Biological Studies in Schizophrenia

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Abstract

The question of whether schizophrenia is associated with structural or functional abnormalities of the nervous system, or both, has become the principal focus of biological studies of schizophrenia. Computed tomography studies have revealed ventricular enlargement and cortical atrophy in a subgroup of schizophrenic patients. While present from the early stages of the illness, they appear to be most severe in patients with negative symptoms and poor outcome. Quantitative neuropathological studies have tentatively demonstrated decreased volume of specific brain areas, neuronal loss, and other changes in the limbic system, basal ganglia, and frontal cortex. Dopamine (DA) remains the neurotransmitter most likely to be involved in schizophrenia, although there is also evidence for disturbances of serotonin and norepinephrine. Post-mortem and positron emission tomographic studies suggest an increased number of D2 DA receptors in some schizophrenics. Neuroendocrine studies reinforce the role of DA in schizophrenics. Viral infections and autoimmune disturbances may be responsible for some types of schizophrenia, but there is no firm experimental evidence to support either hypothesis. The possibility that mixtures of structural abnormalities and functional changes involving DA occur in the same patients rather than independently as part of two syndromes (Type I, II) seems attractive. Future studies should identify subtypes of schizophrenia based on biological criteria and contribute to identification of specific genetic abnormalities which increase vulnerability to manifest the schizophrenic phenotype.

This article will review several areas of current research concerning the biological contribution to the etiology of schizophrenia as well as some biological measures that are potential state or trait markers of schizophrenia. The articles on brain imaging (Buchsbaum and Haier 1987), genetics (Gottesman, McGuffin, and Farmer 1987), and psychophysiology (Holzman 1987) in this Special Report provide essential information concerning the biology of schizophrenia. Since the last Special Report review of the biology of schizophrenia (Bowers 1980), there has been considerable interest in identifying the anatomical substrates of schizophrenia, examination of the brain for evidence of structural changes at the gross level by computed tomography (CT scan) and magnetic resonance imaging (MRI) as well as at post-mortem, identification of neuropathological changes, consideration of viral and autoimmune etiologies, and further development of the dopamine (DA) hypothesis, including the relation of DA abnormalities to structural changes in the brain. This research has taken place in the context of a firm belief in the heterogeneity of schizophrenia, even when diagnosed by modern, relatively narrow criteria.

Structural Abnormalities: Neuropathology and CT Scans

There has been a considerable renewal of interest in the neuropathology of schizophrenia. It is noteworthy that most of the new wave of studies are being done by psychi-
atrists who have received additional training in neuropathology. Early studies, largely European in origin, involved small numbers of patients and controls, used diagnostic methods and criteria that are not accepted as reliable or valid by current standards, were non- or semi-quantitative, and did not produce replicable findings (Weinberger, Wagner, and Wyatt 1983). The renaissance of interest in neuropathological studies of schizophrenia has been based, in part, on the development of quantitative methods, more reliable diagnostic methods, and evidence of ventricular enlargement and cortical atrophy in some schizophrenics (Johnstone et al. 1976; Glück et al. 1980; Golden et al. 1980; Andreasen et al. 1982).

Before considering the neuropathological literature, we will briefly review recent CT findings which have provided much of the impetus for neuropathological studies. This research has been reviewed in depth elsewhere (Shelton and Weinberger 1986). Although at least five studies have not found enlarged ventricles in schizophrenics (Trimble and Kingsley 1978; Glück et al. 1980; Benes et al. 1982; Jernigan et al. 1982; Shima et al. 1985), consideration of all available evidence suggests that there is an excess proportion of schizophrenics with ventricular size outside normal limits (Shelton and Weinberger 1986). Variability of results may be due to measurement differences or differences in clinical populations and control groups. There is some evidence that schizophrenic patients with poor premorbid adjustment, unresponsiveness to neuroleptic treatment, more negative and fewer positive symptoms, neuropsychological test abnormalities, and poor outcome are characterized by lateral ventricular enlargement or cortical atrophy (Weinberger et al. 1980a, 1980b; Bishop et al. 1983; Luchins, Lewine, and Meltzer 1984; Williams et al. 1985; Luchins and Meltzer 1986; Shelton and Weinberger 1986). However, some studies have found increased ventricle-brain ratios (VBR) in recent onset, young schizophrenics (Schulz et al. 1983; Turner, Toone, and Brett-Jones 1986), and other studies have found no relation between ventricular enlargement and negative symptoms (Nasrallah, McCalley-Whitters, and Jacoby 1982; Boronow et al. 1983; Nasrallah et al. 1983; Luchins, Lewine, and Meltzer 1984; Owens et al. 1985; Lozonczy et al. 1986; Panderangi et al. 1986) or poor response to neuroleptic treatment (Nasrallah et al. 1983; Smith et al. 1985; Losonczy et al. 1980). Difficulty in assessing negative symptoms, as well as the influence of other factors that influence ventricular size, may account for this discrepancy. Enlarged ventricles are, in any event, not specific for schizophrenia, having been found in patients with affective disorders (Pearlson and Veroff 1981; Luchins, Lewine, and Meltzer 1984; Pearlson et al. 1984) and known organic cerebral disorders such as alcoholism (Ron et al. 1982). Nonspecificity does not, however, rule out importance for pathophysiology. Neuroleptic treatment does not appear to be responsible because of the absence of a strong relationship between duration of illness or total neuroleptic exposure and ventricular dilation (Shelton and Weinberger 1986). Evidence to date suggests that enlarged ventricles in schizophrenics may be due to acquired conditions such as birth complications, viral infections, immune reactions, and toxins, rather than genetic factors (Reveley, Reveley, and Murray 1984). However, other studies have shown that genetic factors influence ventricular size in both normal subjects (Reveley et al. 1982) and schizophrenics (DeLisi et al. 1986).

Neuropathological studies published before 1982 were reviewed in the Schizophrenia Bulletin by Weinberger, Wagner, and Wyatt (1983) and will not be further considered here with the exception of the important study of Stevens (1982). Stevens (1982) examined brains from 25 schizophrenics, aged 21-54, 28 mentally ill patients with various neurologic disorders of similar age who died at the same hospital during the same period, and 20 age-matched nonschizophrenic patients who died in a general hospital. A variety of stains to bring out cellular structures, myelin, or glia were used. Brain weights were all within normal limits. The major finding was patchy fibrillary gliosis that was maximal in the periventricular and periaqueductal regions and the basal forebrain. Neuronal loss was present mainly in the globus pallidus in five cases. Similar neuronal loss involving the globus pallidus or substantia innominata was reported by Hopf (1952). Four of the 25 putative schizophrenics were found to have gross neurological disorders (e.g., Alzheimer's disease, sarcoidosis). The gliosis was comparable in five of the nonschizophrenic organic brain disease patients. Gial fibrils were previously noted in schizophrenia by Nieto and Escobar (1972), Fisman (1975), and Christensen, Moller, and Faarbye (1970). None of the studies used quantitative methods, however. Stevens (1982) speculated that the gliosis may be secondary to earlier infections or immunological disorders. As will be reviewed, other recent studies have failed to note gliosis.

The major areas of current interest for the pathophysiology of schiz-
phrenia are the limbic system, the
frontal cortex, and the nigrostriatal
system (Meltzer and Stahl 1976; Zec
and Weinberger 1986). These are the
brain regions, along with the cere-
bellum, that are also currently the
object of most interest by the neu-opathologists. Bogerts, Häntsch,
and Herzer (1983) carried out a
quantitative study of the dopamin-
ergic neurons of the nigrostriatal
and mesolimbic system (A10) on
Nissl-stained sections of 9 normal
brains, 6 aged-matched brains of
schizophrenics, and 11 patients with
Parkinson's disease. A significant
decrease (21 percent) in the volume
of the lateral part of the nigrostriatal
area was noted, without any in-
crease in the number of glial nuclei.
The mean volume of the nerve cells
in the medial part of the substantia
nigra was decreased (16 percent) but
not the absolute number of nerve
cells. A nonsignificant decrease (16
percent) in the number of nerve cells
in the A10 region was noted.
A subsequent report from this
group involved 13 brains of schizo-
phrenics, collected before the neu-
roleptic era, and 9 control cases
(Bogerts, Meertz, and Schönfeldt-
Bausch 1985). The mean duration of
illness was 10 years. The volume of
the basal ganglia and limbic system
was measured by morphometric
(planimetry) methods. The study
was designed to be blind, but half of
the schizophrenics could be identi-
fied by the small size of the hippo-
campus. No difference in the size of
the caudate nucleus, putamen, or
external pallidum was noted.
However, there was a statistically
significant 20 percent decrease in the
size of the internal pallidum in the
schizophrenics, possibly relevant to
motor and attentional deficits noted
in some schizophrenics. The limbic
portions of the temporal lobe, in-
cluding the dentate gyrus, and sub-
culum of the hippocampus,
parahippocampal gyrus, and amygd-
ala, were decreased 20-40 percent
in the schizophrenics. No change in
the volume of the nucleus ac-
cumbens was noted. Bogerts,
Meertz, and Schönfeldt-Bausch
(1985) discuss the possibility that
limbic structures such as the hippo-
campal formation, parahippocampal
gyrus, and amygdala, together with
their connections to the neocortex
and paleocortex, may be the major
sites of brain dysfunction in schizo-
phrenia. Evidence for the impor-
tance of temporal lobe abnormal-
ities, especially in the left hemi-
sphere, for psychosis was pre-
viously discussed by Davison and
Bagley (1969) and Cruzelier and
Hammond (1976). This study is im-
portant because it included pre-
neuroleptic era patients.
Brown et al. (1986) also found an
11 percent decrease in the width of
the parahippocampal gyrus in 34
schizophrenics compared to 21 af-
fective disorder patients. The dif-
ference was present only in the left
hippocampus. It appeared to be due
to an increase in the width in the af-
fective disorder patients rather than
decrease in the schizophrenic pa-
tients as five normal controls had no
significant difference in width of
either side. Because of the large
numbers of comparisons made and
the absence of adequate normal con-
trol data, it is not apparent that
there is any significance to be at-
tached to this particular finding.
The organization of the pyramidal
cells of the hippocampus of 10 neu-
roleptic-treated paranoid schizo-
phrenics and 8 nonschizophrenics
was examined by Kovelman and
Scheibel (1984). Using a quantitative
approach, they observed a marked
disorganization of the pyramidal cell
layer of the hippocampus. Even
more extensive changes of the same
kind had been noted in a previous
study of eight schizophrenic pa-
tients (four paranoid, one hebephre-
nic, and three chronic undifferen-
tiated) and eight nonschizophrenic
controls (Scheibel and Kovelman
1981). Similar changes were re-
ported to be present in the hippo-
campal pyramidal cells of the
schizophrenic brain tissue in the
Yakolev collection (Kovelman and
Scheibel 1984). Most of these brains
were collected before the neuroleptic
era. Further study of the effect of
neuroleptic treatment and inde-
pendent replication of these results
are indicated.
Lesch and Bogerts (1984) specifi-
cally sought to relate atrophy of
periventricular structures to ven-
tricular enlargement. However, they
found no differences in the volume
of the thalamus and large sub-
thalamic nuclei in 15 schizophrenics
and 12 controls. Age, sex, psycho-
pathology, or duration of illness did
not relate to any of the measures.
The only significantly diminished
value within the diencephalon was
the thickness of the periventricular
gray matter surrounding the third
ventricle, where a 20 percent de-
crease was noted. Abnormalities of
the thalamus and diencephalon pro-
duce symptoms closer to those asso-
ciated with Type II than with Type I
schizophrenia.
Brown et al. (1986) also noted a
slightly smaller brain weight in 41
schizophrenics compared to 29 af-
fective disorders diagnosed by the cri-
tera of Feighner et al. (1972).
Compared to a group of normal
brains studied elsewhere, 18 percent
of the 41 schizophrenic brains fell
below the 95 percent confidence
limit. The schizophrenic brains had
significantly larger temporal horn
areas and a trend toward larger lat-
eral ventricles, but no difference in
third ventricle size compared to the
affective disorders. The average parahippocampal cortical thickness was decreased in the schizophrenics compared to affective disorders. Thus, this study provided post-mortem confirmation of reports of ventricular enlargement in radiological studies. They indicate loss of cells in the temporal lobe may account for ventricular enlargement. The authors note previous speculations that the temporal lobe may be relevant to schizophrenia (Davison and Bagley 1969; Torrey and Peterson 1974). A number of other measures, including width of the cingulate and insular-opercular cortical areas, corpus callosum thickness, and various measures of the corpus striatum, did not differ between affective disorders and schizophrenics. Thus, generalized cortical atrophy was not present in this group of schizophrenics.

Benes, Davidson, and Bird (1986) compared prefrontal, anterior cingulate, and primary motor cortex in 10 controls and 10 schizophrenics. A trend toward reduced numbers of neurons in the three cortical areas, significant in 3 of 18 layers examined, was found in the schizophrenics. A discriminant function showed that layers II, III, and VI of the prefrontal cortex distinguished schizophrenics from controls. Despite evidence that this may be related to post-mortem interval, adjusting for this factor did not eliminate the differences between schizophrenics and controls. There was a trend toward fewer rather than more glial cells in the schizophrenics, arguing against a process of neuronal degeneration in schizophrenic cortex. Other histopathological criteria such as the neuron-glia ratio and neuronal size failed to provide supportive evidence for the occurrence of a degenerative process in the cortex of the schizophrenics. Thus, there was evidence of modest abnormalities in the prefrontal cortex of the schizophrenics. The authors speculate that the normal process of neuronal dropout may be accelerated in schizophrenia. The findings are of interest in relation to blood flow studies and metabolic studies using positron emission tomography (PET) and neuropsychological studies that have been interpreted to indicate hypofrontality and functional deficits of the frontal lobes in schizophrenics, independent of medication effect (Buchsbaum et al. 1984; Berman, Zec, and Weinberger 1986; DeLisi et al. 1986a; Weinberger, Berman, and Zec 1986). Decreased frontal lobe electrical activity, correlated with frontal lobe atrophy as noted in CT scans, has also been reported in schizophrenics (Morihisa, Duffy, and Wyatt 1983; Morihisa and McAnulty 1985).

These results should be pursued in a larger sample, including patients with affective disorders, to determine their specificity and the possible influence of psychotropic drugs.

Further evidence for a frontal lobe abnormality in schizophrenia was provided by Andreasen et al. (1986) who examined cerebral area, frontal area, and cranial size using magnetic resonance imaging (MRI) in 38 schizophrenics (28 male) and 49 normal controls (25 male). Male schizophrenics had smaller frontal, cerebral, and cranial areas. Nearly 40 percent of the men were reported to have markedly smaller frontal lobes. Small cerebral and cranial size was associated with greater negative symptoms, but frontal size was not. These findings were made on sagittal slices but also appeared in coronal slices. Frontal lobe functioning, as assessed by the Wisconsin Card Sort test and other measures, correlated positively with adjusted cranial and cerebral size but not frontal size. These results are of considerable interest, but as the reliability of making such measures with MRI is not yet established, they must be viewed cautiously.

A recent study reported that a series of periventricular injections of the demyelinating agent lysophosphatidyl choline to adult rats produces ventricular enlargement and periventricular demyelination (Kline and Reid 1985). The behavioral effects were loss of weight, decreased emotionality, extreme postural indifference (cataplexy), inappropriate aggressive responses, and impaired grooming. It was suggested that this might constitute an animal model for schizophrenia. Neither the behavioral effects nor the neuropathological changes have any specificity for schizophrenia, however.

**Conclusions**

Recent neuropathological studies, in aggregate, and in conjunction with the CT scan and MRI studies showing ventricular enlargement and cortical atrophy, contribute to the view that there is a structural brain abnormality in at least some forms of schizophrenia. A slight decrease in brain weight; a decrease in the volume of the basal ganglia, temporal lobe, or limbic regions; disorganization of the pyramidal cell layer of the hippocampus; and atrophy of particular cortical layers are the intriguing results from the most recent round of neuropathological studies. The important study of Benes, Davidson, and Bird (1986) appears to exclude marked neuronal degeneration in prefrontal, anterior cingulate, and motor cortex while demonstrating reduced numbers of neurons in specific layers of prefrontal cortex. However, all of the stud-
ies with the exception of Brown et al. (1986) are too small in size to warrant confidence in their validity. Examination of sex differences, lateralized effects, covariance of age, drug treatment or electroconvulsive therapy, and duration of illness effects may be required for unambiguous identification of authentic neuropathological abnormalities in schizophrenics. The new studies have not demonstrated the presence of pathognomonic lesions in schizophrenia. The use of affective disorders as a control group, as done by Brown et al. (1986), is valuable, but only if normal controls are also studied, since affective disorder patients seem to share with schizophrenics a number of abnormalities possibly relevant to neuropathology, e.g., relative hypofrontality and increased volume of the lateral ventricles. The influence of neuroleptic treatment requires much further study since haloperidol treatment has been found to affect synaptic patterns in rat striatum (Benes, Paskevich, and Domesic 1983; Benes et al. 1985). Lack of correlation with crude estimates of lifetime exposure to neuroleptics does not rule out the influence of neuroleptic treatment on the observed abnormalities in patients.

If there are structural changes that are functionally significant in some cases of schizophrenia, it is likely that sprouting of surviving neurons will occur to compensate, even if the degeneration occurred in adolescence or beyond (Haracz 1985). We have demonstrated sprouting of subterminal motor nerves in schizophrenics (Meltzer and Crayton 1974) and argued that if neuronal sprouting occurred in brain, it could produce major effects on behavior that would usually, but not always, be irreversible (Meltzer 1976a). There is no evidence from either the neuropathological studies or from the CT scan studies, which show no progression in the size of the VBR, at least over a 3-year period (Nasrallah et al. 1986b), for any active degenerative process.

It is to be hoped that the collection of brains from schizophrenics at autopsy will become more frequent, together with extensive information about the clinical course, symptoms, and drug treatment of these individuals. Rigorous quantitative neuropathological studies can contribute to our understanding of the pathophysiology and heterogeneity of schizophrenia. Such studies could also include examination of the enzymes and receptors involved in neurotransmitter synthesis, release, and action using quantitative autoradiographic and immunocytochemical methods. However, agonal changes, drug treatment, and postmortem changes will make interpretation of such studies extremely difficult.

**Spinal Fluid Circulation**

Ventricular enlargement may be due to an alteration of fluid and pressure homeostasis within the cerebrospinal fluid (CSF) in addition to or instead of primary loss of cells within the brain (Oxenstierna et al. 1984). The CSF circulation was found to be abnormal with isotope cisternography in 10/30 schizophrenic patients by Oxenstierna et al. (1984). Four of the 10 had persistent radioactivity within the ventricles and a markedly reduced distribution of radioactivity over the hemispheres. Six others had a slowing of the CSF circulation, predominantly in the upper and posterior frontal region. Ten of the 30 had cerebral atrophy by CT scan. Disturbed circulation and the CT abnormalities were independent. The significance of the CSF circulatory abnormalities is obscure: they do not appear to cause cerebral atrophy and did not relate to CSF monoamine metabolites. Replication and further study of this interesting finding appears warranted.

**The Dopamine Hypothesis**

The role of dopamine (DA) in the pathophysiology of schizophrenia has been the predominant focus of research in the biology of schizophrenia for several decades. It has had immense heuristic value, stimulating and shaping extensive exploration of myriad aspects of DA neurons, including their gross anatomy and fine structure; interactions of DA with other neurotransmitters—e.g., γ-aminobutyric acid (GABA), acetylcholine, serotonin, and neuropeptides; regulatory mechanisms for DA synthesis, release, and uptake; subtypes of DA receptors and their interactions; and much more. Innumerable biochemical, neuroendocrine, and pharmacological studies in man have also been stimulated by the DA hypothesis. We have reviewed this in the Schizophrenia Bulletin previously (Meltzer and Stahl 1976). Other reviews have appeared more recently (Haracz 1982; Carlton and Manowitz 1984). It is beyond the scope of this article to review this literature in detail. A few of the most salient developments will be discussed.

The core of the DA hypothesis is the concept that a relative overactivity of mesolimbic, mesocortical, or nigrostriatal dopaminergic neurons may be present, in at least some schizophrenic individuals. This increase may relate to specific symptoms, such as delusions or hallucinations, or to specific mechanisms, such as attentional impairment. This formulation is based largely on the clinical evidence that
effective antipsychotic drugs such as the neuroleptics block DA receptors (Snyder et al. 1974) or, as with α-methyltyrosine (AMPT), inhibit DA synthesis (Larsson et al. 1984), and that indirect DA agonists such as amphetamine and phencyclidine can produce or exacerbate psychotic symptoms (Meltzer and Stahl 1976; Meltzer 1979).

DA and the Heterogeneity of Schizophrenia. It has long been clear that an abnormality of DA could not, by itself, account for the multifaceted, variegated symptomatology, the diverse response to neuroleptics, the frequently changing clinical course, and the overlap between schizophrenia and the affective and organic psychoses (Meltzer and Stahl 1976). As a result, several modifications of the DA hypothesis have been proposed: (a) that some patients with the schizophrenic phenotype may have an entirely non-DA-dependent disorder; (b) that increased DA may be most relevant to the early (acute) stages of the disorder; and (c) that some aspects of schizophrenia, particularly components of the negative symptom-deficit state type of psychopathology could be due to decreased dopaminergic activity (Meltzer and Stahl 1976; Mackay 1980; Meltzer 1985). We proposed that viral infections, autoimmune disturbances, cell-mediated toxicity, increased branching or sprouting of central neurons, or dysregulation of normally integrated neuronal systems should be considered as primary etiological factors for the core schizophrenic symptomatology with increased dopaminergic activity as a secondary response to one or more of these factors (Meltzer and Stahl 1976; Meltzer 1979). Identification of enlarged lateral ventricles and other signs of brain atrophy by CT scan in chronic schizophrenic patients led Crow (1980, 1985) to hypothesize that schizophrenia might best be considered as a composite of two syndromes: (1) a Type I syndrome characterized by reversible delusions, hallucinations, and thought disorder with good response to neuroleptic treatment and possibly due to increased numbers of striatal and limbic DA receptors; and (2) a Type II syndrome, characterized by frequently unremitting negative symptoms (flat affect, social withdrawal, poverty of thought content), poor response to neuroleptics, and a presumptive etiology of cell loss and structural brain damage, possibly due to a viral infection. This model is also discussed in the Special Report article by Andreasen (1987).

The Type I-Type II model has had a very important impact on studies of the biology of schizophrenia as investigators have explored its utility to reduce the heterogeneity of the schizophrenic population being studied by relating biological measures to the characteristics of these two syndromes. Thus, it has contributed to a renewed effort to relate biological measures to specific types of psychopathology and, in particular, to obtain evidence for irreversible, structural abnormalities in the brains of schizophrenics through neuropsychological studies, CT scans, and MRI. As we have discussed elsewhere (Meltzer 1985), most of the evidence that has been accumulated to date does not fully support the existence of two independent syndromes. Rather, the classificatory elements in the Crow model (e.g., positive and negative symptoms, response to neuroleptic treatment, and structural brain abnormalities) appear to be better thought of as dimensions that are interrelated. We have demonstrated that positive and negative symptoms rarely occur independently in schizophrenics (Meltzer 1985), although Andreasen and Olsen (1982) found that 34 out of 52 schizophrenics could be classified as positive (Type I) or negative (Type II) on the basis of symptoms alone. Our findings have been supported by Rosen et al. (1984). Interactions between DA and presumptive ventricular enlargement also cast doubt on the Type II hypothesis. Thus, studies have reported correlations between catecholamine-related indices—e.g., CSF homovanillic acid (HVA), the major metabolite of DA—and increased VBR (van Kammen et al. 1983, 1986; Nybäck et al. 1983). In a mixed group of psychotics, Luchins, Jackman, and Meltzer (1983) reported a tendency for those with larger lateral ventricles to develop neuroleptic-induced parkinsonism, an indicator of possible decreased striatal dopaminergic activity. Low CSF levels of HVA were also reported to be correlated with negative symptoms in schizophrenics (Lindstrom 1985). This would link the Type II syndrome to DA neurotransmission. However, no relation between serum dopamine-β-hydroxylase (DBH) activity, an enzyme that may reflect sympathetic nervous system activity, and VBR was found (Meltzer, Tong, and Luchins 1984). Two studies have failed to find any correlation between viral antibody titers and CT results (Torrey et al. 1983; King et al. 1985b). One study which involved a small number of subjects found an association between high titers of IgM antibody to cytomegalovirus and cerebral atrophy (Kaufmann et al. 1983). The Type II syndrome is also open to the criticism that the data used by Crow to argue that negative symptoms do not respond to neuroleptics were quite minimal. There is extensive ev-
idence that negative symptoms do respond to neuroleptic treatment (Goldberg 1985; Meltzer 1985; Meltzer, Sommers, and Luchins, in press). Further studies are clearly needed to assess directly in schizophrenics as many components of central dopaminergic neurotransmission and structural elements of the brain, using CT or MRI, as possible. As will be discussed, PET and neuroendocrine challenge tests may be the best means of assessing central dopaminergic neurotransmission.

CSF and Plasma Homovanillic Acid (HVA). CSF and plasma levels of HVA are of interest as potential indices of brain dopaminergic activity. CSF levels of HVA have been studied in the basal state and following treatment with probenecid to block the transport of HVA, but this method introduces other problems that have precluded its widespread adoption. Increased CSF HVA levels have been found in schizophrenics with a family history of schizophrenia (Sedvall and Wode-Helgödt 1980) or with poor premorbid sexual adjustment (Leckman, Bowers, and Sturges 1981). However, most studies report no differences in CSF HVA levels between schizophrenics and controls (Post et al. 1975). There is also no evidence from post-mortem studies of brain DA or its metabolites for increased DA turnover in schizophrenia (Crow et al. 1984; Bridge et al. 1985). On the other hand, increased concentrations of DA were reported in the nucleus accumbens and caudate nucleus of schizophrenics (Mackay et al. 1982).

Lindström (1985) reported lower levels of CSF HVA in 40 drug-free schizophrenics compared to 15 normal controls. They also found no relationship between CSF HVA levels and family history of schizophrenia. However, they did find negative correlations between CSF HVA levels and psychomotor retardation, lack of energy, and low social interest and competence, which were interpreted as measures of negative symptoms. This would suggest decreased dopaminergic activity may be related to negative symptoms. Van Kammen et al. (1983) reported an association between lower CSF HVA levels and both cortical atrophy and increased VBR. Nybäck et al. (1983) found CSF HVA levels to be negatively correlated with lateral ventricular size in schizophrenic patients but not healthy volunteers. Van Kammen et al. (1986) recently reported that 10 of 33 schizophrenics showed cortical atrophy on CT scan. CSF levels of HVA, dihydroxyphenylacetic acid (DOPAC), conjugated DOPAC, and dopamine sulfate (DASO) were measured during a drug-free state. Patients with cortical atrophy had lower CSF levels of HVA, DOPAC, and conjugated DOPAC but higher DASO. Patients without cortical atrophy and a combined measure of DA utilization above the mean showed more psychotic symptoms.

These results suggest that the loss of dopaminergic neurons may be a part of cerebral atrophy or lead to decreased dopamine neurotransmission. It is possible that only some DA neurons that do not contribute heavily to the CSF are overactive in schizophrenia, but it is more likely that increased activity of DA neurons, per se, is not an important factor in the etiology of schizophrenia. Dopaminergic transmission might be increased due to increased numbers of DA receptors or an enhanced secondary response to DA receptor stimulation. These possibilities will be discussed subsequently.

Studies of CSF HVA during neuroleptic treatment may be relevant to the pathophysiology of extrapyramidal side effects. Bowers and Heninger (1981) reported that patients who showed tolerance to the increase in CSF HVA during neuroleptic treatment had significantly fewer symptoms and parkinsonism side effects. Those without tolerance had a relatively poor clinical response and more extrapyramidal side effects, including catatonia (Bowers 1985).

Substantial interest in recent years has developed in assessing plasma HVA concentrations as a measure, in part, of central dopaminergic activity. Administration of either DA receptor agonists or antagonists has been reported to produce parallel changes in brain and plasma HVA in subhuman primates and rodents via central, rather than peripheral, effects (Kendler, Heninger, and Roth 1981, 1982). Diet, activity, stress, age, sex, weight, circadian and seasonal variation, and neuroleptic treatment are among the factors that can affect plasma HVA (Kendler, Mohs, and Davis 1983). There have been several studies of plasma HVA in unmedicated schizophrenics and following neuroleptic treatment. Pickar et al. (1984) reported elevated plasma HVA in eight unmedicated schizophrenics compared to eight normal controls. We did not replicate this in a group of 34 unmedicated chronic schizophrenics and 15 normal controls (Koyama and Meltzer, in preparation). Elevated plasma HVA was also found in a group of female melancholic patients (Devanand et al. 1985). Davis et al. (1985) reported a significant negative correlation between global severity of illness and plasma HVA, both before and after neuroleptic treatment, in 18 male schizophrenics. We have also
not replicated this finding (Koyama, Ohmori, and Meltzer, in preparation).

There have been several studies of the effect of neuroleptic treatment on plasma HVA. Harris et al. (1984) reported plasma HVA increased in response to neuroleptic treatment and decreased when neuroleptic medication was withdrawn. No relation between plasma HVA level and clinical response was found. Kirch et al. (1983) also found no effect of neuroleptic withdrawal on plasma HVA or relation to psychopathology. Pickar et al. (1984, 1986) reported subchronic neuroleptic treatment produced a decrease in plasma HVA. The levels of plasma HVA measured during treatment and after withdrawal were highly correlated with psychosis ratings. Changes in HVA predicted clinical response. However, we have found no significant change in plasma HVA following treatment with chlorpromazine (CPZ), 40 mg/day, for 3 weeks followed by 3 weeks of treatment with CPZ, 1000 mg/day, in 20 schizophrenics (Meltzer and Ohmori, in preparation).

Another area of DA research that has been illuminated by studies of plasma HVA has been the role of DA autoreceptors. DA autoreceptors are located on the cell bodies and nerve terminals of DA neurons. Stimulation of DA autoreceptors by DA agonists can diminish the activity of DA neurons. Low doses of DA agonists diminish plasma HVA levels in the rat (Kendler, Heninger, and Roth 1982). Cutler et al. (1982) reported plasma HVA decreased following apomorphine in neuroleptic-treated schizophrenics, but others were unable to find any effect of apomorphine, even in drug-free patients (Scheinin 1984; Davidson et al. 1985). We have also been unable to find a consistent effect of apomorphine or plasma HVA in drug-free schizophrenics or normal controls (Ohmori and Meltzer, in preparation).

Subsensitivity of DA autoreceptors could lead to the same increase in the release of DA that would result from amphetamine administration. Subchronic methamphetamine administration, which produces a paranoid psychosis in man (Connell 1958), produces subsensitivity of mesolimbic DA autoreceptors (Watanabe 1985). There is also evidence that chronic methamphetamine administration may increase DA D₂ receptor binding in the mesolimbic area of rat brain (Akiyama et al. 1982) along with supersensitivity to the locomotor effects of methamphetamine (Akiyama, Sato, and Otsuki 1982). It is possible that an endogenous amphetamine-like substance produces DA autoreceptor subsensitivity and DA postsynaptic receptor supersensitivity in some regions of the brain in paranoid schizophrenics. Such a mechanism could account for the extreme vulnerability to relapse into paranoid psychoses of some patients who used methamphetamine following long-term abstinence (Sato et al. 1983). Chronic administration of d-amphetamine to monkeys and rats, subcutaneously or via orally implanted slow-release silicone pellets, produces severe motor stereotypies, followed by inactivity, and then overresponsiveness to environmental stimuli and a series of behaviors that have been described as “hallucinatory-like.” These are associated with depletions of brain catecholamines and serotonin, decreased tyrosine hydroxylase and DA receptors in the caudate and frontal cortex, and neurotoxic effects in the caudate nucleus but not mesolimbic DA neurons (Ellison and Eison 1983; Ridley et al. 1982). While these changes differ from those found in schizophrenic brain post-mortem, they do not rule out the possibility that some stages of the schizophrenic process may be associated with effects on dopaminergic neurons comparable to those produced by amphetamine-like compounds.

Phencyclidine (PCP) might be a better model for schizophrenia than amphetamine since chronic PCP psychoses resemble schizophrenia more closely than amphetamine psychoses (Allen and Young 1978; Rainey and Crowder 1975). PCP has indirect DA agonist properties (Meltzer et al. 1981) but also has effects on sigma-type opiate receptors some of which may be present on DA neurons and regulate DA release (French, Pilapit, and Quirion 1985). On the basis of animal studies, Meltzer et al. (1979) suggested reserpine might be a good treatment for PCP psychosis. This was confirmed by Berlant (1985). The possibility that an endogenous PCP-like substance may be important for some cases of schizophrenia should be considered.

DA Receptors and the DA Hypothesis of Schizophrenia. Because of the absence of evidence for increased presynaptic dopaminergic activity, increased postsynaptic DA receptor sensitivity has been postulated to be important to the etiology of schizophrenia (Lee and Seeman 1980). There are two major subtypes of DA receptors: (1) the DA D₁ receptor, which has a low affinity for [3H]spiperone and is positively coupled to adenylate cyclase; and (2) the DA D₂ receptor, which has a high affinity for spiperone but is negatively coupled to adenylate cyclase (Kebabian and Calne 1979). Most neuroleptics are mixed D₁-D₂ DA antagonists (chlorpromazine) or selective D₂ DA an-
tagonists (sulpiride). There have been no clinical studies of selective D1 antagonists whereas the benzamidine drugs such as sulpiride are highly effective antipsychotic agents. Rodent studies suggest some behaviors, such as locomotor activity, may have both D1, DA and D2 DA components that are independent and synergistic (Arnt and Hyttel 1985). However, biochemical studies indicate synergistic effects of D2 DA antagonists and D1, DA agonists, and antagonistic effects from simultaneous D1, and D2 receptor blockade (Saller and Salama 1986). D2 DA receptors are postsynaptic in the mesolimbic, striatal, and frontal cortex (Seeman 1980). They are also located on the cell bodies of the A9 DA region which projects to the nucleus accumbens (White and Wang 1984). A recent report indicated there were no D2 DA receptors in human cortex (DeKeyser et al. 1985). This suggests the action of neuroleptics must be subcortical. D2 DA receptors are located on striatal GABAergic interneurons and on presynaptic sites in terminals of striatal-nigral neurons (Porceddu et al. 1986). They are also present in the nucleus accumbens (White and Wang 1986). The ability of D1 and D2 DA receptors to increase in number or otherwise enhance their response to DA agonists is critical to the concept that an increase in one or both types of receptors is relevant to the pathophysiology of schizophrenia, tardive dyskinesia, or other consequences of long-term neuroleptic use. Chronic haloperidol and sulpiride administration increase D2 but not D1 receptor density (Porceddu et al. 1986). However, chronic administration of the selective D1 receptor blocker SCH 23390 increases the number of D1 receptor binding sites in striatal membranes (Porceddu, Orgini, and Biggio 1985). Since D1 and D2 receptors may antagonize each other, it is clearly possible that net dopaminergic activity may be increased or decreased depending on which predominates. The ability of one or both receptors to increase selectively in response to neuroleptics could be a factor in this regard. This is another way in which both increased and decreased dopaminergic activity might be present in different regions of the brain.

Several studies have reported increased numbers of D2 DA receptor binding sites in the basal ganglia and nucleus accumbens of schizophrenics (Lee and Seeman 1980; Cross, Crow, and Owen 1981; Mackay et al. 1982; Seeman et al. 1984) as well as the substantia nigra (Owen et al. 1984), but it is possible that in some subjects this was due to prior neuroleptic treatment. Seeman et al. (1984) reported a bimodal distribution of D2 receptors in the caudate, putamen, and accumbens of a large group of schizophrenics which he suggested was consistent with the idea of DA and non-DA subtypes of schizophrenia as suggested by Crow (1980). However, both modes had elevated numbers of DA receptors relative to controls. Crow et al. (1984) reported the number of 3H-spiperone binding sites in the basal ganglia of 14 schizophrenics showed a highly significant positive correlation (r = 0.70) with the history of delusions and hallucinations before death. One study reported an increased efficiency in D1 DA receptor activation in schizophrenic brain (Memo, Kleinman, and Hanbauer 1983), but no increase in D1 receptor binding sites has been noted (Cross, Crow, and Owen 1981; Pimoule et al. 1985). The absence of data on D1 DA or D2 DA receptor density in manics or delusional depressives is a striking deficiency in this area. It seems unlikely that further study of DA receptors in post-mortem specimens from patients treated with neuroleptic drugs will provide definitive information.

PET studies have the potential for quantification of DA receptors, at least in the striatum (Sedvall et al. 1986). The resolution of PET cameras, at present, is such (4–8 mm) that areas such as the frontal or temporal cortex and parts of the mesolimbic system cannot be visualized. There have been three preliminary studies of DA receptors in the basal ganglia of living schizophrenics with PET or related techniques. No differences in striatal 11C-N-methylspiperone binding in schizophrenics withdrawn from neuroleptics was reported by Tune et al. (1985). However, Crawley et al. (1986), using 11Br-spiperone and single photon emission tomography (SPECT), found a slight increase in D1A binding in the basal ganglia of schizophrenics from whom neuroleptic treatment had been withdrawn. The Karolinska group has developed the most sophisticated method so far for quantifying D1A receptors with PET, using 11C-raclopride as ligand (Farde et al. 1986a). They found slight increases in the number of D1A receptors in the putamen of six schizophrenics compared with normal controls (Sedvall et al. 1986). More such studies, with an emphasis on never-medicated schizophrenics, are needed.

Normal or even decreased release of DA might produce increased responses in DA-dependent systems in the presence of DA receptor supersensitivity. If there was only a selective increase in the number of DA receptors or response to the stimulation of these receptors, but a generalized decrease in dopaminergic activity, one might have a mixture of both decreased and increased dopaminergic activity. Bjerkenstedt
et al. (1985) recently demonstrated that schizophrenics have increased plasma concentrations of six amino acids which compete with tyrosine, the precursor of DA and noradrenaline (NE), for transport into the brain. Some increases in amino acid levels were noted in CSF as well. CSF HVA and 5-hydroxyindoleacetic acid (5HIAA) levels of the schizophrenic patients were significantly and negatively correlated with the branched amino acids (valine, isoleucine, and leucine), phenylalanine, and lysine. CSF HVA levels were reduced in the schizophrenics. They postulated that decreased synthesis of DA, possibly due to excessive competition of amino acids with tyrosine for entry into the brain, might lead to DA receptor supersensitivity and an overall increase in dopaminergic activity. This is a very intriguing theory which requires further investigation.

PET studies have confirmed the conclusions about the time of onset and offset of DA receptor blockade following neuroleptic administration and withdrawal that were generated from neuroendocrine studies. Meltzer and Fang (1976) indicated that serum prolactin increased within minutes of neuroleptic administration and that prolactin levels returned to normal within 24-48 hours of neuroleptic withdrawal. We noted the disparity between this time course and the time course of antipsychotic effects of neuroleptic administration or withdrawal. Sedvall et al. (1986) found that DA receptors in the basal ganglia were occupied by raclopride, a benzamide, within a few hours after the first dose as indicated by competition with $^3$H-raclopride. They found evidence for the vacancy of the DA receptor within a day of withdrawal (Farde et al. 1986b).

If increased numbers of DA receptor binding sites are found through PET studies, it will still be difficult to interpret their significance without some measure of DA turnover. Increased numbers of DA receptors might just compensate for decreased release of DA. It is also possible that altered efficiency of coupling of the DA receptor to the neuroleptic binding site might affect the overall dopaminergic activity.

Some evidence for an exacerbation of psychotic symptoms during or following withdrawal of neuroleptic treatment, due to development of supersensitive DA receptors, has been reported. First proposed by Chouinard and Jones (1980), in patients requiring increasing doses of parenteral high potency neuroleptics, it has also been invoked as an explanation of the rapid relapse noted in some patients following sudden withdrawal of clozapine (Ekbloom, Eriksson, and Lindstrom 1984) or reserpine (Kent and Wilber 1982). The ability of insulin to inhibit the neuroleptic-induced increase in DA receptor sensitivity has been used to suggest that insulin coma therapy of schizophrenia might work via the ability to modulate the sensitivity of brain DA receptors (Lozovsky, Kopin, and Saller 1985).

Recent Developments in Dopaminergic Neurotransmission. It is beyond the scope of this review to consider the vastly increased understanding of the physiology of the dopaminergic system that has emerged in recent years. However, some of the important conceptual advances that need to be appreciated to understand the newer approaches to investigating the role of DA in schizophrenia will be discussed. The prefrontal cortex has been the subject of considerable speculation as the locus of some of the psychopathology of schizophrenia, especially volitional, affective, and cognitive disturbances (Seidman 1983). Afferents of mesocortical DA neurons, with cell bodies in the medial ventral tegmentum ($A_{10}$) region, to the prefrontal cortex have been described (Bannon and Roth 1983). Large lesions of the prefrontal cortex (Scatton et al. 1982) or more selective lesions that interrupt the afferent DA neurons to this region can produce chronic hyperactivity of subcortical DA systems (Pycock, Carter, and Kerwin 1980). Abnormalities of the prefrontal cortex thus might be associated with decreased cortical dopaminergic activity and negative symptoms and increased subcortical DA activity and positive symptoms (Bannon and Roth 1983). This is of interest in regard to recent PET studies showing increased activity of the basal ganglia in schizophrenia (DeLisi et al. 1985).

Stevens and Livermore (1978) have suggested that "kindling," i.e., the epileptogenic effect of repeated electrical discharge, might lead to increased activity of the nucleus accumbens. Epileptic discharges within the limbic cortex, especially the amygdala, can increase the density of $D_2$ DA receptors in the accumbens (Csernansky et al. 1985). The antipsychotic effect of anticonvulsants such as clonazepam and carbamazepine might be related to their effect on the kindling mechanism.

The physiology and pharmacology of the mesocortical DA neurons have been reviewed by Bannon and Roth (1983). The DA projection to the prefrontal cortex is selectively activated by footshock stress and shows a diminished response to acute administration of DA agonists or antagonists. These DA neurons fail to develop tolerance to the
chronic effect of neuroleptic drug administration. The turnover of DA in this region is approximately twice as fast as that of the mesolimbic DA system and four times faster than the nigrostriatal DA system (Bannon, Wolf, and Roth 1983). This increased turnover may be due to the absence of DA autoreceptors that modulate DA synthesis directly. However, DA agonists can inhibit DA synthesis in the mesocortical DA neurons by decreasing DA release, thereby increasing intraneuronal levels of DA, which inhibits tyrosine hydroxylase directly (Galloway, Wolf, and Roth 1986). The activity of these neurons may be inhibited by neurons originating in or passing through the lateral habenula as well as neurons from the dorsal raphe.

Subchronic (21-day) treatment with classical neuroleptics markedly reduced the number of electrically active DA cells in both the rat substantia nigra zona compacta (A9) and ventral tegmental (A10) areas. These silent DA neurons were suggested to be in a state of tonic depolarization inactivation. Clozapine, an atypical neuroleptic, produced depolarization inactivation only in the A10 cells. It was proposed that the antipsychotic action was due to blockade of A10 neurons (Chiodo and Bunney 1983). This is an intriguing theory, but it seems unlikely that such profound interference with DA function occurs in man. One might expect much more severe and prolonged parkinsonian effects due to depolarization inactivation than are actually observed. Studies of the effect of chronic neuroleptic treatment and its withdrawal on CSF HVA levels in schizophrenics indicate that elevations of CSF HVA levels persist in many subjects and return to basal levels after withdrawal (Bowers 1985). This could simply indicate intraneuronal metabolism of DA. The possible importance of neuropeptides in schizophrenia will be considered in a later section. Important interactions between DA and opiate peptides (Schmauss and Emrich 1985), neuropeptides (Nemeroff 1986), and cholecystokinin (Schneider, Alpert, and Iversen 1983; van Ree, Gaffori, and deWied 1983) have been described.

Norepinephrine and Schizophrenia

Dopamine is not the only catecholamine that has been implicated in schizophrenia. Hornykiewicz (1982) has summarized the evidence implicating brain norepinephrine (NE) in schizophrenia. Briefly, some antipsychotics are potent α₂-adrenergic blockers, but this effect does not correlate with their antipsychotic efficacy. The α-adrenergic blocker prazosin is not antipsychotic (Homer et al. 1984). The β-adrenergic blocker propranolol may be an effective antipsychotic in some schizophrenics (for references, see Melzter 1986). Hornykiewicz argues that the hyperarousal of schizophrenia may be mediated by increased noradrenergic activity and summarized a series of studies showing increased NE in brain and CSF of schizophrenics. He also suggested NE may act by virtue of its influence on dopaminergic neurotransmission.

Bridge et al. (1985) found increased brain NE in the hypothalamus in seven nondemented schizophrenics but no difference in six demented schizophrenics. On the other hand, NE and DA concentrations were decreased in the nucleus accumbens. Gattaz et al. (1983) could not replicate the increase in CSF NE reported by others and suggested previous reports were the result of neuroleptic treatment. Jeste, Doongaji, and Linnoila (1984) found elevated CSF NE in eight patients with tardive dyskinesia (TD) but not in 15 without TD. They suggested TD may be related to noradrenergic hyperactivity. Kemali et al. (1985b) found increased CSF NE in acute schizophrenics. A relationship among CSF NE concentrations, computerized electroencephalographic indicators, psychosis ratings, and platelet monoamine oxidase was noted. Thus, these results agree with Hornykiewicz (1982) that increased NE may reflect CNS arousal. Dajas et al. (1983) and Barbeito et al. (1984) reported additional evidence of increased plasma NE in neuroleptic-treated or drug-free schizophrenics. According to Dajas et al. (1983), plasma NE correlated significantly with global psychopathology, positive symptoms, and paranoid symptomatology. The elevations in plasma NE were suggested to reflect increased arousal. However, Rice et al. (1984) did not find increased plasma NE in schizophrenics.

Sternberg et al. (1982) found that clonidine, an α-adrenergic agonist, decreases plasma 3-methoxy-4-hydroxyphenylglycol (MHPG) content in normal controls but not in medicated schizophrenics, a finding that suggests a functional subsensitivity of α₂-adrenergic receptors. Kafka and van Kammen (1983) found no difference in the number of platelet α₂ receptors using ³H-clonidine and ³H-yohimbine in 10 schizophrenics who were withdrawn from neuroleptics for 2 weeks. In a subsequent study involving nine drug-free schizophrenics, lower levels of ³H-clonidine binding sites were associated with more negative symp-
Toms (Rosen et al. 1985). Patients with fewer $^3$H-clonidine binding sites also showed less response to neuroleptic treatment (Rosen et al. 1985). These results need to be replicated.

The consistency of the findings of increased brain, CSF, and plasma NE and its association with paranoid symptomatology is intriguing. Some of the results may reflect stress and nonspecific hyperarousal. While no marked efficacy in schizophrenia has been shown by $\alpha_2$-receptor blockers or the $\alpha_2$-agonist clonidine, the beneficial effects of $\beta$-adrenergic blockers (Eccleston et al. 1985) would suggest further research is in order.

**Serotonin and Schizophrenia**

There are a number of reasons for an interest in the neurotransmitter serotonin (5HT) and schizophrenia. An extensive literature demonstrates highly complex interactions between DA and 5HT in the brain (Carter and Pycock 1978; Balsara, Jadhav, and Chandorkar 1979; Blackburn, Cox, and Lee 1982; Lee and Geyer 1982; Korsgaard, Gerlach, and Christensson 1985). Indole hallucinogenic drugs have been suggested as a model for hallucinations in schizophrenia (Fischman 1983). We have obtained evidence that a major feature of atypical neuroleptic drugs such as clozapine and melperone that differentiates them from typical neuroleptics is their potent inhibitory effect on 5HT; receptors (Meltzer, Gudelsky, and Nash, unpublished data). A similar profile has been reported for setoperone (Ceulemans et al. 1985) Space limitations preclude more than a brief mention of some of the relevant literature. Levels of 5HT, its precursor tryptophan, its metabolite 5-hydroxyindoleacetic acid (5HIAA), and kynurenine, another metabolite of tryptophan, were found to be normal in the brains of 15 schizophrenics compared to 23 normal controls (Joseph et al. 1979).

However, Bucht et al. (1979) found lower levels of 5HT in the hypothalamus, mesencephalon, hippocampus, and medulla and lower concentrations of 5HIAA in the cingulate gyrus and frontal cortex of 12 aged, neuroleptic-treated schizophrenics compared to 28 age-matched controls. Decreased CSF 5HIAA has also been reported in schizophrenia (Ashcroft et al. 1966; Bowers, Heninger, and Gerbode 1969; Potkin et al. 1983). The last group noted that the decrease in CSF 5HIAA was present only in patients with enlarged ventricles. By contrast, Sedvall and Wode-Helgodt (1980) found a positive family history of schizophrenia to be associated with low or high CSF 5HIAA levels, but no overall group difference between schizophrenics and controls. They suggested that abnormal monoamine metabolism is related to genetically determined schizophrenia, which would correspond to the concept that schizophrenia associated with structural abnormalities revealed by CT is not genetically mediated. R. King et al. (1985c) reported positive correlations between both peripheral (platelet serotonin levels) and central (CSF concentrations of 5HIAA) measures of 5HT metabolism and peculiar or unusual mannerisms and posturing in schizophrenic patients. These authors discuss the possible role of 5HT in causing eye-tracking dysfunction and hypofrontal metabolic activity in schizophrenia. No abnormality in plasma or CSF tryptophan levels in schizophrenics was observed by either Potkin et al. (1982) or Rimón et al. (1982).

Several studies have found elevated platelet 5HT in unmedicated schizophrenics (Garelis et al. 1975; DeLisi et al. 1981a; Freedman et al. 1981; Jackman, Luchins, and Meltzer 1983; Stahl et al. 1983). Jackman, Luchins, and Meltzer (1983) found that elevated platelet 5HT was related to cortical atrophy, but Jackman, Luchins, and Meltzer (1983) could not replicate these results, possibly because of differences in patient populations. These results are of particular interest because elevated platelet 5HT levels are common in organic brain disease, especially mental retardation (Partington, Tu, and Wong 1975), and may provide a link between some types of schizophrenia, particularly the genetically determined form, and developmental brain abnormalities.

There have also been attempts to treat schizophrenia by increasing serotonergic activity, e.g., by administering its precursors 5-hydroxytryptophan (5HTP) (Bigelow et al. 1979) or tryptophan, the latter with a monoamine oxidase inhibitor (Polkin, Cardon, and Kety 1961) and without one (Gillin, Kaplan, and Wyatt 1976). The tryptophan has been successful in treating schizophrenia or have exacerbated symptoms. Interventions designed to decrease serotonergic activity, e.g., inhibition of 5HT synthesis with $p$-chlorophenylalanine (DeLisi et al. 1982a) or fenfluramine, a 5HT releaser (Shore et al. 1985), have also generally been ineffective.

The evidence reviewed above does not provide any clear picture of how 5HT is relevant to schizophrenia. However, the hallucinatory effect of some indoles, the elevated platelet 5HT content, and the 5HT$_2$
receptor blocking properties of atypical neuroleptics suggest further study is indicated.

**Platelet Monoamine Oxidase (MAO) Activity**

There has been intensive investigation of MAO activity in the blood platelets of schizophrenics as a possible biological marker for this syndrome. Decreased mean platelet MAO activity (compared with that of nonhallucinating schizophrenics or normal controls) has been frequently reported in schizophrenics with auditory hallucinations (Becker and Shaskan 1977; Orsulak et al. 1978; Bond et al. 1979; Adler et al. 1980; Meltzer and Arora 1980; Meltzer et al. 1980) or paranoid symptoms (Potkin et al. 1978; Van Valkenburg and Crowe 1978; Jeste et al. 1982). However, other studies have reported no association between low platelet MAO activity and either auditory hallucinations or paranoia (Carpenter, Murphy, and Wyatt 1975; Groshong et al. 1978; Mann and Thomas 1979; Owen et al. 1981; Baron et al. 1984).

A simple comparison of the number of studies reporting significantly lower platelet MAO activity among paranoid or hallucinating schizophrenics, compared with that of nonparanoid or nonhallucinating schizophrenics or with that of normal controls, is potentially misleading. Such a comparison may be biased in favor of studies with larger sample sizes, because the statistical power of an analysis increases with sample size, all other relevant factors being equal. Furthermore, a simple comparison gives equal weight to differences of unequal magnitude, as long as the differences are statistically significant.

A more informative comparison would allow a quantitative evaluation of the overall relationship of paranoid subtype and auditory hallucinations to platelet MAO activity, based on results from all studies regardless of the statistical significance of the findings. This evaluation is achieved by means of a secondary or meta-analysis, which transforms the results of each study to a common metric—a standardized measure of the difference in platelet MAO activity between two groups. This measure is termed an effect size (ES) (Cohen 1977). The average ES for groups of paranoid and nonparanoid schizophrenics would represent the overall difference in platelet MAO activity between these two groups, expressed in standard deviation units.

We conducted a meta-analysis of the results of eight studies that examined platelet MAO activity of 117 paranoid and 220 nonparanoid schizophrenics (Zureick and Meltzer, in press). The comparison of platelet MAO activity of paranoid vs. nonparanoid schizophrenics yielded an average ES of \(-.60\) (SD = .56), indicating that the typical paranoid schizophrenic studied had platelet MAO activity lower than that of 73 percent of nonparanoid schizophrenics. Similar comparison of paranoid schizophrenia vs. normal controls yielded an average ES of \(-.88\) (SD = .34), indicating that paranoid schizophrenics had platelet MAO activity lower than that of 81 percent of normal controls. Meta-analysis of the results of six separate studies, comprising 130 hallucinating and 81 nonhallucinating schizophrenics, and 186 normal controls, indicated that the average schizophrenic experiencing auditory hallucinations had platelet MAO activity lower than that of 79 percent of nonhallucinating schizophrenics (ES = \(-.82\); SD = .99), and lower than that of 75 percent of normal controls (ES = \(-.68\); SD = .71). Nonhallucinating schizophrenics, however, had mean platelet MAO activity greater than that of 66 percent of normal controls (ES = .41; SD = .65). In general, results of these meta-analyses indicate that platelet MAO activity of paranoid, nonparanoid, and hallucinating schizophrenics is lower than that of normal controls, while nonhallucinating schizophrenics have platelet MAO activity higher than that of normal controls. Within groups of schizophrenic patients, paranoid subtype and presence of auditory hallucinations are associated with decreased platelet MAO activity.

Results of these meta-analyses do not, however, directly address the question of whether low platelet MAO activity is independently associated with auditory hallucinations and paranoid subtype, or with some interaction of these factors. Recent analyses from our laboratory (Meltzer and Zureick, in press) indicate that there are significant interactive effects of auditory hallucinations with gender, with paranoid subtype and gender, and with paranoid subtype and race in the prediction of platelet MAO activity in schizophrenics. The patient sample comprised 37 female and 64 male schizophrenics of paranoid or undifferentiated subtype, according to Research Diagnostic Criteria. In general, auditory hallucinations were associated with decreased platelet MAO activity among paranoid, but not undifferentiated, subgroups of male and black schizophrenics. Decreased platelet MAO activity was associated with paranoid subtype alone among white, male schizophrenics. These findings could not be attributed to a disproportionate incidence of auditory hallucinations among racial or
sex subgroups of schizophrenic patients, since analysis indicated no statistically significant relationship of presence of auditory hallucinations to diagnostic subtype, gender, or race.

These findings of statistically significant differences in platelet MAO activity among subgroups of schizophrenics characterized by specific clinical features have also contributed to our interest in the relationship of platelet MAO activity to positive (hallucinations and delusions) and negative (e.g., blunted or inappropriate affect, loose associations, and slowed speech) symptoms in schizophrenics. In a study of the relationship between platelet MAO activity and scores on the negative and positive symptom subscales developed by Lewine, Fogg, and Meltzer (1983), Lewine and Meltzer (1984) found a highly significant positive Spearman correlation \( r = .53; n = 42; p = .0003 \) between platelet MAO activity of unmedicated male schizophrenics, and negative symptom scores. This correlation held up in split halves of the group as well: \( p = .49 \) \( (p = .023) \) and \( p = .61 \) \( (p = .003) \). The relationship of platelet MAO activity to negative symptoms for female schizophrenics was not statistically significant. Nor did platelet MAO activity correlate with positive symptoms in either male or female schizophrenics. However, it was not possible to replicate these results on an expanded sample of 63 male and 37 female schizophrenics, despite identical diagnostic assessment, blood sampling, and assay procedures. Psychometric characteristics of the negative and positive symptom scales might be related to this failure to replicate. Hierarchical symptom scales have indicated three, rather than one, consistent clusters of negative symptoms described by items relating to cognitive, motivational, and motor/emotional deficits. Scores on the motivational deficit cluster were significantly related to platelet MAO activity \( (p = .34, p = .05) \) among male, but not female, schizophrenics.

The relationship of platelet MAO activity to clinical and diagnostic features among schizophrenics suggests that the activity of this enzyme might also be related to rehospitalization. Followup data at 12-14 months after discharge were obtained for 25 male and 14 female chronic schizophrenic patients. After statistical adjustment for the effects of gender, it was found that mean \((\pm SD)\) platelet MAO activity of the 13 males who had not been rehospitalized \( (7.5 \pm 1.4 \text{ nmole/10 platelets}) \) was significantly lower than that of the 12 rehospitalized males \( (9.6 \pm 1.9) \). Similarly, adjusted mean platelet MAO activity of the seven females who had not been rehospitalized during a 12- to 14-month period \( (10.2 \pm 1.6) \) was significantly lower than that of the seven rehospitalized females \( (16.7 \pm 1.6) \). Thus, low platelet MAO activity predicted the ability to remain out of the hospital in both male and female schizophrenics. There was also a statistically significant inverse relationship between duration of nonhospitalization and platelet MAO activity among male \( (r = -.39, p = .05) \) and female \( (r = -.60, p = .02) \) schizophrenics. These findings are consistent with the report by Carpenter, Murphy, and Wyatt (1975) of better prognosis among patients having low platelet MAO activity.

Platelet MAO activity has been studied in relation to several other biological markers. It did not relate to smooth pursuit eye tracking abnormalities (Siever et al. 1982). However, Tachiki et al. (1984) found a correlation between platelet MAO and VBR in nonparanoid schizophrenics. Low platelet MAO activity is not associated with a family history of schizophrenia (Duncavage, Luchins, and Meltzer 1982; Kemali et al. 1985).

A monoclonal antibody to platelet MAO B was developed (Fritz et al. 1986) and used to measure total platelet immunoreactive MAO protein in relation to MAO activity. Male schizophrenics had reduced platelet MAO activity and significantly lower molecular activities but higher specific MAO concentration (Rose et al. 1986). Summers et al. (1985) found no abnormality in MAO specific activity or turnover number between schizophrenics and their first degree relatives, indicating neither measure could be used in risk estimation for the development of schizophrenia in members of these families.

**Peptides and Schizophrenia**

With the demonstration of neuropeptides as neurotransmitters or cotransmitters and neuromodulators, the possibility of a neuropeptide abnormality as a basis for schizophrenia achieved considerable currency. Only some of the major recent developments can be reviewed here.

Initial attempts to clarify possible peptidergic abnormalities in schizophrenia focused on treatment studies. These have largely been disappointing. Reports of clinical efficacy of \( \beta \)-endorphin, enkephalin analogs, des-try- or des-enkephalin-\( \gamma \)-endorphin, thyrotropin-releasing hormone, and cholecystokinin have generally not been replicated (Gerner et al. 1980; Meltzer et al. 1982; Meltzer 1986;
Tammenga et al. 1986). It is likely that differences in dosage, subtypes of schizophrenia, and small sample sizes account for some of the discrepancies; nevertheless, it is difficult to remain optimistic about this approach, at least until ways to deliver larger amounts of active peptides to brain are developed (e.g., with specific peptidase inhibitors, protected forms of the peptides, or novel delivery systems). There are several reports of modest beneficial effects of vasopressin in small groups of schizophrenics, especially on negative symptoms (Korsgaard et al. 1981; lager et al. 1986) and as yet no negative studies. Naloxone treatment has been shown to diminish auditory hallucinations, other psychotic symptoms, unusual thought content, and tension in a small number of schizophrenics in a variety of studies, some of which were double blind. These have been reviewed by Mueser and Dysken (1983). A long-acting opiate antagonist, naltraxone, has been less effective as an antipsychotic as a rule (Mueser and Dysken 1983). The antipsychotic effects of opioid agonists and antagonists, both of which are controversial, have been postulated to be related to their ability to modulate dopaminergic activity (Schmauss and Emrich 1985). The evidence offered in support of this hypothesis, mainly from preclinical studies, demonstrates important mutual interactions of these two systems but does not convincingly establish that the occasional ability of opioid drugs to decrease hallucinations and other positive psychotic symptoms related to the Type I syndrome is due to decreased dopaminergic activity. Effects on specific opioid mechanisms, especially the μ-receptor, are as likely to be relevant.

Serum levels of opiate peptides have been measured in schizophrenics. Serum opioid levels have been reported to be normal (Höllt et al. 1979; Ross, Berger, and Goldstein 1979; Naber, Nedopil, and Eben 1984), high (Emrich et al. 1979; Brambilla et al. 1984), low (Bianco, Castro, and Sanchez 1981), or more variable than normal throughout the day (Gil-Ad et al. 1986). Assay and sample differences most likely account for these inconsistent findings.

Another approach has been to measure spinal fluid (CSF) concentrations of various neuropeptides. These presumably reflect central nervous system (CNS) levels but may also be influenced by spinal cord metabolism during passage from the brain to the lumbar region. There are many conflicting studies of the levels of β-endorphin-like peptides in CSF. The preponderance of evidence is against any deviation from normal (Naber et al. 1981; van Kammen et al. 1981). Lower CSF levels of dynorphin (1–8) immunoreactivity were recently reported in 35 acute, first-break schizophrenics (Zhang et al. 1985).

Spinal fluid neurotensin levels have been reported to be low in subgroups of schizophrenics (Widerlöv et al. 1982), but there has been no independent replication of this finding. Neurotensin has been suggested to be an endogenous DA antagonist (Nemeroff et al. 1983a). Vasopressin was reported to be reduced by approximately 40 percent (p < .01) in the CSF of male schizophrenics in one study (van Kammen et al. 1981), but no difference was found in either vasopressin or oxytocin levels in a more recent study, which included 28 male paranoid schizophrenics (Beckmann, Lang, and Gattaz 1985). CSF oxytocin levels were reported to be increased in drug-free schizophrenics and further increased by neuroleptic treatment (Beckmann, Lang, and Gattaz 1985). Oxytocin has been reported to have effects opposite to vasopressin, i.e., to inhibit dopaminergic and noradrenergic neurotransmission in some brain regions (Telegdy and Kovacs 1979). Linkowski et al. (1984) reported decreased concentrations of neurophysin I and increased levels of neurophysin II, carriers of vasopressin and oxytocin, respectively, in the hypothalamus. Decreased somatostatin levels in schizophrenic, depressed, and demented patients were reported by Bissette et al. (1984); no differences were noted by Gerner and Yamada (1982) in one study, while increased concentrations were found in a followup study (Gerner 1984). Cholecystokinin (CCK) levels were found to be low in the CSF of 15 schizophrenics by Verbanck et al. (1983). Somatostatin levels in schizophrenics were reported to be in the normal range (Doran et al. 1986).

Several studies have examined post-mortem levels of peptides in various regions of schizophrenic brain. In general, neuropeptides are very stable in post-mortem tissue. Decreased levels of CCK have been reported in the hippocampus, amygdala, and temporal cortex of Type II schizophrenics by Ferrer et al. (1983). Type I schizophrenic patients had elevated levels of vasoactive intestinal peptide. Kleinman et al. (1983) could not replicate the CCK findings. Farmery et al. (1985) found decreased CCK binding sites in the hippocampus and frontal cortex but not the amygdala or temporal cortex. Decreases in somatostatin and thyrotropin-releasing hormone and increases in neuropeptides reported by Nemeroff et al. (1983b) were not found by Ferrer et al. (1983), Kleinman et al. (1983), or Biggins et al. (1983).

It should be clear from this brief
review that there is as yet no clear evidence for a neuropeptidergic mechanism in schizophrenia. Treatment with peptides seems relatively futile at this point because of the difficulty of achieving high enough concentrations of active peptides in the brain, but also because correcting a deficiency of any single peptide is unlikely to have a marked effect on the functional relationship of interacting neurotransmitter systems. Analytic problems with antisera that may react with inactive material, post-mortem decay, neuroleptic effects, and the ubiquitous heterogeneity problem in schizophrenia, which may dictate that only a few subjects in any study would have relevant peptidergic abnormalities, make the search for reliable evidence of peptide abnormalities with available methods appear relatively un-promising. Because peptides are clearly important to neurotransmission and endocrine regulation, however, it is to be hoped that the study of peptide physiology in schizophrenia will continue with attention to all the factors that affect peptide assay levels and turnover. Basic research studies of the effect of peptides on neurotransmitters, especially DA, 5HT, and NE, appear specifically indicated.

Neuroendocrine Studies

Endocrine studies in schizophrenia have been reviewed by us in detail elsewhere (Meltzer, Busch, and Fang 1981; Meltzer and Lowy, in press). The possibility that endocrine disturbances predispose to or actually cause schizophrenia has been considered because peaks in the age of onset and changes in the intensity of symptoms in schizophrenia parallel major shifts in neuroendocrine function and because disturbances of adrenal, thyroid, and gonadal function have frequently been reported in schizophrenia. However, these must be considered secondary responses, perhaps the result of neurotransmitter effects on hypothalamic hormones. More recently, the major aims of neuroendocrine research have been to obtain indirect evidence of the function of neurotransmitters that regulate the secretion of these hormones, to assess drug action on neurotransmitter dynamics or receptors via hormone release, to assess the relationship between hormone levels and psychopathology, and to predict clinical response or relapse following neuroleptic withdrawal.

One interesting area of neuroendocrine research in schizophrenia is worth noting because of its relation to the DA hypothesis. This is the study of the effect of the DA agonist apomorphine to increase growth hormone (GH) and decrease prolactin secretion in unmedicated schizophrenics. We reported (Meltzer et al. 1984) no overall difference in the GH or prolactin responses between 40 schizophrenics and 21 controls. The GH response, adjusted for weight, was significantly negatively correlated with duration of illness. This correlation disappeared when age was removed. The same correlation was noted in 56 non-schizophrenic patients (mainly affective disorders) even after the effect of age was removed. The GH response in the schizophrenics was significantly correlated with both positive and negative symptoms and with the total score on the Brief Psychiatric Rating Scale (BPRS). The prolactin response was significantly positively correlated with depression ratings but not with positive or negative symptoms or total BPRS score. The relation of the GH response to duration of illness in all subjects suggests that this is not likely to be due to previous neuroleptic treatment but may relate to some progressive changes in DA receptor sensitivity or in the secretion of somatostatin and GH-releasing factor (GHRF), which regulate GH secretion. The relationships between psychopathology and these hormonal responses are intriguing but must be replicated in an independent group of patients.

Zelman et al. (1985) also found a diminished GH response in chronic schizophrenics and a negative relationship between CSF HVA levels and the GH response to apomorphine. This suggests that the DA receptors that mediate somatostatin and GHRF secretion are directly responsive to the release of brain DA. Recent onset, acutely ill schizophrenics may have greater GH responses to apomorphine than chronic schizophrenics (Pandey et al. 1977; Ferrier, Johnstone, and Crow 1984) and normal controls (Pandey et al. 1977; Cleghorn et al. 1983). This may suggest increased DA receptor sensitivity in more acute patients.

Interpretation of GH and prolactin responses to apomorphine is difficult because of the heterogeneity of schizophrenia, the confounding effects of previous treatment with neuroleptic and other psychotropic drugs, pharmacokinetic factors, differences in GH clearance, and the many factors other than DA that regulate GH secretion and might compensate for the effect of DA receptor stimulation by apomorphine. Further studies in which these variables are addressed directly are required.

Elevated activity of the hypothalamic-pituitary-adrenal (HPA) axis in schizophrenia has recently been reported. Christie et al. (1986) reported elevated cortisol in afternoon
but not morning plasma samples. However,Gattaz, Hannak, and Beckmann (1985) reported CSF cortisol levels in drug-free schizophrenics (4 weeks) were significantly lower than in normal controls. They suggested this might reflect decreased serotonergic and cholinergic activity. A study of CSF and plasma cortisol in the same subjects is needed to reconcile these differences. Abnormal dexamethasone suppression tests (DSTs) have also been observed in schizophrenics in excess of the normal population (Castro et al. 1983; Banki, Arató, and Rihmer 1984; Dewan et al. 1985). There is some evidence that catatonic schizophrenics may be non-suppressors more frequently than other schizophrenic subtypes (Banki, Arató, and Rihmer 1984). A wide range of biological parameters, including CT and platelet MAO activity, did not differentiate suppressors and non-suppressors (Dewan et al. 1985). It may be desirable to include the determination of cortisol secretion and the DST as part of the study of other biological parameters that are sensitive to the action of glucocorticoids.

Adolescent schizophrenic males have been shown to respond to a thyrotropin-releasing hormone (TRH) infusion with an unexpected increase in GH secretion (Gil-Ad et al. 1981; Weizman et al. 1982; DeMilio 1984). No differences in the thyroid-stimulating hormone (TSH) response to TRH were noted. The increase in GH secretion (Gil-Ad et al. 1981; Weizman et al. 1982; Dewan et al. 1986) was suggested to result from an abnormal influence of monoamines on the hypothalamic-pituitary response system.

The GABAergic drug sodium valproate (SV) failed to diminish serum prolactin levels in 20 drug-withdrawn schizophrenic females but produced a significant decrease in 18 normal females (Monteleone, Zontini, and Steardo 1985). Mean plasma SV levels did not differ. The results suggest a possible failure of the GABA system. It has been previously suggested that schizophrenics might have an inadequate GABA-dependent inhibitory system (Roberts 1972).

Autoimmune, Immunologic Incompetence and Viral Hypotheses

The possibility that schizophrenia is due to an abnormality of the immune system leading to an allergic reaction to brain proteins was first proposed over 70 years ago. Bowers (1980) and Prilipko (1986) have partially reviewed this topic in the Schizophrenia Bulletin. Other reviews of interest are those of Knight (1984) and DeLisi (1986). The various types of lymphocytes are the key cellular component of the immune system. The B-cells are responsible for immunoglobulin production, or humoral immunity; T-cells produce lymphokines, which mediate cellular immunity. Other lymphocytes are known as helper or suppressor cells because of their influence on B-cells and T-cells. There have been some recent reports of disproporions of subtypes of B-cells (increased), T-cells (decreased), and suppressor T-cells (increased or decreased) in small groups of schizophrenic patients (DeLisi et al. 1982b; Coffee, Sullivan, and Rice 1983). The significance of such changes is unclear. They could be related to the effect of neuroleptic treatment. Reports of morphologically atypical lymphocytes and abnormalities in the immunocompetency of lymphocytes of schizophrenics have not revealed any specific changes that could not be due to stress or neuroleptic treatment. Fudenberg et al. (1984) recently demonstrated phenocyclidine (PCP) receptors on T- and B-lymphocytes and proposed that antibodies to these and comparable PCP receptors in brain, i.e., the opiate sigmoid receptors, might be responsible for both altered immune function and neurotransmitter abnormalities. No direct evidence is available to support this hypothesis.

Direct measures of brain antibodies in the sera of schizophrenics were recently reviewed by DeLisi, Weber, and Pert (1985). Eleven of the 15 studies cited showed brain antibodies in the schizophrenics more commonly than in controls. These earlier studies did not adequately consider the issue of specificity of the antibody for brain or schizophrenia. DeLisi, Weber, and Pert (1985) reported antibodies to caudate nucleus in the sera of 3/50 schizophrenics but found even higher levels in 2/11 affective disorders. All five patients with antibodies were nonresponders who were chronically hospitalized. This suggests the possibility that further study of the immune hypothesis might be concentrated on treatment-resistant psychotic patients, regardless of diagnosis, using antibodies to specific brain proteins, especially those related to neurotransmitters and cell membranes. Antibodies to native DNA, usually present in autoimmune disorders, have not been found in any of the studies of brain antibodies in the sera of schizophrenics although increased antinuclear antibody titers, another feature of autoimmune disorders,
have been found in approximately 20 percent of hospitalized psychiatric patients (DeLisi 1986). Knight (1982) has proposed that the symptoms of schizophrenia that respond to neuroleptic drugs could be caused by autoantibodies that stimulate postsynaptic DA receptors, and that the defect state in schizophrenia might be related to antibodies that diminish DA release or block DA receptors. No direct evidence in support of this hypothesis is available. One study shows increased levels of antibodies to the nicotinic cholinergic receptor in schizophrenics (Lieberman et al. 1984), but there were few subjects and the specificity of the antibody was unclear. Consideration must also be given to the possibility that decreased competence of the immune system is present in some schizophrenics, producing increased vulnerability to infectious agents which might produce the primary symptoms of the disorder and perhaps further compromise the immune system. However, this would link schizophrenia to an acquired immunodeficiency syndrome (AIDS)-like clinical course, and there is no evidence to suggest a sequence such as this. Jankovic (1985) found a delayed hypersensitivity reaction to 5–100 protein injected intradermally in 153/167 schizophrenics, but it was also found to the same extent in alcoholism, depression, dementia, and cerebral atrophy of unknown origin.

In summary, there is slight evidence for disturbance in immunofunction in schizophrenics, but it has not yet been linked to specific brain antigens or to clinical populations. Pharmacological treatment may be a factor in producing the minimal alterations found. Immunological abnormalities might be secondary to changes in the blood-brain barrier that have been reported in schizophrenia. Whether immunological incompetence might contribute to viral and other infections that could have a primary etiological role, or whether such infections could cause secondary changes in the immune system, is a topic for further study.

Immunoglobulin concentrations in CSF and sera have been extensively investigated in schizophrenics to test both the autoimmune and viral hypotheses. However, total immunoglobulin concentrations may be normal or even decreased, rather than elevated, in both conditions (DeLisi 1986). We examined CSF and sera from 32 schizophrenics and 26 normal controls and found no abnormalities of CSF or serum IgG, M and A, or albumin. No evidence of endogenous CNS immunoglobulin production (high CNS:serum ratio) was found. The group included recent onset as well as residual schizophrenics (Roos, Davis, and Meltzer 1985). DeLisi et al. (1981b) found significantly lower serum and CSF levels of IgG, M and A in chronically institutionalized schizophrenics. However, Kirch et al. (1985) reported elevated endogenous CNS IgG production in 8/24 (33 percent) schizophrenics along with evidence for increased blood-brain barrier permeability in 7/24 (29 percent) patients, i.e., increased ratio of CSF to serum albumin. The elevated IgG index was due to increased CSF IgG production, which apparently resulted from previous electroconvulsive therapy. Both Kirch et al. (1985) and Roos, Davis, and Meltzer (1985) found no or minimal (1/8, 12 percent) oligoclonal immunoglobulin bands in CSF or serum. However, Ahokas et al. (1985) found oligoclonal bands in 9/25 (36 percent) schizophrenics but in 0/46 nonpsychiatric controls. They were also present in 8/16 (50 percent) reactive psychoses, 3/6 (50 percent) other psychoses, and 2/5 personality disorders. Oligoclonal bands indicate immunoglobulin production in the CNS and are found in multiple sclerosis, herpes simplex virus encephalitis, and many chronic CNS infections (Chu et al. 1983). The reason for the discrepancies between studies is unclear. They may relate to assay methodology and patient sample characteristics. The results of the Ahokas study suggest further study is indicated.

The hypothesis that viruses are etiological factors in the pathogenesis of schizophrenia has been an attractive one. Arguments in favor of this hypothesis have been offered by Crow (1983) and Torrey and Kaufmann (1986) and challenged by Murray and Reveley (1983). It is likely that some instances of what is called schizophrenia, even by narrow criteria, are due to viruses. The evidence for a viral etiology of schizophrenia is entirely indirect. Recent reports of the isolation of viral-like agents from CSF of schizophrenics (Tyrell et al. 1979) could not be replicated by the same investigators (Taylor et al. 1982). Some cases of acute viral encephalitis, especially herpes simplex, are characterized by schizophreniaiform symptoms. A slow virus infection might account for in utero transmission with later development of the disorder. Viruses can affect the turnover of neurotransmitters including DA. Incorporation of viruses into the genome (e.g., retroviruses) of germ cells would be compatible with genetic transmission of vulnerability to schizophrenia. Taylor and Crow (1986) found no evidence that DNA sequences from herpes simplex virus type 1 and human cytomegalovirus were incorporated into the DNA of schizophrenics. Epi-
demiological findings, such as increased incidence of schizophrenia in people born in late winter and early spring, have been offered as an argument for a viral etiology. Seasonal variation is found in other polygenic disorders, however, and does not mandate an infectious agent (Murray and Reveley 1983). The evidence for variations in incidence of schizophrenia among different nationalities or within regions, which are not accounted for by genetic factors, is also limited. Evidence for horizontal transmission within families is also weak. Murray and Reveley (1983) argue that there is no proof of a difference in concordance rates among dizygotic twins and siblings, and that the evidence for a difference in the incidence of schizophrenia in same-sex and opposite-sex pairs of dizygotic twins is very weak, thus vitiating an important part of Crow's (1983) argument.

There have been numerous surveys of antibodies to specific viruses in the CSF of schizophrenics. Increased titers to measles, cytomegalovirus (CMV), and herpes simplex virus (HSV) have been noted (King et al. 1985a), but there are no studies showing increasing titers of antibodies during the course of a schizophrenic episode. A recent study of antibodies to eight viruses (measles, mumps, CMV, HSV, varicella zoster virus, adenovirus, rubella, and Epstein-Barr) in 222 schizophrenics showed no significant differences between the schizophrenics and any of the comparison groups, including 143 controls and 60 patients with affective disorders (King et al. 1985a). There was some evidence for neuroleptic-treated schizophrenics to have lower mumps antibody titers. In a companion study, CSF and serum antibodies to all of the above-mentioned viruses, except the Epstein-Barr virus, were measured in 20 chronic schizophrenics and 17 controls. Titers of the mumps antibodies as well as IgG levels were decreased. The CSF/serum ratios showed a reduction in the patients, statistically significant for measles, rubella, mumps, and IgG. However, the effects of medication and institutionalization were not controlled for. It is premature to assume that there is a relative deficiency in the immune response to viruses in schizophrenics. King et al. (1985b) also found no association between enlarged ventricles on CT scan and any of the antibody data, arguing against an association between Type II schizophrenia and viruses.

Interferons are endogenously produced glycoproteins with marked antiviral activity (Kirchner 1984). Interferon levels in serum were not increased in one study (Rimón et al. 1985) but were elevated in the CSF in another study (Libikova et al. 1979). Preble and Torrey (1985) found elevated serum interferon levels in 20/82 psychotic patients, of whom 11 were schizophrenic and 6 schizoaffective by DSM-III criteria. Moises et al. (1985) examined the production of interferon in leukocyte cultures of neuroleptic-treated schizophrenic patients and normal controls. Lymphoproliferation in response to one bacterial recall antigen (PPD) and four mitogens were also studied. Both interferon production and lymphoproliferation were diminished in the schizophrenics in response to some of the challenge tests. It is not clear if the results were influenced by neuroleptic treatment. Interferon administration was reported to have some benefit in an open placebo-controlled trial in four neuroleptic-treated schizophrenics (Cantell et al. 1980), but the results need replication.

Taken together, the evidence for an autoimmune disorder, immunological deficiency, or viral infection as significant factors in the etiology of schizophrenia seems fairly tenuous at this point. Clearly, a small fraction of diagnosable schizophrenia will have a viral and possibly autoimmune basis. However, while the viral hypothesis remains attractive as a means of integrating environmental and inherited factors, the vast majority of cases would not seem likely to be primarily related to any of these mechanisms. Although it is known that an infection of germ cells by viruses can occur, permitting the transfer of viral DNA to later generations in a mendelian fashion, there is no convincing evidence that the genetics of schizophrenia are related to such a mechanism (Murray and Reveley 1983). Rather, it seems more likely that viral infections may be related to sporadic, nonfamilial cases. Neuropathological studies have not provided any evidence of an infectious etiology, but it is not unlikely that neuroleptic effects on immune mechanisms might influence the course of the illness. Further surveys of antibody titers to specific viruses seem unlikely to yield valuable results. As antibodies to specific monoamine receptors are developed, however, it may be of value to quantify them in the sera or CSF of not previously treated schizophrenics.

Biological Markers of Uncertain Significance

Lymphocyte 3H-Spiroperidol Binding. Initial attempts to identify DA receptors in lymphocytes (LeFur, Phan, and Uzan 1980) produced results that could not be replicated. Subsequent improvement in methodology suggests there may be an increase in the number of such bind-
Increased Serum Creatine Kinase Activity. Elevations of creatine kinase (CK) serum activity during acute psychotic phases of schizophrenia and affective disorders have been extensively reported (Meltzer 1976b). The increases are frequently substantial, but attention to possible artifacts such as muscle trauma due to injections or bruising is essential. The major source of CK activity is skeletal muscle. The increased enzyme release is associated with other evidence of neuromuscular abnormalities.

A recent study has reported the presence of the cardiac form of CK activity in a small number of acute schizophrenics (Lockers-Wreton and Vassilopoulos 1985). Whether this represents subtle evidence of cardiac involvement, instability in skeletal muscle CK, or production of cardiac muscle CK by another tissue remains to be determined.

Increased CK activity may be present in patients during remission and in some first degree relatives of schizophrenics (Meltzer, Ross-Stanton, and Schlessinger 1980; Kumar, Upadhyaya, and Trivedi 1984). Recently, Tsoi, Candlisch, and Kuo (1985) reported elevated serum CK activity in 149 chronically institutionalized male schizophrenics compared to normal controls. Seventy-eight (52 percent) exceeded normal levels. Patients with elevated serum CK levels did not differ in psychopathology from those with normal levels, but they were receiving high doses of neuroleptics. While neuroleptics do not affect CK activity, the higher neuroleptic doses may reflect other relevant differences that bear on increased serum CK levels, e.g., increased locomotor activity in 20 schizophrenics and a lesser increase in 20 of their first degree relatives compared to 43 normal controls. The increases were greater in males as we have previously reported. The increase in serum CK activity may represent evidence of increased muscle cell membrane permeability. The possible causes are multiple. In view of the evidence that serum CK activity is genetically regulated (Meltzer et al. 1976), it is possible it might be useful for some genetic marker studies.

Phospholipids and Prostaglandins in Schizophrenia. There have been some attempts to identify membrane lipid pathology in schizophrenia by examining the lipid composition of red cell membranes in schizophrenics and controls. Two early studies reported marked increases in phosphatidyl serine (PS), smaller decreases in phosphatidylcholine and phosphatidylethanolamine, and differing PS/PE ratios (Stevens 1972; Henn 1980). Lautin et al. (1982) found no differences, but these results have been at least partially replicated by others (Sengupta, Datta, and Sengupta 1981; Hitzemann and Garver 1982; Tolbert et al. 1983).

Further study of phospholipid methylation and phospholipid composition in brain and their relation to various membrane-dependant processes and specific enzymes appears indicated. Phospholipid abnormalities, if they occur in brain, might have important effects on neurotransmission.

A series of studies of prostaglandin E (PGE)-stimulated cyclic adenosine monophosphate (cAMP) synthesis in schizophrenia have demonstrated decreased $[^3]H$-cAMP accumulation in schizophrenics (Rotstein et al. 1978, 1980; Garver, Johnson, and Kanter 1982; Kafka and van Kammen 1983). Studies of CSF levels of prostaglandins have not demonstrated any consistent abnormalities (Mathé et al. 1980; Gerner and Merrill 1983; Linnoila et al. 1983).

Summary

There is increasing evidence of both structural and functional abnormalities in schizophrenics. Computed tomography (CT) and magnetic resonance imaging (MRI) have demonstrated structural abnormalities such as enlarged lateral ventricles, enlarged third ventricles, asymmetries, and cortical atrophy. These abnormalities appear to be present from the earliest stages of the illness. Twin studies suggest that the observed structural abnormalities are due to acquired causes rather than to genetic factors. Cerebral atrophy and ventricular enlargement is present in only a small proportion of schizophrenics. There is some evidence suggesting these changes may be most common in patients with negative symptoms, poor response to neuroleptic drugs, and poor outcome. These patients have been called Type II schizophrenics by Crow (1980) and have been linked to viral infections and abnormalities in cholecystokinin (CCK). Type I schizophrenia is associated with positive symptoms (delusions, hallucinations) and good response to neuroleptic treatment; it may be associated with increased numbers of dopamine (DA) receptors. There is, however, considerable evidence favoring a dimensional rather than a categorical conceptualization of the elements en-
increased in schizophrenics. The in-
diminished dopaminergic activity. 
receptors do not appear to be 
and cortical atrophy may have 
thesis. Patients with large ventri-
comprised by the Type I/Type II hy-
ners and D2 receptors interact with 
ence in schizophrenia by virtue of 
may have an effect on 
effect on DA neurons independ-
ner numbers of neurons have been 
 several cortical areas. Frontal 
abnormalities have also been 
schizophrenics with MRI, 
 done in schizophrenia by virtue of 
creased and decreased dopaminergic 
activity may be present in different 
regions of the brain in schizo-
phenics. Serotonin, nor-
epinephrine, and GABA are the 
other neurotransmitters most fre-
linked to schizophrenia.

Neuropeptides such as cho-
lecystokinin, β-endorphin, and 
roretension may have an effect on 
schizophrenia by virtue of their 
effect on DA neurons independ-
ly, but there is no direct evidence for 
a peptide abnormality in schizo-

The evidence for a DA disturb-
ance in schizophrenia remains indi-
irect. There is no evidence for 
creased output of DA based on 
asurement of DA metabolites in 
SF, plasma, or post-mortem sub-
stances. Plasma homovanillic acid 
(HVA) provides some measure of 
brain dopaminergic activity. There is 
no conclusive evidence of its ability to 
 predict neuroleptic response or 
ent of psychopathology. DA au-
toreceptor subsensitivity could ac-
count for increased dopamine 
activity. Endogeneous amphetamine or phenylcyclidine-like substances 
that might have toxic effects on DA 
neurons or alter DA receptor sen-
sitivity have been postulated. Post-
mortem studies indicate increased 
numbers of D3 receptors in the 
striatum and nucleus accumbens of 
some schizophrenics, but the possi-
ble influence of prior neuroleptic 
treatment has not been convincingly 
excluded. Quantitative PET studies 
of DA receptors in schizophrenics 
should be much more informative. 
D3 DA receptors do not appear to be 
increased in schizophrenics. The in-
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An Invitation to Readers

Providing a forum for a lively exchange of ideas ranks high among the Schizophrenia Bulletin's objectives. In the section At Issue, readers are asked to comment on specific controversial subjects that merit wide discussion. But remarks need not be confined to the issues we have identified. At Issue is open to any schizophrenia-related topic that needs airing. It is a place for readers to discuss articles that appear in the Bulletin or elsewhere in the professional literature, to report informally on experiences in the clinic, laboratory, or community, and to share ideas—including those that might seem to be radical notions. We welcome all comments.—The Editors.

Send your remarks to:

At Issue
Schizophrenia Research Branch
National Institute of Mental Health
Alcohol, Drug Abuse, and Mental Health Administration
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Videotapes on Schizophrenia Available

The Video Center of the George Warren Brown School of Social Work, in cooperation with several community and mental health organizations, has produced four videotapes on the following topics relating to survival issues for chronically mentally ill persons and their families in the community.

Coping With a Chronically Mentally Ill Relative in the Community—The two videotapes on this topic were produced in cooperation with the Alliance for the Mentally Ill, St. Louis Chapter. Each videotape presents the experiences of a family which has had some success surviving the multiple problems arising from caring for a mentally ill relative in the community. The videotapes are intended for an audience of parents and relatives of chronically mentally ill persons who could benefit from a vicarious sharing of experiences with the families on the videotapes.

Psychosocial Rehabilitation: Two Agencies Based on the Fountain House Model—These two videotapes were produced in cooperation with the Missouri Department of Mental Health, Independence Center, and Places for People, St. Louis, MO. Each videotape presents a psychosocial rehabilitation agency from the point of view of its members. The tapes are intended for professional audiences as well as for families and mentally ill persons who could benefit from knowing what it’s like to experience psychosocial rehabilitation “from the inside.”

For more information about the rental or purchase of these videotapes, please contact: Dr. David Katz, Video Center, Box 1196, Washington University, St. Louis, MO 63130.
Maryland’s largest community support program for the deinstitutionalised mentally ill, established in collaboration with the Department of Psychiatry of Sinai Hospital.

PEP seeks your assistance in collecting exceptional works of art, painting, sculpture, and craft by persons who have, or have had mental illness. It is our intention to establish a dynamic, national museum center for the exhibition of fine works which express the complexity, power, and beauty of the human spirit.

The art work of many talented individuals with histories of mental illness has too often failed to gain the support and recognition it merits. In addition to evolving a large, quality, non-saleable permanent museum collection through donations, PEP needs help in identifying especially talented artists whose works warrant exhibition in the gallery component. The greater percentage of gallery art sales will go directly to the artist and the rest to help us assist other artists with mental illness to continue their craft.

Initial inquiry should be made by sending photographs of specific pieces. All work will be juried by the PEP Art Advisory Committee for possible inclusion into the museum and/or gallery. Please provide brief biographical information on the artist when possible. Confidentiality wishes will be respected.

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The Walters Art Gallery
Leroy Hoffberger, Art Collector
John B. Imboden, M.D., Chief of Psychiatry, Sinai Hospital
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Fred Lazarus, President,
Maryland Institute College of Art
Karl Metzler, Art Therapist
Amalie Rothschild, Artist

Direct all photographs and questions to:
Rebecca Alban Puharich, Development Director
People Encouraging People, Inc.
The Northwest Plaza
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Baltimore, MD 21215
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