nervous system might have an etiological role in mental illness and that "anti-endorphins" such as the available opiate antagonists might be therapeutic. Conversely, Jacquet and Marks (1976) proposed that a deficiency of beta-endorphin-like substances might be implicated in those mental illnesses improved by neuroleptic drugs.

These hypotheses have since been tested by a number of investigators. Narcotic antagonists such as naloxone and naltrexone, a long-acting agent, have been given to acute and chronic schizophrenics with mixed, mainly negative results. Four of six chronic schizophrenic patients with auditory hallucinations were reported to respond well to naloxone (Gunne, Lindstrom, and Terenius 1977). Similar results were reported by Emrich et al. (1977) and Watson et al. (1978). However, Volavka et al. (1977), Davis et al. (1977), Janowsky et al. (1977), Kurland et al. (1977), and Mielke and Gallant (1977) were unable to confirm these results. Indeed, none of the five negative studies found a single schizophrenic who could reliably be identified as a responder to naloxone or naltrexone.

Lindstrom et al. (1978) reported increased levels of a beta-endorphin-like substance in the spinal fluid of six out of nine drug-free, acutely disturbed schizophrenics. However, the radioreceptor assay employed requires further verification.

Only one published study has tested the hypothesis of a beta-endorphin deficiency in mental illness. Kline et al. (1977) administered beta-endorphin to a small number of depressed and schizophrenic patients. The three schizophrenic patients showed a worsening of cognitive functioning, while the two depressed patients improved in mood. Further verification of the results of this uncontrolled study is awaited.

Recently, evidence has been presented that [des-Tyr1]-gamma-endorphin, which is the 62-77 amino acid fragment of beta-lipotropin was markedly or moderately effective in producing symptomatic improvement in 8 of 13 chronic schizophrenics. In 7 of the subjects, the effect lasted several weeks after stopping the agent (Van Ree et al. 1978). Part of the study was double-blind, placebo-controlled. The investigators proposed that the peptide was an endogenous neuroleptic.

There are many other peptides found in the central nervous system that have central or behavioral effects in laboratory animals. This includes, TRH, ACTH and fragments thereof, somatostatin, melanocyte-stimulating hormone, and luteinizing hormone-releasing hormone (see Prange, Nemeroff, and Lipton 1978). There has been limited testing of these agents for behavioral effects.
in man, but research is continuing actively in this area. The unlimited number of possible peptides makes them excellent candidates for roles as factors contributing to the heterogeneity of schizophrenia through action as neuromodulators or neurotransmitters.

**Platelet MAO Activity**

Monoamine oxidase (MAO), the enzyme that catabolizes biogenic amines such as dopamine, norepinephrine, and serotonin, has been extensively studied in various tissues of schizophrenics. The vast majority of studies have been of platelet MAO activity, not only because the platelet is accessible but because it shares a number of significant characteristics with serotonergic nerve terminals (Snellson 1973; Stahl 1977).

The interest in platelet MAO activity in schizophrenics developed from the work of Murphy and Wyatt who reported that MAO activity in the platelets of acute and chronic schizophrenics was reduced (Murphy and Wyatt 1972) and that platelet MAO activity was under genetic control (Wyatt et al. 1973). Over 30 additional studies have appeared since then on this topic, with the reports being about equally divided as to whether there is a decrease in platelet MAO activity in schizophrenics or a subgroup thereof. We have reviewed the literature on platelet MAO in detail elsewhere (Meltzer, in press). The major factors accounting for the discrepancies may be both analytic errors and diagnostic errors. Here we will review those studies which indicate that platelet MAO activity may be reduced in a subgroup of schizophrenic patients.

Domino and Khanna (1976) and Owen et al. (1976) both studied chronic schizophrenics who do not have an exacerbation of symptoms when treated without antipsychotic drugs. Domino and Khanna found decreased platelet MAO activity in their patients, whereas Owen et al. did not. Van Kammen et al. (1978) reported that platelet MAO activity was decreased in a group of eight schizoaffective patients whose psychotic symptoms remitted without treatment with neuroleptic drugs. They suggested a relationship between their patients that of Domino and Khanna (1976), but the latter patients were chronically ill and were nonresponders to neuroleptic medications, whereas the patients of Van Kammen et al. were worsened by drug treatment and went into spontaneous remission.

Schildkraut (1976), Becker and Shaskan (1977), Meltzer et al. (1977), and Orsulak et al. (1978) have reported that schizophrenics as a group do not have significantly lower platelet MAO than controls but that the subgroup who manifest auditory or visual hallucinations do. However, Owen et al. (1976) and Carpenter, Murphy, and Wyatt (1975) found no association between hallucinations and low MAO activity. We have replicated the association between low platelet MAO activity and hallucinations in a larger group of schizophrenics (H.Y. Meltzer, unpublished data).

Another cluster of studies have found significantly lower platelet MAO activity in paranoid schizophrenics than in other types of schizophrenics (Demisch et al. 1977; Potkin et al. 1978; Wyatt et al. 1978), but paranoid schizophrenics did not have significantly lower platelet MAO activity in the studies of Meltzer et al. (1977), Owen et al. (1976), or Berger et al. (1978).

Schizophrenics with a positive family history of schizophrenia did not differ in platelet MAO activity from so-called “nongenetic phenocopies”; that is, schizophrenics with no family history of schizophrenia (Belmaker et al. 1978). On the other hand, Book and Wetterberg (in press) have studied a large cohort of schizophrenics and their nonaffected relatives in a remote and isolated Swedish area and found that the affected individuals had significantly lower MAO activity than their normal relatives.

It should be clear from this brief review that there is no consensus as to the clinical characteristics of schizophrenic patients with low platelet MAO activity. Because most investigators have not reported the reliability of their assays and because there may be significant error in the assessment of clinical characteristics, further research is warranted in this area with strict attention to analytic accuracy and reliable clinical assessment.

**Neuromuscular Dysfunction**

Serum creatine phosphokinase (CPK) activity has been reported to be increased in some but not all acutely psychotic patients (see Meltzer 1976 for review). The increase in serum CPK activity is not specific for schizophrenia; it may also occur in patients with affective psychoses and periodic catatonia (Meltzer 1976; Kruger and Löhse 1975). Meltzer (1975) reported that excitement was present significantly more frequently in psychotic patients with increased serum CPK activity. This finding has been confirmed in a larger study (Meltzer, unpublished data).

No other reliable differences in premorbid functioning, type of psychopathology, or prognosis have been found in psychotic patients with increased serum CPK activity.
However, we have reported (Meltzer 1975) and recently confirmed (Meltzer, Ross-Stanton, and Schlessinger, in press) that the mean daily serum CPK levels of patients recovering from a psychotic episode who had had increased serum CPK levels during that psychosis are significantly greater than mean daily serum CPK levels of psychotic patients who had never had increased serum CPK activity. Further, patients who have had increased serum CPK activity have a significantly higher incidence of first degree relatives with serum CPK levels that exceed the 95 percent upper limit of normal than patients who did not have increased serum CPK activity. Thus, there appears to be a subgroup of psychotic patients with high mean daily serum CPK levels (which are under genetic control) (Meltzer et al. 1976; Meltzer, Ross-Stanton, and Schlessinger, in press), who will frequently have increased serum CPK activity when psychotic and who have first degree relatives with a tendency to have increased serum CPK activity, despite not being symptomatic. These increases in serum CPK activity could be a marker for a skeletal muscle membrane defect that leads to increased efflux of CPK from skeletal muscle.

Several other major forms of neuromuscular dysfunction have been reported in schizophrenics, as well as in other psychotic patients. These include skeletal muscle fiber abnormalities (Meltzer 1972), increased branching and sprouting of subterminal motor nerves (Meltzer and Crayton 1974), increased motor fiber density (Crayton, Stalberg, and Hilton-Brown 1977; Peters 1978), and abnormal Hoffmann (H)-reflex recovery curves (Goode et al. 1977). The increased branching and sprouting of subterminal motor nerves is significantly more common in paranoid than nonparanoid schizophrenics (Ross-Stanton and Meltzer, unpublished data). Peters (1978) found increased motor unit fiber density, indicative of denervation, in 10 of 18 chronic schizophrenics. Six of 45 first degree relatives had a related abnormality, increased jitter (see Crayton, Stalberg, and Hilton-Brown 1977) and all six had schizophrenic pathology. The possible relationship of these findings to schizophrenic subtypes was not discussed. Chronic schizophrenics have increased H-reflex recovery curves compared to normal controls. The reverse is true for acute schizophrenics (Goode et al., in press; Metz, Goode, and Meltzer, submitted for publication). As previously noted in the discussion of dopamine and schizophrenia subtyping, the H-reflex recovery curve is facilitated by decreased dopaminergic activity; the reverse is true with increased dopaminergic activity (Goode et al. 1977). These results suggest that at least some unmedicated chronic schizophrenics could have decreased dopaminergic activity in the descending dopaminergic pathway, which originates in the substantia nigra and has synapses on alpha-motor neurons or interneurons. The reverse would be true of acute schizophrenics.

**Viral Theory**

The possibility that some pheno-
copies of schizophrenia may be due to regular viruses or slow viruses has been extensively reviewed (Tor-
rey and Peterson 1973, 1976). Various forms of encephalitis, particularly herpes simplex encephalitis, have been known to mimic acute or chronic schizophrenia (Chacon, Monro, and Harper 1975; Glaser and Pincus 1969; Glaser, Solitare, and Manuelidis 1968; Himmelhoch et al. 1970; Petrov 1970; Raskin and Frank 1974; Shearer and Finch 1964; Wilson 1976). The natural history of slow virus diseases such as Jakob-Creutzfeldt and kuru with long latent periods and eventual profound, even fatal neurological damage has at least superficial similarity to those forms of schizophrenia that produce or are associated with a deteriorating course.

Torrey and Peterson (1976) have reviewed the evidence for protein abnormalities in the CSF and serum of schizophrenics that may be consistent with a viral etiology—for example, a large increase in one of the types of CSF immunoglobulins (Baron et al. 1977; Schneck and Claman 1969; Strahilevitz et al. 1976; Torrey et al. 1978). The results of these studies have been inconsistent but some individuals with generally accepted schizophrenic symptoms and course have evidence of prior viral infection. Thus, Torrey et al. (1978) reported that multiple admission schizophrenic patients had an elevated percentage of IgG to total protein in the CSF. First admission schizophrenics had a significantly elevated percentage of mean IgA to total protein in the CSF. Attempts to characterize further the relationship between increased CSF IgG or IgA were unsuccessful. Antibodies to measles, HSV-1, and CMV were present in the sera and CSF of many schizophrenic patients, occasionally in high titer. In terms of percentage of abnormal CSF, the multiple admission schizophrenic group (6/17) was most similar to severely ill neurological patients. The relation of these abnormalities to the psychopathology is unknown; they may reflect etiology, may be secondary developments, or may be altogether unre-
It has been known for many years that a graft elicits an immune response if it carries antigens that the host recognizes as foreign. Genes that play a role in graft rejection are called histocompatibility loci, and the products determined by their alleles are histocompatibility antigens. In man, the only major histocompatibility locus, frequently referred to as the major histocompatibility complex or MHC, is called the HLA locus. These genes are located on chromosome 6, including the A, B, and C loci controlling cell surface glycoproteins, and are detectable serologically (SD). The D locus controls cell surface antigens detectable in mixed lymphocyte reactions (MLC) and other loci control various components of complement and transplantation antigens (Bach and Van Rood 1976a; Kahan and Reisfeld 1972). These loci are polymorphic, which implies that in some way they are of general benefit for the survival of the population, possibly as a defense against viral agents (Doherty and Zinkernagel 1976). As reviewed by Bach and Van Rood (1976a, 1976b, 1976c), the MHC is important in such processes as immune responsiveness, development, and susceptibility to disease through its determination of cell.surface structures and hence cell interactions that are significant for morphogenesis and the maintenance of individuality.

Typing of humans as to their HLA antigens is of major importance in the study of many diseases since it may yield pertinent clues to the genetics and pathogenesis of the diseases in question. Subtypes of the disease may be identified, as is the case with myasthenia gravis (Alter et al. 1976). A number of diseases, especially multiple sclerosis, myasthenia gravis, ankylosing spondylitis, and Reiter’s disease, have shown associations with specific HLA antigens (Alter et al. 1976; Bach and Van Rood 1976a, 1976b, 1976c).

These studies are complicated by choice of patients and controls, anti-sera, and statistics. Controls and patients should be matched for race and should come from the same population and geographical area. There may be error in typing. Usually the frequencies of 20 or more HLA antigens are compared, and on an average, one of these will show a significant difference at the 5-percent probability level even if there is no true difference between the groups compared. This can be corrected by multiplying the p values by the number of comparisons made. When small populations are studied, rejection of true differences is difficult to avoid. A large number of controls makes it easier to detect increased antigen frequencies in the patient group, whereas a decreased frequency can only become significant when a large number of patients are studied. These issues are discussed in detail by Svejgaard et al. (1975) and Bach and Van Rood (1976a, 1976b, 1976c).

There have been several studies of the HLA antigens in schizophrenia. Smiraldi et al. (1976b) found no association between HLA antigens and schizophrenia except that hebephrenics had a higher incidence of HLA than paranoid patients. However, there was no correction for the number of comparisons made. In a second study of 33 schizophrenic patients, Smiraldi et al. (1976a) reported a highly significant positive correlation between response to chlorpromazine and HLA-A1; HLA-A2 positive patients showed a significant negative correlation to chlorpromazine treatment. This finding was replicated in a second smaller group of patients. Eberhard, Franzen, and Low (1975) found a significant, comparison-adjusted increase in HLA-A9 frequency in a

**Autoimmune Hypothesis**

The autoimmune hypothesis of schizophrenia, which was advocated by Fessel (1962), Burch (1964), and Heath et al. (1967), has not been sustained by the majority of experimental evidence (Whittingham et al. 1968). The hypothesis has recently been revived by Witz, Anavni, and Weisenbeck (1977), who developed a radioimmunofixation method of identifying substances that bind to brain in sera. Baron et al. (1977) found increased levels of this factor in 17 of 27 (63 percent) schizophrenics and 5 of 28 (17 percent) of relatives of the schizophrenics compared to only 2 of 117 (2 percent) healthy controls. They concluded the brain-binding substances may be a genetic marker for the vulnerability to schizophrenia. There has been a recent proposal that certain types of schizophrenia may result from an "immunopharmacological" blockade at limbic dopamine receptors (Abramsky and Litvin 1978). According to this concept, the action of dopamine receptors at excitatory or inhibitory postsynaptic sites might be inhibited or mimicked by humoral antibodies or immunocytes and/or nonimmunoglobulin substances elaborated by them (Lennon and Carnegie 1971).

**HLA Antigens and Schizophrenic Subtypes**

It has been known for many years that a proportion of cases diagnosed as schizophrenia based solely on phenomenological criteria are due to viral infections. The size of this proportion is unknown and will remain so until there are reliable methods for screening large numbers of psychiatric patients for stigmata of viral infection.

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group of Swedish schizophrenics. Smeraldi, Bellodi, and Cazzullo (1976) reported a reduced incidence of HLA-A10 even after correction for the number of comparisons in a second group of patients. When Smeraldi, Bellodi, and Cazzullo (1976) combined their results with those of Eberhard, Franzen, and Low (1975), they still found a decreased HLA-A10 frequency. Ivanyi, Zemek, and Ivanyi (1976), however, found a slightly higher incidence of HLA-A10 in 148 Czech chronic schizophrenics than in 1,200 controls. McGuffin, Farmer, and Rajah (1978) studied 80 schizophrenic patients and found an increased incidence of HLA-BW5 and a decrease in HLA-AW29 and HLA-BW17 as compared with healthy controls. In the subgroup of patients who reported Schneider’s (1959) first rank symptoms (N = 57), there was an increased incidence of HLA-A1, while HLA-A2 and HLA-BW17 were decreased compared to controls. These results may be congruent with those of Smeraldi et al. (1976a, 1976b).

The limited agreement between these results is not surprising in light of the heterogeneity inherent in the schizophrenic syndrome, the difficulty in reliable diagnosis, and the problem of appropriate controls. Conceivably, an extremely meticulous study of the type just reviewed, could lead to the identification of reproducible associations between HLA antigens and subtypes of schizophrenia; it would need to use highly reliable HLA typing and to involve upwards of 500 patients and 2,500 controls of the most homogeneous ethnic background. Still more useful, however, would be a family study, in which it were determined whether there is an association with a subtype of schizophrenia and a particular HLA haplotype in a family with two to three generations of affected and unaffected members, a large number of whom are informative about the linkage.

**Genetic Strategies for Subtyping**

The role of genetics in subtyping schizophrenics has been reviewed elsewhere in this issue (Caneco 1979). Genetic strategies are particularly useful for a biological approach to the identification of subtypes of schizophrenia as pointed out by Rieder and Gershon (1978). The significance of specific biological characteristics such as elevated mean serum creatine phosphokinase activity or low platelet monoamine oxidase activity to the heterogeneity of schizophrenia can be illuminated by studying the pedigrees of probands with these characteristics. One strategy involves demonstration that an inherited characteristic, which conceivably could be related to the etiology or pathophysiology of brain dysfunction, is present exclusively or is quantitatively in excess in the members of the pedigrees who develop schizophrenia. This assumes homogeneity of genetic causes of illness within a pedigree. The analysis of large pedigrees is particularly helpful here. The association of schizophrenia and a particular factor within the pedigree could be tested by a 2 x 2 contingency table. The generalizability of such data may be very limited, however, unless it is found to hold for a large number of pedigrees. It must be kept in mind that the association of the factor and schizophrenia may be due to chromosomal linkage rather than to its being a primary etiologic factor. If linkage is present, then linkage in repulsion (segregation of nonillness) with the biological marker should be found in some pedigrees. The effects of a shared environment in such a pedigree study must be kept in the forefront. Baron (1976) reported a pedigree study in which albinism and schizoaffective illness, depressed type, were linked within a pedigree. Of interest to the question of the relationship between schizophrenic illness and schizoaffective illness is that one member of the pedigree who was a nonalbino had a chronic core schizophrenic clinical picture.

Another genetic method of value for biological studies is the so-called single sib paradigm. This involves studying a particular biological factor, which is present in the well state, in a suitably large number of unrelated schizophrenic probands and one randomly sampled sibling of each. Various means may be used to determine if the factor under study is a necessary or protective influence against developing schizophrenia (Rieder and Gershon 1978).

**Conclusions**

This article is not a comprehensive review of the literature concerning attempts to identify subtypes of schizophrenia by relating biological measures to specific axes or dimensions of psychopathology, clinical course, or family history. Such a task would easily consume this entire issue. Rather, I have attempted to discuss the methodology that is most useful in such endeavors. I have presented what are, in my judgment, some of the more interesting recent biological studies, with an emphasis on biochemistry, that have dealt with the issue of subtyping.

There have been some replicated studies of specific biochemical markers for schizophrenic subtypes—for example, low platelet MAO activity.
in hallucinating schizophrenics and increased growth hormone response to apomorphine in acute schizophrenics. The significance of such results, however, must await the more stringent tests that were described in discussing a possible way to determine if a biological abnormality is relevant to the psychopathology of the individuals in whom it is present (pp. 462-463). This may require more extensive investigation of single cases and their families with the aim of confirming or refuting specific hypotheses that stem from an understanding of the biological measures under investigation and the nature of schizophrenic psychopathology.

This is a rather slim list of accomplishments for the massive efforts to use biologic measures to identify schizophrenic subtypes. It is indicative of our limited knowledge of what schizophrenia is and is not and our limited understanding of the pathophysiology of schizophrenia. There is ground for optimism, however, in our increasing ability to describe the patient population and our rapidly increasing knowledge of central nervous system mechanisms.

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