the dopamine hypothesis of schizophrenia: a review*

Herbert Y. Meltzer and Stephen M. Stahl

The predominant biological hypothesis for a neurochemical defect in schizophrenia is currently the so-called "dopamine (DA) hypothesis." In its simplest form, this hypothesis states that schizophrenia may be related to a relative excess of DA-dependent neuronal activity. It is derived from pharmacologic evidence that drugs that decrease DA activity (e.g., the phenothiazines) may be antipsychotic and drugs that promote DA activity (e.g., amphetamine) may be psychotomimetic. The particular means by which "too much dopamine" is produced in schizophrenia is not yet known.

If, as Karl Popper (1959) says, the value of a hypothesis lies not so much in whether it is right or wrong but in its capacity to stimulate attempts to refute it, then the DA hypothesis of schizophrenia has been extraordinarily successful. Indeed, this hypothesis has stimulated a legion of basic and clinical scientists to investigate the anatomy, biochemistry, and function of DA as it might relate to the behavioral characteristics of schizophrenia.

Some of the evidence for the DA hypothesis has been reviewed previously (Klawans, Goetz, and Westheimer 1972, Matthysse 1973 and 1974, Snyder 1972, Snyder, Aghajanian, and Matthysse 1972, and Snyder et al. 1974a). Significant segments of recent symposia on catecholamines or DA are devoted to this topic or are highly relevant (Galne, Chase, and Barbeau 1975, Kety and Matthysse 1972, Usdin 1974, Usdin and Bunney 1975, and Usdin and Snyder 1973).

For the reader's convenience, table 1 lists the abbreviations employed in the text.

Major Dopamine Tracts

DA is not present uniformly throughout the brain, but is localized in a number of discrete pathways that are still being identified and characterized in the brains of laboratory animals as well as in postmortem human brains. There is good evidence from histofluorescent and biochemical studies for at least six distinct DA neuronal tracts: 1) retinal DA fibers, 2) incertohypothalamic DA tract, 3) nigrostriatal DA tract, 4) tubero-infundibular DA tract, 5) mesolimbic DA tract, and 6) mesocortical DA neurons (Lindvall and Bjorklund 1974 and Ungerstedt 1971a). The functional anatomy of these tracts and their possible relation to schizophrenia will now be reviewed. A summary of some properties of the major tracts is given in table 2. A schematic presentation of their location and connections is given in figure 1.
Table 1. Abbreviations employed in the text.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>ACh</td>
<td>acetylcholine</td>
</tr>
<tr>
<td>AMPT</td>
<td>alpha-methyl-para-tyrosine</td>
</tr>
<tr>
<td>cAMP</td>
<td>cyclic adenosine-3',5'-monophosphate</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>COMT</td>
<td>catechol-O-methyl-transferase</td>
</tr>
<tr>
<td>DA</td>
<td>dopamine</td>
</tr>
<tr>
<td>DBH</td>
<td>dopamine-beta-hydroxylase</td>
</tr>
<tr>
<td>DOPAC</td>
<td>dihydroxyphenylacetic acid</td>
</tr>
<tr>
<td>EPS</td>
<td>extrapyramidal symptoms</td>
</tr>
<tr>
<td>GABA</td>
<td>gamma-amino-butyric acid</td>
</tr>
<tr>
<td>5-HIAA</td>
<td>5-hydroxyindoleacetic acid</td>
</tr>
<tr>
<td>5-HT</td>
<td>5-hydroxytryptamine (serotonin)</td>
</tr>
<tr>
<td>HVA</td>
<td>homovanillic acid</td>
</tr>
<tr>
<td>MAO</td>
<td>monoamine oxidase</td>
</tr>
<tr>
<td>MHPG</td>
<td>3-methoxy-4-hydroxy-phenyl glycol</td>
</tr>
<tr>
<td>NE</td>
<td>norepinephrine</td>
</tr>
<tr>
<td>PIF</td>
<td>prolactin inhibitory factor</td>
</tr>
<tr>
<td>PCP</td>
<td>phenylcyclopidine</td>
</tr>
<tr>
<td>6-OHDA</td>
<td>6-hydroxydopamine</td>
</tr>
<tr>
<td>GAD</td>
<td>glutamic acid decarboxylase</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
</tr>
<tr>
<td>VTA</td>
<td>ventral tegmental area</td>
</tr>
<tr>
<td>CPK</td>
<td>creatine phosphokinase</td>
</tr>
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</table>

Nigrostriatal System

The largest and by far most thoroughly investigated DA tract is the nigrostriatal system. The cell bodies for this tract (designated A9 in the rat) are located in the pars compacta of the substantia nigra, a pigmented nucleus in the brain stem. These cells give rise to a large pathway that ascends through the lateral hypothalamus, enters the crus cerebri in mid-hypothalamus to mix with the myelinated bundles of the internal capsule, and then fans out in the globus pallidus, finally terminating in the caudate-putamen of the neostriatum (Ungerstedt 1971a). The neurons in the neostriatum upon which the nigrostriatal DA neurons terminate contain the receptors for DA and are themselves thought to be small interneurons that employ acetylcholine (ACh) as neurotransmitter (McGeer, Grewaal, and McGeer 1974). These cholinergic interneurons may ultimately feed back on the cell bodies of nigral dopaminergic neurons (Bunney and Aghajanian 1975). (See figure 5 on p. 30 for an example.)

The major function of the nigrostriatal DA tract is to regulate the extrapyramidal nervous system in its control of certain motor movements. Stimulation of DA release from these nigral neurons by amphetamine and a direct effect of apomorphine upon these striatal DA receptors are believed to underlie the stereotyped motor behavior that develops in animals given these drugs (Randrup and Munkvard 1970). Degeneration of nigral DA neurons is believed to be the cause of Parkinson's disease (Hornykiewicz 1972 and 1973). Blockade of DA receptors in the neostriatum is thought to be the cause of extrapyramidal side effects (EPS) of neuroleptic drugs—that is, drug-induced parkinsonism (Hornykiewicz 1966 and Klawans 1973a and 1973b).

While it is generally held that the striatum is not involved in producing psychotic symptoms in schizophrenia, Klawans, Goetz, and Westheimer (1972) and Wiesel and Sedvall (1975) have proposed that this region should be considered, along with the mesolimbic region to be discussed subsequently, as the site of the antipsychotic action of the neuroleptic drugs. Crow and Gilbe (1974) have raised the possibility that the cell bodies of the nigrostriatal and mesolimbic DA neurons form a continuous sheet and function as a single unit whose purpose is to promote a variety of goal-directed, appetitive behaviors. Antelman and Szechtman (1975) have found that the nigrostriatal DA system may play an important role in regulating the organism's responsiveness to a wide variety of environmental stimuli. The role of the substantia nigra in certain types of memory has been stressed by Routtenberg and Holzman (1973).

Retinal Dopamine Fibers

The fluorescence histochemical method of Falck et al. (1962) has shown that there are a small number of DA-containing neurons whose cell bodies are found mostly among amacrine cells (Ehringer 1966, Laties and Jacobowitz 1966, and Malmfors 1963). These DA neurons seem to send processes to both the outer and inner plexiform layers of the retina (Ehringer and Falck 1969 and Laties 1972), but the synaptic connections made by these neurons are not known. The function of these retinal DA neurons has not yet been ascertained.

Tubero-Infundibular Dopamine System

The tuberoinfundibular DA tract consists of dopaminergic neurons that have their cell bodies in the
Figure 1. Major dopamine pathways.

arcuate nucleus of the hypothalamus (designated A12 in the rat) and have their terminals in the external layer of the median eminence. The dopaminergic cells of this system have some morphologic characteristics that resemble classical neurosecretory cells (Fuxe and Hokfelt 1966 and Hokfelt 1967). The function of tubero-infundibular dopaminergic neurons is to exert a tonic inhibitory effect on the secretion of prolactin from the posterior lobe of the pituitary gland (Fuxe and Hokfelt 1969 and Hokfelt and Fuxe 1972).

Incertohypothalamic Dopamine Tract

Using the glyoxylic acid histochemical fluorescence method, Bjorklund, Lindvall, and Nobin (1975) recently discovered a weakly fluorescent fiber system with fine, delicate varicosities in the zona incerta, hypothalamus, and caudal septum. This fiber system is basically a set of short, intradiencephalic dopaminergic connections. Although the detailed anatomic organization is not yet known, Bjorklund, Lindvall, and Nobin suggested that
Table 2. Properties of the four major dopamine tracts.

<table>
<thead>
<tr>
<th>Item</th>
<th>Nigrostriatal</th>
<th>Tubero-infundibular</th>
<th>Mesolimbic</th>
<th>Mesocortical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell bodies</td>
<td>Pars compacts of substantia nigra</td>
<td>Arcuate nucleus</td>
<td>Ventral tegmental</td>
<td>? Ventral tegmental area</td>
</tr>
<tr>
<td>Terminals</td>
<td>Caudate nucleus of neostriatum</td>
<td>Median eminence</td>
<td>Nucleus accumbens, olfactory tubercle, and stria terminals of limbic forebrain</td>
<td>Limbic Cortex</td>
</tr>
<tr>
<td>Physiological role</td>
<td>Regulates extrapyramidal motor system</td>
<td>Regulates prolactin secretion</td>
<td>? Regulates behavior, stereotypy</td>
<td>? &quot;Higher functions&quot;</td>
</tr>
<tr>
<td>Effect of receptor</td>
<td>EPS</td>
<td>Prolactin ↑</td>
<td>? Antipsychotic</td>
<td>? Antipsychotic</td>
</tr>
<tr>
<td>blockade</td>
<td>Parkinson's disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect of receptor</td>
<td>? Tardive dyskinesies</td>
<td>Prolactin ↓</td>
<td>? Psychosis stereotypy</td>
<td>? Psychosis</td>
</tr>
<tr>
<td>stimulation</td>
<td>? Huntington's chorea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect of L-dopa/</td>
<td>Reverses EPS, hyperkinesias</td>
<td>Prolactin ↓</td>
<td>? Stereotypy</td>
<td>? Psychosis</td>
</tr>
<tr>
<td>amphetamine</td>
<td></td>
<td></td>
<td>? Psychosis</td>
<td></td>
</tr>
<tr>
<td>Effect of chlorpromazine</td>
<td>EPS</td>
<td>Prolactin ↑</td>
<td>? Antipsychotic</td>
<td>? Antipsychotic</td>
</tr>
<tr>
<td>/haloperidol</td>
<td></td>
<td></td>
<td>Blocks stereotypy</td>
<td></td>
</tr>
<tr>
<td>Effect of thioridazine/</td>
<td>No or few EPS</td>
<td>Prolactin ↑</td>
<td>? Antipsychotic</td>
<td>? Antipsychotic</td>
</tr>
<tr>
<td>clozapine</td>
<td></td>
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<td></td>
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<tr>
<td>neuronal systems</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>? Amphetamine psychosis</td>
<td>? Schizophrenia</td>
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<td></td>
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<td>? Temporal lobe (psychomotor) epilepsy</td>
<td>? Amphetamine psychosis</td>
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<td></td>
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<td></td>
<td></td>
<td>? Temporal lobe (psychomotor) epilepsy</td>
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</tbody>
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the incertohypothalamic DA system has a caudal and a rostral subdivision. The caudal subdivision is believed to arise in DA cell bodies of the posterior hypothalamus and medial zona incerta (designated A11 and A13 in rat) and to project diffusely to the anterior and dorsal hypothalamus, the dorsal part of dorsomedial nucleus, and the zona incerta. The rostral subdivision constitutes a periventricular-preoptic system. Its DA cell bodies are located within and lateral to the periventricular nucleus (designated A14 in the rat) and give rise to periventricular, preoptic, septal, and anterior hypothalamic fibers. The localization of incertohypothalamic fiber projection areas in dorsal and anterior parts of medial hypothalamus strongly suggests an involvement of the incertohypothalamic DA system (along with the tubero-infundibular DA neurons) in neuroendocrine regulation.

**Mesolimbic DA System**

The mesolimbic DA neuronal cell bodies are located dorsal to the interpeduncular nucleus in the ventral tegmental area (VTA) (designated A10 in the rat) and project to terminals just anterior to the head of the caudate nucleus in the nucleus accumbens septi, the bed
nucleus of the stria terminalis, and the deep portion of the olfactory tubercle (Ungerstedt 1971a). These three structures (nucleus accumbens, stria terminalis, and olfactory tubercle) are important elements of limbic forebrain structures. DA terminals have been described in 1) all layers of the olfactory tubercle, 2) the central amygdaloid nucleus, 3) the dorsolateral portion of the interstitial nucleus of the stria terminalis, and 4) areas in the nucleus of the diagonal band (Carlsson et al. 1965, Corrodi et al. 1970, and Fuxe 1965). These areas of the brain and other limbic nuclei are interconnected. The outflow of the limbic striatum is to the septum, hypothalamus, frontal lobe, and other cortical areas (Lewis and Shute 1967 and Wilson 1972). The entire limbic system includes the cingulate and hippocampal gyri, the amygdala, the septal area, and according to Isaacs (1974), the hypothalamus as well because of the extensive interconnections it has to the other areas.

The function of the limbic system has not been completely ascertained. On the basis of lesion and electrical stimulation studies in animals and of human disease, ablation, and stimulation studies, there is circumstantial evidence that the limbic system mediates various autonomic, neuroendocrine, memory, learning, affective, and behavioral functions (Adey and Tokizane 1967, Bargmann and Schadé 1963, Isaacs 1974, Lichtensteiger and Keller 1974, MacLean 1952, and Pincus and Tucker 1974). Recent evidence suggests that the mesolimbic DA system is also important in controlling and mediating the stereotyped motor behavior that develops in rats after treatment with apomorphine or amphetamine. (This phenomenon is discussed in greater detail in the section on dopamine and behavior.)

The mesolimbic tract has been suggested as the relevant dopaminergic tract for amphetamine psychosis (Snyder 1972) (see the section on dopamine release and amphetamine psychosis for further discussion). As Snyder, Aghajanian, and Matthysse (1972), Stevens (1973), and Torrey and Peterson (1974) have recently reviewed the evidence that the mesolimbic DA system may be the DA tract involved in schizophrenia, this evidence will only be briefly cited here. Impairment of the ability to filter out multiple stimuli and disturbances in behavior and affect may be the result of lesions of the limbic system in animals and are important aspects of some types of schizophrenia (Smythies and Adye 1966). Electrical stimulation of the dorsal hippocampus (part of the outflow of the limbic striatum) has been reported to produce disturbances in thinking and hallucinations (Horowitz and Adams 1970). Other changes produced by stimulation or ablation of the limbic system in humans include paranoia, depersonalization, perceptual distortion, catatoniclike illness, and disturbances of mood and emotion (Torrey and Peterson 1974). In a study of 18 patients with intracranial neoplasms affecting limbic structures, Melamud (1967) found that all had been originally diagnosed as having a psychiatric disorder and that 10 had been thought to be schizophrenic. It is well known that prominent behavioral symptoms are often the presenting complaint of patients with subacute and chronic forms of viral encephalitis. This is particularly true of viral infections involving the temporal lobe (Brierley et al. 1960, Drachman and Adams 1962, Glaser and Pincus 1969, and Himmelhoch et al. 1970).

Another intriguing finding linking schizophrenia to pathology of the limbic system is the relationship between seizure disorders and psychosis. Some clinical manifestations of psychomotor epilepsy (believed to be predominantly a temporal lobe disorder) are reminiscent of the symptoms of psychosis: subjective feelings of forced, repetitive, and disturbing thoughts; alterations of mood; sensations of impending disaster and anxiety; 

déjà vu, jamais vu; episodes of depersonalization; dreamlike states; visual and auditory distortions; and olfactory and gustatory hallucinations (Pincus and Tucker 1974). Gibbs (1951) found that psychiatric disorders were three times more common in patients with anterior temporal seizure foci than those with seizure foci located elsewhere in the brain.

**Mesocortical DA System**

The presence of cortical DA fibers was first demonstrated by Thierry et al. (1973). After destruction of the ascending norepinephrine (NE) pathways, these investigators still observed the presence of an appreciable amount of DA and a persistent synthesis of DA in synaptosomes from rat cortex, while the synthesis of NE was completely abolished. Thierry et al. (1974) further characterized the uptake of catecholamines in the cerebral cortex as sensitive both to benztpine (inhibitor of the dopaminergic pump) and to desipramine (inhibitor of the noradrenergic pump), whereas the cerebellum (noradrenergic area) was sensitive only to desipramine and the caudate nucleus (dopaminergic area) only to benztropine. These investigators inter-
subcortical areas. Recording of the electrical activity of these regions in schizophrenics might also be of great value, but it is difficult to conceive of situations in which such data could be obtained ethically.

The purpose of this section is to highlight some of the recent findings that drugs causing the stimulation of DA receptors (e.g., amphetamine, L-dopa, and apomorphine) all induce or enhance stereotyped behavior, whereas drugs that block DA receptors (phenothiazines, haloperidol) inhibit amphetamine-induced stereotypy (Randrup and Munkvard 1968). A series of recent anatomical studies has provided evidence that the nigrostriatal and mesolimbic dopaminergic tracts are important in stereotypy (see Creese and Iversen 1975 for references and discussion).

Another form of animal behavior for which there is a prominent dopaminergic influence is the rotational behavior of rats that develops after unilateral destruction of the nigrostriatal DA system. Ungerstedt (1971b) has demonstrated that these animals rotate away from the side of stimulation of striatal DA receptors. If these rats are given a DA-releasing drug such as amphetamine, DA receptors are stimulated only on the side of the brain where DA neurons remain. This causes vigorous rotation of the animal toward the lesioned side (i.e., away from its stimulated DA receptors). If a rat with a unilateral substantia nigra lesion is given a DA-receptor-stimulating drug (e.g., L-dopa or apomorphine), the animal again shows strong circling movements, but in the opposite direction from those caused by amphetamine. These results have been interpreted to mean that DA receptor

Dopamine and Behavior

The preceding discussion of DA tracts primarily focused on their anatomy, what little is known of their function in man, and their possible role in schizophrenia. The purpose of this section is to highlight some of the major behavioral functions in animals that are believed to be, at least in part, under dopaminergic control.
stimulants affect the lesioned side's striatal DA receptors more than the nonlesioned side's receptors. Ungerstedt has suggested, therefore, that this preferential stimulation of the lesioned side is due to a supersensitivity of the denervated DA receptors that develops after degeneration of the nigrostriatal DA system. Rotational behavior in rats with unilateral destruction of the nigrostriatal DA system has thus been proposed as a model for denervation supersensitivity of DA receptors (see pp. 47-48). This behavior may also serve as an animal model for Parkinson's disease. Recent studies (Andén and Bédard 1971 and Costall and Naylor 1974) have established that turning behavior may also be influenced by neurotransmitters other than DA (e.g., serotonin—see p. 46).

In a series of investigations based on the selective depletion of NE or DA by varying the conditions of administration of the neurotoxic agent 6-hydroxydopamine (6-OHDA) to rats, Breese, Cooper, Grant, and their collaborators provided evidence for the importance of DA for normal growth and development, active avoidance responding, consummatory behavior, and food-reinforced operant responding (see Breese, Cooper, and Hollister 1974 for references). In a study based on neuroleptic blockade of food and water intake, Zis and Fibiger (1975) found that DA is important to consummatory behavior in rats and that the lateral hypothalamic syndrome in rats is the result of damage to the nigrostriatal system. The report by Antelman and Szechtman (1975) that nigrostriatal ablation with 6-OHDA abolishes eating, gnawing, or licking behavior in rats may be related to these studies. Rolls et al. (1974) proposed that the effect of neuroleptics on self-stimulation, eating, and drinking is due to an interference with volitional motor behavior but not to simple motor incapacitation.

Schechter and Cook (1975) found that a rat's ability to differentiate between d-amphetamine and saline in a state-dependent task (shock avoidance) depended on the catecholamine DA rather than the catecholamine NE because it was blocked by alpha-methyl-para-tyrosine (AMPT) and haloperidol but not by a dopamine-beta-hydroxylase inhibitor or by alpha- or beta-adrenergic blockers. (For a rationale, see the section on synthetic pathways.)

The acoustic startle response in rats may be mediated by DA (Davis, Svensson, and Aghajanian 1973), but this conclusion is based largely on studies with d- and l-amphetamine, a method whose validity is questionable (see the section on dopamine release and amphetamine psychosis).

Crow and Gilbe (1974), in their discussion of the role of DA in behavior, attempt to formulate a synthetic concept of the role of dopaminergic mechanisms in overall behavioral control. First, DA mechanisms facilitate motor behavior; second, the behaviors promoted are "appetitive" in that they seek out food; and, finally, these mechanisms are "rewarding" insofar as self-stimulation experiments may be interpreted in this way. They then discuss how this view of the function of DA pathways can be reconciled with the hypothesis of increased DA in schizophrenia. They describe schizophrenia as usually characterized by decreased activity, lack of drive, and lack of pleasure. To reconcile this description with the three principles of DA function mentioned above, Crow and Gilbe postulate that the schizophrenic syndrome might be thought of as an increase of stereotypic, nonadaptive motor activity directed toward goals that give no pleasure.

While such attempts to relate the hypothesis of an increase in DA activity to specific DA-mediated behaviors in animals are important, it must be realized that they are proceeding from virtually complete ignorance of DA function in man, except for the motor functions that relate to the nigrostriatal system. In relating DA hyperactivity to schizophrenia, Crow and Gilbe (1974) described behaviors that are largely nigrostriatal except for self-stimulation, which can be supported by mesolimbic system areas (for discussion, see Lieberman and Butcher 1974 and Stein et al. 1974). As stated previously, the DA hypothesis of schizophrenia rests mainly on our understanding of the mechanism of action of 1) neuroleptic drugs, 2) amphetamine as it produces amphetamine psychosis, and 3) other pharmacologic studies in man and laboratory animals. Until our understanding of all DA systems is increased, it is in these three areas, which will now be reviewed, that we must look for clues to the etiology of schizophrenia in relation to DA.

**Pharmacology of Dopamine**

It should be apparent from the preceding discussion that if schizophrenia is associated with a relative hyperactivity of some DA neurons, the mesolimbic, mesocortical, and perhaps nigrostriatal tracts are the
most likely candidates to have initiated the perceptual, cognitive, and affective disturbances characterizing this group of disorders. Hyperactivity of all tracts might be present, of course, but there is now some evidence that this is not the case.

In the sections that follow, we review the basic mechanisms of synthesis, catabolism, and regulation of DA chemistry and also the effects of selected psychotomimetic and antipsychotic drugs affecting DA metabolism. Following the basic research section, clinical studies are related to these basic concepts, and data relevant to the equivalent of increased DA activity either as a precursor or concomitant of schizophrenia are reviewed.

**Synthetic Pathways**

DA synthesis begins with the amino acid tyrosine, which must be actively transported into DA neurons and then hydroxylated to form L-dopa by tyrosine hydroxylase (figure 2). Plasma tyrosine is the usual precursor. The hydroxylation of tyrosine is the usual rate-limiting step for DA synthesis (Levitt et al. 1965) and a key control point at which the DA neuron regulates the amount and availability of its neurotransmitter DA. This regulation is necessary if the DA neuron is to adjust the synthesis of its neurotransmitter to respond to alterations in DA storage, release, metabolism, or impulse flow induced by functional demands or drugs. Certain amino acid analogs of tyrosine including alpha-methyl-para-tyrosine (AMPT) inhibit the enzyme tyrosine hydroxylase and cause marked depletions of the catecholamines DA and NE (Spector, Sjoerdsma, and Udenfriend 1965). Tetrahydrobiopterin, a cofactor for the activity of tyrosine hydroxylase, is usually present in excess but, under certain conditions, could become rate limiting (Musacchio and D'Angelo 1971).

The hydroxylation of tyrosine is followed by a rapid decarboxylation of L-dopa to form DA via dopa decarboxylase (figure 2). Plasma tyrosine is the usual precursor. The hydroxylation of tyrosine is the usual rate-limiting step for DA synthesis (Levitt et al. 1965) and a key control point at which the DA neuron regulates the amount and availability of its neurotransmitter DA. This regulation is necessary if the DA neuron is to adjust the synthesis of its neurotransmitter to respond to alterations in DA storage, release, metabolism, or impulse flow induced by functional demands or drugs. Certain amino acid analogs of tyrosine including alpha-methyl-para-tyrosine (AMPT) inhibit the enzyme tyrosine hydroxylase and cause marked depletions of the catecholamines DA and NE (Spector, Sjoerdsma, and Udenfriend 1965). Tetrahydrobiopterin, a cofactor for the activity of tyrosine hydroxylase, is usually present in excess but, under certain conditions, could become rate limiting (Musacchio and D'Angelo 1971).

The hydroxylation of tyrosine is followed by a rapid decarboxylation of L-dopa to form DA via dopa decarboxylase (figure 2). This enzyme is present in relative excess and can be markedly inhibited by drugs such as NSD-1015, MK-486, and R04-4602 without affecting the levels of brain catecholamines (Carlsson et al. 1972a). On the other hand, marked elevations in brain DA and small, variable changes in brain NE can occur after peripheral administration of L-dopa, which crosses the blood-brain barrier and is then rapidly decarboxylated to DA (Chalmers, Baldessarini, and Wurtman 1971, Everett and Borschdering 1970, and Narotsky et al. 1973).

In neurons that employ NE as a neurotransmitter, this sequence of reactions is followed by hydroxylation of DA at the beta carbon by dopamine-beta-hydroxylase (DBH), which is contained within and bound to the inside of the vesicle membrane, to form NE (figure 2). Dopa decarboxylase is a cytoplasmic enzyme, so DA must be transported to the amine storage granules before it can be converted to NE. Synthesis of NE but not DA can be blocked by drugs such as fusaric acid and disulfiram that inhibit DBH (figure 2) (Goldstein 1966 and Nagatsu et al. 1970). In DA neurons, however, DBH is absent so that DA, once synthesized, is either stored within synaptic vesicles, metabolized intraneuronally by monoamine oxidase (MAO), or released and metabolized extraneuronally by catechol-O-methyl transferase (COMT) and MAO.

**Regulation of Dopamine Synthesis and Other Neuronal Activities**

One of the most important strides in our understanding of the DA neuron has been an appreciation that it is a dynamic unit, constantly adjusting mutually interregulatory forces in a synchronized fashion to express its functional activity in the form of nerve impulses (see figure 3). Since these homeostatic forces are largely directed at maintaining a stable level of DA, it is obvious that absolute tissue levels of DA are a relatively insensitive index of neuronal function because the steady-state levels of DA will change only when the neuron can no longer compensate for the influences that play upon it. The measurement of "turnover" or flux of DA through the competing processes of storage, release, and metabolism, therefore, has provided much more information. However, even this refinement does not always correlate well with function since an alteration in DA turnover does not necessarily indicate an alteration in nerve impulse flow (for discussion, see Cooper, Bloom, and Roth 1974, Ch. 6). Ultimately, one wishes to know how each individual regulatory mechanism contributes to changes in impulse flow as well as how changes in impulse flow feed back upon individual regulatory mechanisms.

Control of tyrosine hydroxylase, the usual rate-limiting enzyme for catecholamine synthesis, best illustrates the complex interrelationship between nerve impulse activity...
Figure 2. Synthesis of catecholamines.

Flow and DA regulation. Both DA and NE, end products of tyrosine hydroxylase activity, can directly inhibit tyrosine hydroxylase by competing with enzyme cofactors to produce an end product feedback inhibition (figure 4) (Nagatsu, Levitt, and Udenfriend 1964, Neff and Costa 1966, and Spector et al. 1967). Through such a mechanism, increased release of DA from neurons during repetitive firing could release tyrosine hydroxylase from feedback inhibition and thus lead to increased DA synthesis (Costa, Guidotti, and Zivkovic 1974). The physiologic importance of this mechanism has been disputed (Carlsson, Kehr, and Lindqvist 1974), but it remains theoretically possible. Prolonged release of catecholamines (for at least 24 hours), as in chronic stress situations, stimulates the synthesis of additional tyrosine hydroxylase molecules (Mueller, Thoenen, and Axelrod 1969), which in turn increases the synthesis of the catecholamines DA and NE. Although this mechanism of increasing catecholamine synthesis has been demonstrated in the peripheral sympathetic nervous system, long-term changes in tyrosine hydroxylase synthesis in brain are delayed in onset and are much smaller in magnitude (Besson et al. 1973 and Musacchio et al. 1969). There is some evidence that cyclic adenosine monophosphate (cAMP), nerve growth factor, and hormones such as corticosteroids can influence the synthesis of tyrosine hydroxylase, dopamine-beta-hydroxylase (DBH), and phenylethanolamine N-methyltransferase in peripheral adrenergic neurons and in the adrenal gland (see Molinoff 1974 for references); however, there is as yet no evidence that these factors affect tyrosine hydroxylase in central dopaminergic neurons.

In addition to end product feedback regulation, there are possibly two other forms of feedback regulation: 1) short-loop feedback via presynaptic DA receptors...
Figure 3. Schematic model of dopamine synapse.¹

¹ 1=tyrosine uptake, 2=tyrosine hydroxylase, 3=dopa decarboxylase, 4=monoamine oxidase, 5=aldehyde dehydrogenase, 6=storage in synaptic vesicles, 7=release, 8=neuronal reuptake, 9=catechol-O-methyl transferase, 10=interaction with receptors, 11=stimulation of adenylate cyclase, 12=phosphodiesterase, 13=protein kinase activation, 14=membrane phosphorylation, DA=dopamine, O-Me-DA=O-methyl-dopamine, DOPAC=dihydroxyphenylacetic acid, HVA=homovanillic acid, cAMP=cyclic adenosine monophosphate.
(figure 4) and 2) long-loop feedback mediated via postsynaptic receptors and a neuronal loop impinging back on the dopaminergic cell bodies (figure 5). The short-loop concept (Aghajanian and Bunney 1974, Carlsson, Kehr, and Lindqvist 1974, Kehr et al. 1972, and Roth, Walters, and Morgenroth 1974) proposes that dopaminergic neurons are also dopaminoceptive in that they contain presynaptic DA receptors that can sense the amount of DA being released by the neurons (see figure 4). When they detect a lack of DA release due to decreased impulse flow, intracellular DA levels rise, possibly because tyrosine hydroxylase is in a kinetic form not inhibited by high concentrations of DA (e.g., tyrosine hydroxylase-B in figure 4) (Roth, Walters, and Morgenroth 1974). Presynaptic DA receptors may thus regulate the kinetic forms of tyrosine hydroxylase by
altering the permeability of the presynaptic membrane to calcium (Roth, Walters, and Morgenroth 1974). Alternatively, the presynaptic DA receptor may be an adenylate cyclase, which controls phosphorylation of tyrosine hydroxylase to different kinetic forms (figure 4). These events would presumably be directed at making more DA available for release when impulse flow is decreased and making less DA available for release when impulse flow is increased. An interesting characteristic of the presynaptic DA receptors is that when apomorphine (a DA agonist) is directly applied by microiontophoresis to DA neurons in the rat substantia nigra, it has a powerful inhibitory effect on their firing rate (Aghajanian and Bunney 1973). This finding is consistent with that of Kehr et al. (1972), who reported that apomorphine does not require an intact striatonigral pathway to inhibit DA synthesis. Both effects are presumably mediated by apomorphine on presynaptic DA receptors. When chlorpromazine or haloperidol is applied directly to these same neurons, however, it has no direct effect on their firing rate and does not block the inhibitory effect of DA on firing rate (Aghajanian and Bunney 1973 and Bunney et al. 1973). At any rate, the short loop is a new and complex concept that must
undergo considerable testing and revision before it can be accepted.

The long-loop feedback mechanism (figure 5) proposes that the postsynaptic DA receptor is also able to detect the presence of released DA and to feed this information back to the presynaptic neuron (Carlsson 1971, Carlsson, Kehr, and Lindqvist 1974, and Carlsson and Lindqvist 1963). The information may be fed back via a multisynaptic neuronal loop employing in certain cases gamma-amino-butyric acid (GABA) (Kim et al. 1971, McGeer et al. 1973a, and Precht and Yoshida 1971) and/or ACh (Javoy et al. 1974 and Oliver et al. 1970) as neurotransmitters (see figure 5). Accordingly, when postsynaptic DA receptors are blocked by drugs, this signal is fed back to the presynaptic neuron and more DA is released in an attempt to overcome the blockade. These postsynaptic receptors also seem to adapt the sensitivity of their response according to the availability of DA. That is, in the presence of excess DA, the postsynaptic receptors may become hyposensitive to DA, and in the absence of DA, they may become supersensitive to it (for review, see Calne, Chase, and Barbeau 1975). (These changes in postsynaptic receptor sensitivities are discussed in greater detail on pp. 47-48.)

**Dopamine Turnover and Stress**

The role of stress in the pathogenesis of the acute psychotic state in schizophrenia is generally accepted and has been discussed in relation to a biological basis of schizophrenia by Pollin (1972) and Strahilevitz (1974). It is well established that stress increases the turnover of brain noradrenaline, serotonin, and histamine. The effect of stress on DA turnover in mice or rats, however, is not so clear.

Intense muscular exercise and cold exposure did not affect the synthesis of DA (Gordon et al. 1966). Thierry et al. (1968) found no effect of electric shocks to the feet on the disappearance of $^3$H-DA from the striatum. Corrodi et al. (1971) found that restraint stress decreased disappearance of whole brain DA from AMPT-treated rats, suggesting that stress decreases DA turnover. They also reported that stress decreased DA turnover in the hypothalamus as indicated by fluorescence disappearance. This finding was attributed to a decrease in impulse flow in DA neurons. On the other hand, Bliss and Ailon (1971) and Brown, Snider, and Carlsson (1974) reported an increase in the turnover of DA in mice subjected to foot shocks or grid shocks. While the reason for the discrepancies may be intensity of stress and species variations, it is of interest that acute revolving-drum stress had no effect on DA turnover in mice, although it markedly raised DA levels. Drum stress markedly increased DA turnover, however, in mice that had been given several daily exposures to this type of stress and had become more tolerant to what would be lethal amounts of this stress in naive animals (Goldberg and Salama 1972). This fact points out that previous exposure to stress can affect DA turnover in response to additional stress in mice. It is tempting to speculate that the same process occurs in man, and that in schizophrenics it is even more marked—that is, that DA turnover is greatly accelerated with recurrent stress. This does not appear to be the case with neostriatal DA as evidenced by the lack of increase in cerebrospinal fluid homovanillic acid in acute schizophrenics (see pp. 49-52), but it might be the case in other brain areas.

**Dopamine Storage**

DA is stored in a physiologically inactive form within synaptic vesicles as a chelate with adenosine triphosphate and magnesium. These vesicles serve the dual purposes of protecting DA from intracellular deamination by MAO and storing extra DA for subsequent release during nerve impulse transmission. Thus, it is theoretically possible that a deficit in the storage of DA in vesicles might contribute to the pathogenesis of at least some cases of schizophrenia. There is as yet no experimental evidence for or against this hypothesis.

Reserpine and tetrabenazine block vesicular storage of NE and DA and therefore cause catecholamine depletion due to increased deamination of the unbound amines by MAO (Carlsson et al. 1957 and Holzbauer and Vogt 1956). If schizophrenia is associated with excessive DA activity, one might expect blockers of amine storage such as reserpine to have antipsychotic efficacy. In summarizing the results of 29 double-blind clinical trials of the antipsychotic action of reserpine, Davis and Cole (1975) listed 20 studies that found reserpine to be more effective than placebo and 9 studies that found it to be only equally effective as placebo. The high incidence of extrapyramidal side effects and depression at the doses.
needed for antipsychotic effects limits the therapeutic utility of reserpine.

Studies of Dopamine Synthesis and Regulation in Schizophrenia

Tyrosine Hydroxylase Inhibition

As previously mentioned, AMPT inhibits tyrosine hydroxylase, the usual rate-limiting step in the synthesis of DA and NE (Spector, Sjoerdasma, and Udenfriend 1965). If schizophrenia is associated with excessive DA activity, inhibition of DA synthesis by AMPT might be clinically effective in schizophrenia. Gershon et al. (1967) treated 10 acute paranoid schizophrenics and 3 chronic undifferentiated schizophrenics, free of all other drugs, with doses of 800-2,000 milligrams (mg) AMPT per day for periods of 1 day to 8 weeks. Two patients improved, five did not change, and two became more psychotic. Levels of NE and two of its metabolites did decrease in the urine of three patients, suggesting that tyrosine hydroxylase inhibition had occurred, at least peripherally. The effects of AMPT on 15 chronic schizophrenics (type unspecified), off all other drugs for 10 days, in doses of 2 grams (g) per day for 33-43 days were also studied by Charalampous and Brown (1967). A slight sedative effect was noted in most subjects, but no significant improvement occurred. Nine of the 15 subjects became progressively worse. A decrease in catecholamine metabolites in urine was noted. It is possible that the inhibition of tyrosine hydroxylase achieved by these dose levels did not interfere with DA synthesis to an extent sufficient to produce an interference with dopaminergic transmission.

Carlsson et al. (1972b) reported that five chronic schizophrenic patients with stable symptomatology could be maintained on lower doses of neuroleptics after adding up to 2 g/day of AMPT. Stopping the AMPT produced an exacerbation of their psychosis. Carlsson et al. (1973) replicated this finding in six other chronic schizophrenic patients. AMPT produced a 70-90 percent decrease in spinal fluid homovanillic acid (HVA) levels in all but one case, indicating a marked inhibition of tyrosine hydroxylase. The fact that AMPT potentiated the antipsychotic effect of neuroleptics is consistent with the hypothesis of excessive DA as a factor in schizophrenia.

The explanation for the lack of an antipsychotic effect of AMPT by itself may be that inadequate inhibition of tyrosine hydroxylase was achieved. The chronic administration of phenothiazines probably leads to increased DA synthesis because of the feedback loops previously described (Fyro, Nyback, and Sedvall 1972). The addition of AMPT to a neuroleptic regimen could produce sufficient diminution of DA synthesis to synergize with the DA-blocking properties of the neuroleptics, leading to an enhanced antipsychotic effect (Carlsson et al. 1973).

AMPT tends to produce crystalluria and is too toxic for routine clinical use. If other inhibitors of tyrosine hydroxylase with much less toxicity could be developed, they should be tested as antipsychotic agents with and without neuroleptic treatment. If the preliminary findings of Carlsson et al. (1973) are confirmed, such inhibitors might be quite useful in the treatment of schizophrenia by permitting a reduction in neuroleptic dosage.

Effects of L-dopa in Schizophrenia

One means of determining the effects of increased central dopaminergic activity on behavior is to administer large doses of the DA precursor, L-dopa. L-dopa is also the precursor of NE, but peripheral administration of L-dopa causes only small and variable changes in brain NE levels (Chalmers, Baldessarini, and Wurtman 1971, Everett and Borscherding 1970, and Narotsky et al. 1973). Although the predominant central effect of L-dopa is to increase brain DA levels, several other biochemical changes can also result, including decreases in brain serotonin levels, competition with tryptophan for transport into brain, and displacement of other endogenous amines such as NE and serotonin (for a review, see Carlsson 1971). These several biochemical changes must be kept in mind when attempting to explain the behavioral effects of L-dopa administration.

The mental effects of L-dopa in parkinsonian, normal, and depressed patients, as well as the behavioral effects of L-dopa in animals, have been reviewed by Murphy (1973) and will not be extensively dealt with here. Briefly, the average incidence of specific psychiatric problems after L-dopa treatment in parkinsonian patients is approximately 15 percent, of which one-fifth to one-third may have some psychotic features, mainly of an organic character, but also with paranoid ideation.
and auditory hallucinations that are indistinguishable from those in some schizophrenic patients. L-dopa was noted to produce an intensification of psychotic symptomatology in six patients who were primarily depressed, but who also had previously documented or concomitantly present psychotic symptoms (Goodwin 1972 and Goodwin et al. 1971). Normals and patients with narcolepsy, impotency, or migraine did not suffer adverse behavioral effects after L-dopa.

There are several reported studies of the effects of administration of high doses of L-dopa to schizophrenic patients. Yaryura-Tobias, Diamond, and Merlis (1970) and Yaryura-Tobias et al. (1970) administered relatively low doses of L-dopa (2-3 g/day) to nine chronic schizophrenic patients who were also receiving neuroleptics. Seven of the nine patients developed an exacerbation of their psychosis, including increased paranoia and auditory hallucinations. Since the neuroleptics might be expected to block the effects of the DA produced from L-dopa, this reaction may be an indication of the schizophrenics' increased sensitivity to DA, or possibly that the L-dopa-induced exacerbation of the psychosis is mediated by non-DA mechanisms. Angrist, Sathananthan, and Gershon (1973) administered 3-6 g of L-dopa per day for a mean of 21 days to 10 chronic schizophrenic patients who had been on neuroleptics for an unspecified period of time and who were then placed on a placebo for 5-10 days before beginning L-dopa. All patients were mildly to severely symptomatic prior to L-dopa treatment. Seven of the 10 patients showed a worsening of preexisting psychotic symptomatology. All 10 patients showed signs of stimulation of motor activity. After discontinuing L-dopa, the patients returned to baseline functioning; however, some required neuroleptic treatment in order to do so. The authors discuss the possibility that the exacerbation of psychosis by L-dopa could be due either to a nonspecific mental activation or to a specific dopaminergic stimulation. In a later report, Sathananthan, Angrist, and Gershon (1973) proposed that L-dopa was likely to have a specific dopaminergic effect in schizophrenics. The interpretation of this latter study is clouded by the fact that their patients had recently received neuroleptic drugs that could have made dopaminergic receptors supersensitive to the effects of DA produced from L-dopa. Thus, it is not yet possible to conclude from the last two studies that schizophrenics are more susceptible to specific dopaminergic activation than patients with other types of psychiatric illness. This type of study, however, is potentially most informative and should be repeated in a variety of unmedicated schizophrenic patients, psychiatric controls, and normal controls with appropriate attention to informed consent and subject well-being.

There is a group of Japanese studies on the effects of administration of low doses of L-dopa to schizophrenics concomitantly receiving phenothiazines that have not been previously reviewed in the Western literature. Kawamura et al. (1971), Inanaga et al. (1971 and 1972), Nishikawa, Higasayama, and Kasahara (1972), Yamuchi (1972), Asano et al. (1973), Sarai et al. (1973), Ogura et al. (1974), and Otsuka et al. (1974) reported the results of uncontrolled, open studies in which doses of 300-1,000 mg/day of L-dopa produced additional improvement in about 50 percent of schizophrenics treated with phenothiazines. This finding was replicated in a double-blind controlled study of 104 schizophrenic patients (Inanaga et al. 1975). According to these investigators, 200-600 mg of L-dopa produced fair to excellent improvement in 26 of 52 patients (50 percent) whose neuroleptic treatment was supplemented with L-dopa, whereas fair to moderate improvement (no instances of excellent improvement) occurred in 19 of 52 patients (36 percent) who were supplemented with a placebo. The differences were statistically significant. Benefit was greatest in patients ill for less than 5 years who had symptoms of loss of spontaneity, abulia, apathy, and autism. Treatment lasted for 8 weeks. Some patients relapsed after the L-dopa was discontinued. The authors proposed that the improvement with L-dopa might be understood in terms of Wise and Stein's (1971) theory (see the section on 6-hydroxydopamine-induced damage of the noradrenergic reward system) that schizophrenics are deficient in brain DBH and hence NE. Presumably, the L-dopa was able to promote the synthesis of NE. However, as has been indicated, there is evidence that L-dopa is a poor precursor of brain NE.

These studies must be replicated by other investigators before the finding that L-dopa in low doses is beneficial to a subgroup of schizophrenics receiving neuroleptics is accepted. Even if this is so, it would not constitute a serious challenge to the hypothesis of increased dopaminergic activity in schizophrenia. It could be that the small doses of L-dopa in these patients are countereacting the effects of inhibition of dopaminergic activity by the neuroleptics in DA tracts (e.g., the nigrostriatal) that are not related to the pathogenesis.
of the psychosis. If disabling EPS are diminished by low doses of L-dopa, without overcoming a blockade of mesolimbic DA receptors, patients might indeed experience an increased sense of well-being. Alternatively, low doses of dopamine agonists (i.e., L-dopa, apomorphine) may preferentially stimulate presynaptic DA receptors important in short-loop feedback inhibition of DA synthesis, thus decreasing DA synthesis and subsequent effects at postsynaptic sites. This theory has been proposed as the basis for the beneficial effects of low-dose apomorphine in treating mania (Post et al. 1976).

Dopa Decarboxylase Inhibition

The administration of alpha-methyldopa in high doses leads to a marked depletion of NE, DA, and serotonin in brain (Carlsson and Lindqvist 1962, Hess et al. 1961, Kopin 1968, and Stone and Porter 1966). Part of the difficulty in predicting the antipsychotic effects of this drug is due to limited understanding of the biochemical mechanism of its amine-depleting effects. Two different hypotheses have been proposed to account for its depletion of brain DA and NE. First, it has been suggested that alpha-methyldopa is itself decarboxylated to alpha-methyldopamine, which is then bound to the storage sites for endogenous amines. This would displace the endogenous amines and cause their subsequent breakdown and depletion (Dorris and Shore 1971a and 1971b). The evidence for this mechanism of amine depletion in brain is largely indirect and is based on analogy with the peripheral sympathetic nervous system (Kopin 1968 and Stone and Porter 1966).

A second hypothesis is that the decrease in brain catecholamines after alpha-methyldopa is due to a reduction in catecholamine biosynthesis (Dominic and Moore 1971). Although alpha-methyldopa is a competitive inhibitor of dopa decarboxylase, it is assumed that inhibition of this enzyme cannot explain the decrease in brain catecholamines, since more potent inhibitors of dopa decarboxylase do not produce the same extent or duration of decrease in brain amines (Brodie et al. 1962). Uretsky (1974) has recently provided further evidence for the importance of decreased DA synthesis, perhaps by inhibition of tyrosine hydroxylase, rather than impaired DA storage as the mechanism of DA depletion from rat striatum after alpha-methyldopa (Uretsky 1974 and Uretsky, Chase, and Lorenzo 1975).

Whatever the mechanism of decreased catecholamine levels after alpha-methyldopa, administration of this drug to schizophrenics might be expected to exert an antipsychotic effect due to a decrease in DA activity. Alpha-methyldopa by itself has been shown to have only an occasional beneficial effect in the treatment of schizophrenia and not infrequently causes a worsening (Heckert and Keup 1969, Pecknold et al. 1972, Sourses, Murphy, and Chavey-Lara 1962, and St. Jean, Donald, and Ban 1963). Chouinard et al. (1973) found, however, in an uncontrolled study, that alpha-methyldopa plus chlorpromazine produced significant improvement in 8 of 10 chronic schizophrenic patients (type of schizophrenia and diagnostic criteria not clearly stated) who had not previously responded to antipsychotic medication. A more rigorous study of the clinical potential of this combination was reported to be underway.

The failure of alpha-methyldopa to be clinically effective by itself may be due to inadequate depletion of DA by the doses of alpha-methyldopa employed, or to other biochemical effects of this drug. It depletes NE more than DA and also depletes 5-hydroxytryptamine (5-HT). Nevertheless, potentiation of antipsychotic effects of neuroleptics by alpha-methyldopa is consistent with the hypothesis of excessive DA activity in schizophrenia.

Decarboxylation of L-dopa by Erythrocytes in Schizophrenia

Tran, Laplante, and Lebel (1971) studied the rate of decarboxylation of radio-labeled L-dopa by erythrocytes in nine schizophrenics and seven normals. No specific criteria for schizophrenia were cited. Eight of the schizophrenics had received phenothiazines prior to the study. Five patients who were hallucinating and had thought disorders had a significantly more rapid, sustained decarboxylation of 14C-dopa than the four schizophrenics who were in remission or the seven controls. The possibility of a phenothiazine effect on dopa decarboxylase activity could not be ruled out. This is an interesting study that should be replicated and extended to include multiple determinations on the same patient. It would be of interest to study the effects of a decarboxylase inhibitor on the erythrocyte enzyme from schizophrenics.

We have previously pointed out that dopa decarbox-
ylose is already present in great excess in rat brain in relation to tyrosine hydroxylase, which is rate limiting in the synthesis of DA. It is unlikely, therefore, that increased dopa decarboxylase activity could account for increased DA activity in schizophrenia.

Dopamine Release and Amphetamine Psychosis

When an electrical impulse in a dopaminergic nerve fiber reaches the nerve terminal area, it is believed that there is an inward movement of calcium ions that causes a small proportion of the amine-containing granules to migrate to the cell membrane, fuse with it, and then open to the outside, releasing the amine and proteins contained within the granule in a process known as stimulus-secretion coupling (Douglas 1968) (figures 3 and 4). These concepts are derived from studies of the peripheral nervous system and have not yet been unequivocally demonstrated for the central nervous system.

The major pharmacological effect of the psychotomimetic drug amphetamine is believed to be catecholamine release (Carlsson 1970 and Rutledge, Azzaro, and Ziance 1973), although it can also inhibit catecholamine neuronal uptake, can weakly inhibit MAO, and may have very weak catecholamine agonist effects (Cooper, Bloom, and Roth 1974).

Clinical observations in human amphetamine addicts have revealed that high doses of amphetamines can produce a florid psychosis bearing certain striking similarities to acute paranoid schizophrenia (Connell 1958). Careful clinical studies have shown that this "model psychosis," which may be associated with thought disorder, affective changes, and auditory hallucinations, could be produced at high amphetamine doses in normal individuals who were not prepsychotic (Angrist, Lee, and Gershon 1974 and Griffith, Oates, and Cavanaugh 1968). These studies have essentially eliminated the possibility that amphetamine merely activates latent psychosis. The reproduction of the fundamental symptoms of schizophrenia in these volunteers also helps to rule out the possibility that amphetamine acts by nonspecific excitation or sleep deprivation (Snyder 1972). Phentolamines and haloperidol ameliorate amphetamine psychosis and thus strengthen the analogy to true schizophrenia (Angrist, Lee, and Gershon 1974).

In schizophrenic patients, amphetamine activates or worsens preexisting psychotic symptoms, again placing the action of this drug on fundamental symptoms of schizophrenia (Angrist, Lee, and Gershon 1974). Janowsky et al. (1973b) found that administering small intravenous doses of methylphenidate, an isomer of amphetamine, to actively ill schizophrenics produced a marked worsening of preexisting psychotic symptoms, but did not have a major psychotogenic effect in remitted patients or normals. A wide range of psychotic symptoms was promoted, not simply paranoia. The authors caution against using this test for diagnostic purposes.

The studies of Randrup and Munkvard (1968) and Ellinwood, Sudilovsky, and Nelson (1973) have contributed extensively to our understanding of amphetamine-mediated behavioral effects, their relationship to DA metabolism, and schizophrenia. Space precludes a detailed review of their studies. Garver et al. (1975) rated the behavior of primates chronically given amphetamine. These investigators called attention to the hyperactivity, fragmented and repetitive behavior, and progressive social withdrawal that occur in primates after chronic amphetamine administration. Behavioral scoring techniques have allowed Garver et al. to categorize primate behavior in terms of Bleuler's four A's (autism, association, affect, and ambivalence). In addition, these investigators have cautiously discussed amphetamine-induced primate behavior as a schizophreniform behavioral psychosis on the basis of certain analogies to human schizophrenia.

Because of the direct relevance of the clinical effects of amphetamine to schizophrenia, there has for some time been a keen effort to determine if amphetamine could be used to elucidate the biochemical basis of schizophrenia. In particular, this debate has focused on which behavioral effects of amphetamine are mediated by NE and which by DA release. Based on studies with direct injection of DA or NE into various brain regions, measurement of turnover rate of DA or NE, and use of drugs that inhibit catecholamine synthesis (e.g., DBH inhibitors to block NE synthesis), alpha-adrenergic blockers and DA blockers, it has been concluded that DA is centrally involved in the mediation of stereotyped behavior while it is not yet clear whether one or both catecholamines mediate increased locomotor activity (see Creese and Iversen 1975 for references). Recently, attempts have been made to elucidate the basis for amphetamine action by studies with the stereoisomers of amphetamine. Because this approach...
has been adopted to determine the basis of amphetamine psychosis in man, it will be reviewed in some detail.

Coyle and Snyder (1969b) reported that d-amphetamine is 10 times more potent than l-amphetamine in inhibiting NE neuronal reuptake, but equipotent to l-amphetamine in inhibiting DA neuronal reuptake. They further proposed that this information could be used to determine whether a given behavioral effect of amphetamine was due to its action on NE or on DA neurons. Thus, if d-amphetamine were 10 times more potent than l-amphetamine in producing a given behavior, then one could conclude that behavior was controlled mostly by NE neurons. On the other hand, if d- and l-amphetamine were equipotent or nearly so in producing a given behavior, then that behavior was controlled mostly by DA neurons. D-amphetamine was found to be 10 times as potent as l-amphetamine in enhancing locomotor activity, while it is only twice as potent in eliciting stereotypy (Taylor and Snyder 1971). From these data it was concluded that the locomotor stimulation was due to NE release while the stereotypy was due to DA release. Phillips and Fibiger (1973) used the isomer-effectiveness ratio to conclude that both DA and NE could support intracranial self-stimulation, the supposed substrate for positive reinforcement.

The interpretation of behavioral data using the principle proposed by Coyle and Snyder may not be valid because at least five groups of independent investigators have not been able to confirm Coyle and Snyder's original data (Ferris, Tang, and Maxwell 1972, Harris and Baldessarini 1973, Heikkila et al. 1975, Scheel-Kruger 1972, and Thornburg and Moore 1973). In fact, these studies have obtained nearly the opposite results from Coyle and Snyder (1969b). However, Bunney et al. (1973) pointed out that great caution should be exercised in the use of the isomers to draw conclusions about those behaviors induced by lower doses of d- than l-amphetamine may be mediated via the DA system” (p. 188). This conclusion is in fact opposite to that of Coyle and Snyder (1969b). However, Bunney et al. (1975) studied the effect of amphetamine isomers on the electrical activity of the substantia nigra (DA) and locus coeruleus (NE) in anesthetized rats and found that the isomers were equally effective in inhibiting the noradrenergic neurons, but the d-isomer was more potent than the l-isomer in inhibiting the DA neurons. They concluded: “... behaviors produced by equally low doses of d- and l-amphetamine are probably mediated predominantly via the NE system, whereas those behaviors induced by lower doses of d- than l-amphetamine may be mediated via the DA system”.

The effects of amphetamine isomers on mental status have been studied in human amphetamine abusers (Angrist, Shopsin, and Gershon 1971 and Gunne and Anggard 1973) and in schizophrenic patients (Janowsky and Davis 1974). These studies reported, respectively, a 1.3:1, 4:1, and 1.5-3.1:1 greater potency of the d-isomer than the l-isomer in producing changes in mental status. These investigators attributed these effects of amphetamine to a dopaminergic mechanism based on Coyle and
Snyder's (1969b) postulate that if an amphetamine effect is produced by approximately the same dose of d- and l-amphetamine, it is related to the dopaminergic system. On the basis of their studies, Bunney et al. (1975) concluded that the human studies indicate that the catecholamine system that mediates amphetamine psychosis or amphetamine activation of schizophrenia is noradrenergic. It should be apparent that at the present time the stereoisomers of amphetamine cannot provide unequivocal information as to which catecholamine is involved in amphetamine psychosis or activation of schizophrenia. Key questions of their relative potency on various biochemical processes and what constitutes a significant difference in behavioral effects must first be settled.

Fortunately, there is independent evidence that DA rather than NE is relevant to the psychotomimetic effects of amphetamine. As we have indicated, it is well established that the neuroleptics are potent antidotes both to human amphetamine psychosis (Angrist, Lee, and Gershon 1974) and to the amphetamine effects on primate behavior (Garver et al. 1975). The reasons for concluding that neuroleptic blockade indicates a dopaminergic mechanism for amphetamine psychosis have been reviewed by these authors and by Snyder (1972) and will not be repeated here. However, the neuroleptic drugs also have antiadrenergic properties, albeit weaker than their anti-DA effects. The recent report that pimozide, formerly thought to be a neuroleptic specific for DA blockade, is a potent inhibitor of an NE-stimulated adenylate cyclase, a possible NE receptor, has prompted the speculation that NE blockade may be relevant to antipsychotic effects (Blumberg, Taylor, and Sulser 1975). Nevertheless, it seems to us that the evidence in favor of an anti-DA mechanism for the neuroleptics is very strong and does support the contention that increased DA is the mechanism of amphetamine psychosis. This conclusion is also strengthened by the report that the alpha-NE blocker phenoxybenzamine and the beta-blocker propranolol did not inhibit the euphoriant effects of high doses of amphetamine in detoxified amphetamine addicts (Gunne and Anggard 1973). Their finding that AMP pretreatment blocked the amphetamine effect is consistent with either a DA or an NE hypothesis. The report by Janowsky, El-Yousef, and Davis (1973) that methylphenidate, which is more potent as a central DA releaser than an NE releaser (Ferris, Tang, and Maxwell 1972), can activate schizophrenia more potently than d-amphetamine supports the idea that activation of psychosis is due to a DA rather than to an NE effect.

The finding that amphetamine stimulates brain DA turnover in man as demonstrated by an increased cerebrospinal fluid (CSF) HVA after probenecid without an increase in CSF MHPG (3-methoxy-4-hydroxy-phenyl glycol) suggests that amphetamine has a more potent effect on brain DA than NE (Angrist et al. 1974). However, this finding does not specifically link the increased DA turnover to the central effects of amphetamine (for explanation, see the section on inactivation of dopamine).

All evidence considered, it appears safe to conclude that increased DA plays a significant role in the induction of euphoria, an acute paranoid state, and an exacerbation of schizophrenia by amphetamine.

Before leaving the discussion of amphetamine, it is interesting to point out the finding that the impairment in acquisition of a conditioned avoidance response by rats nursed by mothers who received neuroleptics is counteracted by d-amphetamine (Ahlenius, Engel, and Lundborg 1975). This finding is important in indicating a possible role of DA neurons in mediating acquisition of avoidance behavior and has major implications for the high risk studies of offspring of schizophrenic mothers if the mothers received neuroleptics during gestation or nursing. Conceivably, there may well be drug-induced delays in development in such children if a sufficient amount of the drug passes through the placenta or is present in breast milk.

Neuroleptics and the Dopamine Hypothesis of Schizophrenia

The belief that the mechanism of the antipsychotic effect of the neuroleptic drugs is interference with DA neuronal activity is one of the cornerstones of the DA hypothesis of schizophrenia. The older evidence that relates their antipsychotic action to DA has been reviewed by Snyder et al. (1974) and will not be repeated here. Selected aspects of the pharmacology of the neuroleptics, as well as their clinical effects, are discussed throughout this review. Here we wish to discuss several important areas of research concerning the neuroleptic drugs that have direct relevance to schizophrenia: 1) interaction with DA-sensitive adenylate cyclase, the possible DA receptor; 2) acute versus long-term effects
of neuroleptics on striatal DA receptors; 3) the relationship between dopaminergic and cholinergic neurons in the striatum and the existence of a DA-ACh balance relevant to schizophrenia, Parkinson's disease, and tardive dyskinesia; 4) effects of neuroleptics on striatal versus limbic DA receptors; 5) effects of phencyclidine, a potent psychotomimetic, on DA-ACh balance; 6) effects of neuroleptics on presynaptic versus postsynaptic DA receptors; and 7) DA receptor supersensitivity.

Dopamine Receptors: Adenylate Cyclase Studies

The neurotransmitters such as DA bring about their effects by interacting with a receptor and thereby initiating a metabolic process. The identification and characterization of the DA receptor(s) that may be relevant to the antipsychotic effect of the neuroleptics is a major aim of current research. There is considerable interest in the hypothesis that the DA receptor is the enzyme adenylate kinase. Sutherland, Rall, and their colleagues have established that most hormones exert their cellular effects by promoting an increase in the concentration of cyclic adenosine-3',5'-monophosphate (cAMP) (Sutherland 1972). The increase in cAMP is brought about by the hormone's stimulation of adenylate cyclase, a membrane-bound enzyme. When turned on by a chemical messenger, adenylate cyclase catalyzes the conversion of adenosine triphosphate to cAMP, which in turn participates in a host of cellular processes. Cyclic AMP acts as a second chemical "messenger" and causes various intracellular enzymes to increase their activity. Most commonly, the enzymes are phosphorylated and the resulting chemical changes bring about the major cellular effects of the original hormone. In the nervous system, it is believed that neurotransmitters such as DA can act like hormones and stimulate the production of cAMP in the postsynaptic neuron. Conceivably, an increase in the concentration of cAMP in a neuron could bring about changes in the ionic permeability of the neuron and lead to hyperpolarization (thus inhibiting neuronal firing) or depolarization (thus promoting neuronal firing).

In the brain, each neurotransmitter may have its own adenylate cyclase. Since adenylate cyclases are located at the external surface of the cell and can account for many of the specific actions of a hormone or neurotransmitter, it has been proposed that the adenylate cyclase may itself be the receptor for its specific hormone or neurotransmitter (Robinson, Butcher, and Sutherland 1971).

The existence of DA-stimulated adenylate cyclase was first demonstrated in the superior cervical ganglion of the rabbit (Kebabian and Greengard 1971). Later studies have found DA-stimulated adenylate cyclases in the retina (Brown and Makman 1973), in the basal ganglia (Kebabian, Petzold, and Greengard 1972, Miller, Horn, and Iversen 1974, and Sheppard and Burghardt 1974), and in the limbic forebrain (Clement-Cormier et al. 1974, Horn, Cuello, and Miller 1974, and Miller, Horn, and Iversen 1974). The adenylate cyclases of the caudate and the limbic regions are sensitive to very low concentrations of DA: half-maximal stimulation occurs at 4.5 micromolar (µM) concentration, and effects are detectable at concentrations as low as 0.3 µM. Apomorphine, a potent DA agonist, stimulates caudate adenylate cyclase more effectively than DA does (Kebabian, Petzold, and Greengard 1972). The net increase in caudate adenylate cyclase was twofold with DA, whereas in the limbic region it was 80-100 percent above basal level (Miller, Horn, and Iversen 1974). These relatively small increases could be physiologically significant, in part because other neurotransmitters may act at other adenylate cyclases to summate with the DA-sensitive system. The low concentration of DA necessary to stimulate adenylate cyclase activity supports the physiologic significance of this process.

The dopaminergic interneurons that have been demonstrated in the rabbit superior cervical ganglion release DA and thereby cause the stimulation of a DA-sensitive adenylate cyclase in the postsynaptic neurons. These events may in turn be responsible for a slow hyperpolarizing inhibitory potential. The superior cervical ganglion may thus serve as a model for dopaminergic neurotransmission of brain and for the role of cAMP in the physiology of synaptic transmission. However, the receptors that respond to DA in the superior cervical ganglion are quite different from those that respond to DA in the central nervous system (CNS). That is, the DA receptors of the superior cervical ganglion have the properties of the classic alpha receptor (e.g., antagonism by the alpha-adrenergic blockers phenolamine and phenoxybenzamine, but not by the beta-blockers propranolol or dichloroisoproterenol) (Schorderet, McAfee, and Greengard 1972). On the other hand, the DA receptors in
agonists (e.g., DA and apomorphine) and antagonists (e.g., chlorpromazine and haloperidol).

The DA-stimulated adenylate cyclase of calf retina seems to be closely related to CNS DA receptors. In retina, as in the caudate nucleus and limbic forebrain, the DA-stimulated activation of adenylate cyclase is potently blocked by neuroleptic drugs, but less so by alpha- or beta-receptor blockers (Bucher and Schorderet 1975). Apomorphine is also capable of potently stimulating the adenylate cyclase in retina (Bucher and Schorderet 1975). Thus, the DA-stimulated adenylate cyclase of retina is probably a better model for the central DA receptor than is the superior cervical ganglion.

Cyclic AMP levels in the caudate nucleus are increased by L-dopa (Garelis and Neff 1974). The neuroleptics competitively inhibit brain DA-sensitive adenylate cyclase at extremely low concentrations: for example, 10^{-9} M for fluphenazine (Clement-Cormier et al. 1974, Karobath and Leitich 1974, Kebabian, Petzold, and Greengard 1972, Miller, Horn, and Iversen 1974). In general the capacity of phenothiazine drugs to inhibit this enzyme parallels their clinical potency. Thus, fluphenazine is 10-20 times as potent an inhibitor as chlorpromazine, whereas promazine and chlorpromazine sulfoxide, which are not antipsychotic, do not significantly inhibit the enzyme at concentrations of less than 10^{-7} M. Only the isomers of thioxanthenes, which are antipsychotic, are potent inhibitors (Miller, Horn, and Iversen 1975). However, the butyrophenones are exceptions. All studies agree that haloperidol, spiroperidol, and the related drug pimozide are far less potent inhibitors of DA-stimulated adenylate cyclases than might be expected based on their clinical potency (Karobath and Leitich 1974, Kebabian, Petzold, and Greengard 1972, and Miller, Horn, and Iversen 1974).

This apparent discrepancy with the hypothesis that interaction with this enzyme is the basis for antipsychotic effects of the neuroleptics could be due to problems with the in-vitro assay with the butyrophenones, which are not water soluble, or because of selective absorption, metabolism, and distribution of these drugs in vivo (Iversen 1975). On the other hand, still another discrepancy exists in that several tricyclic antidepressants, particularly amitryptiline and doxepin, which completely lack antipsychotic activity, are as potent inhibitors of DA-stimulated adenylate cyclase as are pimozide (Clement-Cormier et al. 1974) or haloperidol (Karobath 1975). A possible explanation for their lack of antipsychotic properties, in addition to the factors cited above for the butyrophenones, is that the central antimuscarinic effects of the antidepressant drugs antagonize the effects of these drugs on the DA receptor (Miller and Hiley 1974).

Development of supersensitivity to DA or DA agonists will be discussed subsequently. The fact that this supersensitivity is not accompanied by an increase in DA-stimulated adenylate cyclase activity (Von Voigtlander, Boukma, and Johnson 1973, and Von Voigtlander, Losey, and Trierenberg 1975) does not necessarily mean the DA-stimulated adenylate cyclase is not the DA receptor. It means that supersensitivity is mediated by a mechanism other than an action on this enzyme.

There is, however, additional evidence that has been offered in opposition to the hypothesis that an adenylate cyclase is the DA receptor. As previously mentioned, the ability of apomorphine to induce contralateral turning in rats with 6-OHDA-induced unilateral substantia nigra lesions is believed to reflect the DA agonist effects of apomorphine (Ungerstedt 1971b). Inhibitors of phosphodiesterase (the enzyme that destroys cAMP) should potentiate this turning; although some do (Fuze and Ungerstedt 1974), other potent phosphodiesterase inhibitors do not (Arbuthnot et al. 1974).

Carenzi et al. (1975) obtained autopsy brains from seven chronic schizophrenics and control subjects. DA-stimulated striatal adenylate cyclase activity in both groups was not significantly different and was inhibited equally by haloperidol. The same was true for basal adenylate cyclase activity. In the schizophrenics but not the controls, there was a significant negative correlation (r = - .817) between baseline and DA-stimulated adenylate cyclase activity. The authors speculated on the existence of two groups of schizophrenic patients with markedly different baseline adenylate cyclase activity and sensitivity to DA. This finding will need to be verified in additional autopsy specimens.

A group of NE-sensitive adenylate cyclases widely distributed in rat brain are also inhibited by the neuroleptics (Blumberg, Taylor, and Sulser 1975 and Palmer and Manian 1974). It has been suggested that this adenylate cyclase may also be relevant to the antipsychotic actions of the neuroleptics, as pimozide and...
clozapine are both very potent inhibitors of the enzyme (Blumberg, Taylor, and Sulser 1975). However, inhibition by the neuroleptics of the NE-stimulated adenylate cyclases studied by Palmer and Manian (1974) did not correlate well with antipsychotic potency. Furthermore, the alpha-receptor blocker phenoxybenzamine is not antipsychotic; nor does the central noradrenergic agent clonidine induce psychosis.

An initial report of an effort to identify the rat brain DA receptors by tagging it with \(^3\)H-pimozide was unsuccessful because of nonspecific binding (Rotrosen, Friedman, and Gershon 1975). Recently, Creese, Burt, and Snyder (1975) and Seeman et al. (1975) have reported stereospecific binding of \(^3\)H-DA and \(^3\)H-haloperidol to membrane preparations of the calf caudate and rat striatum, respectively. The capacity of neuroleptic drugs to block the agonist (DA) or antagonist (haloperidol) binding correlated closely with their antipsychotic potency and their capacity to inhibit DA-sensitive adenylate cyclase. The discrepancy between the clinical potency of the butyrophenones and comparative biological activity in the neuroleptic series of drugs that was discussed previously in considering adenylate cyclase as the dopamine receptor was not present in these studies of displacement of stereospecific binding. Therefore, it is more likely that Creese, Burt, and Snyder (1975) and Seeman et al. (1975) have identified a dopamine receptor. Comparable studies in normal and schizophrenic brains will be needed to determine if such receptors are present in these organs and to characterize their properties.

**Acute and Long-Term Effects of Neuroleptics on Striatal Dopamine Receptors**

As first demonstrated by Carlsson and Lindqvist (1963), acute administration of phenothiazines increases DA metabolites in rat brain. The increase has generally been attributed to the phenothiazines' postsynaptic blockade of DA receptors, which activates the DA neurons to release more DA. This activation may be mediated by a cholinergic-GABAminergic loop that is disinhibited when the striatal DA receptors are blocked (see figure 5). Subsequent studies have demonstrated that the entire gamut of neuroleptics can raise striatal HVA or dihydroxyphenylacetic acid (DOPAC) in the neostriatum following acute administration. Nyback, Borzecki, and Sedvall (1968) have shown that synthesis and turnover of DA are increased acutely by antipsychotic neuroleptic drugs in a manner roughly proportional to their clinical efficacy. Andén et al. (1970) found that chlorpromazine, haloperidol, and spiroperidol (clinically effective) but not promethazine (not clinically effective) can acutely increase striatal HVA in the rat. However, Stawarz et al. (1975), using a broader series of antipsychotic drugs, recently found no correlation between antipsychotic potency and capacity to increase striatal HVA acutely. In particular, clozapine and thioridizane were less potent than would have been expected on clinical grounds. This lack of potency may be the result of their anticholinergic properties (Miller and Hiley 1974 and Snyder, Greenberg, and Yamamura 1974) since evidence, which will be reviewed subsequently, indicates that anticholinergic drugs diminish DA turnover by blocking the feedback mechanism. However, Stawarz et al. (1975) argue against this possibility.

Scatton, Garret, and Julou (1975) reported differences in the acute and long-term effects of neuroleptics on striatal DA turnover. These investigators found that 24 hours following daily injection for 12 days of any of three different neuroleptics in humans and following repeated treatments with classical neuroleptics immediately after birth in young animals (Velley et al. 1975), there is a significant decrease in striatal DA turnover. In the former group, however, DA turnover is still stimulated for about 4 hours after the last dose. They have speculated about a second feedback loop that inhibits DA turnover and is sensitive to the low concentrations of DA blockers that are present 24 hours but not 4 hours after administration.

Some studies of schizophrenics given neuroleptics acutely and chronically have shown that the increases in HVA in CSF after acute phenothiazine administration are diminished after chronic phenothiazine administration. (These studies are reviewed on pp. 49-52.) Thus, there is evidence that tolerance develops to the capacity of these phenothiazine drugs to increase striatal DA turnover in schizophrenics. As will be discussed later, no tolerance develops to the effect of neuroleptics on hypothalamo-pituitary DA receptors as indicated by continued elevation of serum prolactin in phenothiazine-treated patients. The explanation for the lack of tolerance to the antipsychotic effects of the neuroleptics probably lies in the difference between the effects of neuroleptics on limbic DA receptors compared to striatal DA receptors. The limbic receptors show no tolerance,
whereas the striatal receptors do, as will be discussed subsequently.

In view of the demonstration by Moller-Nielsen et al. (1974) that tolerance develops to the antistereotypic properties of the neuroleptics in rats and dogs but not to their ability to produce catalepsy or to inhibit the conditioned avoidance response, one might conclude that antistereotypy may not be highly relevant to antipsychotic properties of neuroleptic drugs. To demonstrate the complexity of the area with which we are concerned, Yehuda and Wurtman (1975) found that unilateral lesions of the mesolimbic dopaminergic areas inhibited amphetamine-induced stereotyped behavior but unilateral nigrostriatal lesions did not, indicating stereotypy may be related to mesolimbic stimulation. If so, then antistereotypy should correlate with antipsychotic properties if limbic function is relevant to DA and schizophrenia. Part of the discrepancy could be due to species differences, but it is wise to be cautious about all conclusions in this rapidly developing area.

**Dopaminergic-Cholinergic Interregulation**

Numerous investigations of the role of neurotransmitters in the regulation of discrete behaviors in laboratory animals have demonstrated that frequently two or more neurotransmitters oppose or synergize with each other. Thermoregulation, which is under noradrenergic, serotonergic, cholinergic, and probably dopaminergic control, is a classic example (Lomax 1970, Myers 1969, and Reid et al. 1968). Such complexity allows for more precise regulation of biological processes. Considerable research has been carried out to determine the neuronal tracts, neurotransmitters, and other influences that interact with DA activity of the nigrostriatal, mesolimbic, and tubero-infundibular pathways.

There is increasing evidence that nigrostriatal dopaminergic neurons synapse on striatal cholinergic interneurons, which in turn can feed back on the nigral neurons, perhaps by means of a GABAAergic striatonigral neuron (figure 5). The evidence for the GABA pathway will be reviewed subsequently. Other cholinergic neurons of unknown origin also synapse on nigral dopaminergic neurons (Javoy et al. 1974). Thus, dopaminergic neurons in the substantia nigra and cholinergic neurons in the neostriatum and elsewhere interact in such a way that the net outflow from the system leads to smooth regulation of a variety of motor activities.

Interaction between DA and ACh in the corpus striatum is such that there is a dynamic balance in the activity of these neurotransmitters. This balance is demonstrated by recent findings that drugs affecting striatal DA turnover also influence striatal ACh turnover. Similarly, drugs influencing ACh turnover also alter DA turnover. For example, physostigmine and cholinomimetics enhance striatal DA turnover (Corrodi et al. 1967 and Nose and Takemoto 1974), whereas cholinolytics reduce the turnover and use of DA in the striatum (Andén and Bédard 1971 and Bartholini and Pletscher 1971). Thus, the nigrostriatal DA system is activated by a cholinergic input. On the other hand, there is evidence that striatal cholinergic activity is under an inhibitory dopaminergic mechanism: DA receptor stimulants decrease striatal turnover and the release of ACh, while DA receptor blockers increase striatal turnover and the release of ACh (Ladinsky et al. 1975, McGeer, Grewaal, and McGeer 1974, Sethy and Van Woert 1974, Stadler et al. 1973, and Trabucchi et al. 1975). As will be discussed below, some neuroleptic drugs are not only DA receptor blockers but also potent anticholinergic agents. However, Rommelspacher and Kuhar (1974) presented evidence that the increase in striatal ACh turnover produced by these drugs is due to their action at DA receptors, and not to their anticholinergic actions.

Interference with striatal dopaminergic-cholinergic balance is relevant to the etiology of extrapyramidal symptoms (EPS)—for example, tremor, rigidity, and akinesia, which are seen both in Parkinson's disease and after treatment with neuroleptic drugs. The findings of decreased levels of endogenous DA in the striatum of patients with Parkinson's disease and the therapeutic efficacy of L-dopa have prompted the major hypothesis for the etiology of EPS that characterizes them as a "DA-deficiency syndrome" (Hornykiewicz 1972 and 1973). Furthermore, drugs that increase the availability of DA or stimulate DA receptors (e.g., L-dopa, amphetamine, apomorphine) all improve EPS (Barbeau 1969, Duby et al. 1972, and Miller and Nieburg 1973), whereas drugs that decrease the availability of DA or block DA receptors (e.g., reserpine, phenothiazines) all exacerbate EPS (Hornykiewicz 1972) (see figure 6). However, EPS are not merely a DA-deficiency syndrome but are also, at least in part, an ACh-excess syndrome. Thus, drugs that decrease ACh action by blocking central muscarinic receptors (e.g., atropine) improve EPS (Duvoisin 1967), while the centrally active cholinesterase inhibitor physo-
stigmine aggravates EPS (Duvoisin 1967 and Van Woert, Ambani, and Bowers 1972). The pharmacology of EPS thus represents a combination of both DA deficiency and ACh excess. The hypothesis of a DA-ACh imbalance in EPS states that the mutual antagonism between DA and ACh in the striatum is so altered that the balance tips in favor of ACh (figure 6). This paradigm accounts for the simultaneous presence of ACh excess and DA deficiency.

Classically, the antipsychotic potency of the neuroleptic drugs has been thought to be directly proportional to their ability to produce EPS. In fact, as the derivation of their name suggests, the neuroleptic drugs were originally screened for their antipsychotic effects by determining their ability to produce EPS. The possibility that the capacity of neuroleptic drugs to produce EPS is directly correlated with blockade of striatal DA receptors (Stille 1971) gave rise to the hypothesis that the antipsychotic effects of these drugs could also be directly correlated with the blockade of central DA receptors. However, when it was found that the two potent antipsychotic drugs clozapine and thioridazine produced only weak EPS (Azima, Durost, and Arthurs 1959 and Stille and Hipplius 1971), it appeared that the theory might have to be rejected or modified. The lack of EPS produced by these antipsychotic drugs has recently been attributed to their cholinolytic (anti-cholinergic) properties (Miller and Hiley 1974 and Snyder, Greenberg, and Yamamura 1974). Thus, clozapine and thioridazine, which produce few EPS, are relatively potent cholinolitics, while fluphenazine and haloperidol, which produce a high incidence of EPS, have relatively weak anticholinergic effects. These data are all consistent with the ACh-DA paradigm proposed for Parkinson's disease (figure 6), and exemplify the extreme caution one must employ when extrapolating findings in one central DA system such as the nigrostrial system to any other DA system.

Tardive dyskinesia consists of involuntary, rhythmic, stereotyped movements usually occurring in the oral area—the so-called buccolingualmasticatory syndrome—(Ayd 1967, Crane 1973, and Klawans 1973b). They develop during prolonged treatment with a neuroleptic drug or shortly after a reduction in dosage or discontinuation of such treatments. In analogy to the situation in Parkinson's disease, it has been proposed that tardive dyskinesia can also be conceived as an imbalance in striatal dopaminergic and cholinergic activity, only with the balance tipped in the opposite direction than in parkinsonism such that increased DA or decreased ACh can promote symptoms of tardive dyskinesia, while decreased dopaminergic activity or increased cholinergic activity relieves symptoms of tardive
dyskinesia (figure 7) (Gerlach, Reisby, and Randrup 1974 and Klawans 1973b). Klawans (1973b) summarized the evidence that tardive dyskinesia may be the result of increased responsiveness of DA receptors due to neuroleptic-induced denervation supersensitivity. That is, prolonged blockade of DA receptors by neuroleptic drugs and thus a prolonged reduction of dopaminergic stimulation may cause postsynaptic DA receptors to become more sensitive to DA in order to compensate for DA loss. This receptor supersensitivity causes DA to dominate over ACh in the striatum and thereby produce dyskinesia.

Tardive dyskinesia might then be expected to exhibit almost the opposite pharmacology from Parkinson's disease, and a good deal of data suggest that this is so. For example, drugs that decrease DA activity, such as reserpine, tetrabenazine, AMPT, and even higher doses of neuroleptics, tend to reduce tardive dyskinesia, while L-dopa, which increases DA availability, also exacerbates tardive dyskinesia (see figure 7) (Gerlach, Reisby, and Randrup 1974 and Kazamatsuri, Chien, and Cole 1972a, 1972b, and 1973). On the other hand, physostigmine and deanol, drugs that increase ACh, also improve tardive dyskinesia, whereas anticholinergic drugs, which decrease ACh action, exacerbate symptoms (Casey and Denney 1975, Fann et al. 1974, Gerlach, Reisby, and Randrup 1974, and Klawans 1973b). Therefore, the pharmacology of tardive dyskinesia might represent both a DA-excess syndrome and an ACh-deficiency syndrome.

It has been tentatively proposed that psychosis might have a DA-ACh balance tipped in the same direction as that in tardive dyskinesia (figure 7) and in the opposite direction as that in Parkinson's disease (figure 6) such that increased DA or decreased ACh can promote psychotic symptoms, while decreased DA or increased ACh can relieve psychotic symptoms (figure 8) (Davis 1974, Friedhoff and Alpert 1973, and Janowsky, El-Yousef, and Davis 1973). The neurochemical evidence from animal studies for a DA-ACh balance in the limbic region that might be the basis for the antipsychotic effect will be discussed in the next section, which compares the effects of neuroleptics, anticholinergics, and cholinomimetic drugs on the striatum and limbic regions in rats and rabbits.

The pharmacologic evidence for a cholinergic-dopaminergic balance in man that is relevant to schizophrenia is mixed. Acute administration of arecoline and physostigmine (drugs that increase ACh activity) to
Schizophrenics has been reported to improve some symptoms of schizophrenia (Pfeiffer and Jenney 1957 and Van Andel 1959). Rosenthal and Bigelow (1973) found that chronic administration of low doses of physostigmine was moderately helpful clinically. However, acute intravenous administration of physostigmine does not seem to have any antipsychotic properties (Modestin, Schwartz, and Hunger 1973) and may even cause schizophrenic patients to become more depressed (Janowsky, El-Yousef, and Davis 1973). Janowsky et al. (1973) found that physostigmine prevented the methylphenidate-induced activation of schizophrenia. Cholinolytic agents may themselves produce a psychosis when given in high doses—for example, Ditran (Abood 1968) and benztropine (El-Yousef et al. 1973). The psychoses produced by these cholinolitics are not as similar to schizophrenia as is amphetamine psychosis, but resemble toxic confusional states with disorientation and memory loss. When given to schizophrenics, Ditran can activate schizophrenic symptoms (Gershon and Olariu 1960). However, these cholinolytic agents do not usually activate psychosis when they are given to schizophrenics to alleviate EPS that develop during treatment with neuroleptics. This finding could be related to the report of Andén (1974) that cholinergic receptors of limbic dopaminergic neurons may not be so responsive to cholinolytic agents as are those of the substantia nigra. Therefore, antiparkinsonian effects of cholinolytic drugs might be seen at lower doses than those required to activate psychosis.

In a series of recent reports, Singh and his collaborators (Singh and Kay 1975a, 1975b, and 1975c and Singh and Smith 1973) reported that anticholinergics can reverse the therapeutic effects of neuroleptics, particularly those such as chlorpromazine that have some anticholinergic activity of their own that can summate with the effects of the more potent anticholinergics prescribed for alleviation of EPS. On this basis, they propose that the basic abnormality in schizophrenia may be a relative decrease in cholinergic activity and that the capacity of neuroleptics to promote cholinergic activity may be the basis of their therapeutic effect. We have previously cited the evidence that neuroleptics increase striatal acetylcholine turnover but not limbic acetylcholine turnover. However, those studies were conducted in the cat and may not yet generalize to man. The antitherapeutic effect of anticholinergics reported by Singh and his colleagues requires much further confirmation before it can be accepted. The design of their studies and the statistical analysis of the...
data can be readily criticized. For example, in one study (Singh and Kay 1975a), the behavioral data from the neuroleptic plus anticholinergic period were compared to combined behavioral data from the immediately preceding and following periods. It would have been much more satisfactory to look at the three periods individually in an ABA design with an analysis of variance for repeated measures. Their use of univariate rather than multivariate statistical methods could also have produced very misleading results. In addition, it is important to point out that Singh and Kay (1975a and 1975b) employed benzotropine in their studies. This anticholinergic is also a fairly potent DA releaser and reuptake blocker—properties not shared by all anticholinergics (Coyle and Snyder 1969a, Horn, Coyle, and Snyder 1971, and Goodale and Moore 1975). This effect has not been demonstrated in vivo, but if it were to occur, it might potentiate psychosis by increasing the amount of DA at receptor sites.

Effects of Drugs on Dopamine and Acetylcholine Metabolism in Striatal and Limbic Areas

We have already reviewed some of the studies dealing with acute and chronic effects of neuroleptics and cholinergic drugs on DA and ACh turnover in the striatum. The purpose of this section is to review the recent studies comparing the effects of these drugs in the striatum and limbic regions. Such studies are important to understanding the possible dissociation of the antipsychotic and EPS-inducing properties of the antipsychotic drugs.

Andén and Stock (1973) reported that clozapine, an antipsychotic that produces little or no EPS, increased rabbits' HVA levels to a much greater extent in the limbic region than in the neostriatum, whereas haloperidol affected both regions about equally. The difference was attributed to the intrinsic anticholinergic properties of clozapine. Zivkovic et al. (1975) and Stawarz et al. (1975) found that clozapine had a greater effect on rat limbic tyrosine hydroxylase activation and HVA levels, respectively, than on the same neostriatal functions. On the other hand, haloperidol and pimozide had equal effects in both regions, whereas thioridazine and chlorpromazine had more potent effects in the neostriatum. Bartholini, Keller, and Pletscher (1975) reported results essentially similar to those of Stawarz et al. (1975). However, Wiesel and Sedvall (1975) found that the same four drugs had similar orders of potency for stimulation of DA turnover in the corpus striatum and the olfactory tubercle. The discrepancy could be due to the fact that Wiesel and Sedvall (1975) studied only one part of the limbic forebrain.

Another parameter that has been compared in the striatum and the limbic areas is the effect of neuroleptics on ACh turnover and of cholinergic drugs on DA turnover. Neuroleptics do not increase the release of ACh from the cat septum or nucleus accumbens but they do in the corpus striatum (Lloyd, Stadler, and Bartholini 1973 and Stadler, Gadea-Ciria, and Bartholini 1975). The increase in HVA in the rabbit limbic system produced by neuroleptics is not diminished by anticholinergic drugs as it is in the nigrostriatal system (Andén 1972). Similar results in the rat were reported by Bartholini, Keller, and Pletscher (1975). However, Andén (1974) found that the cholinomimetic drugs oxotremorine and physostigmine increased HVA levels in both the rabbit limbic and striatal systems, whereas Bartholini, Keller, and Pletscher (1975) found that oxotremorine produced a greater HVA elevation in the limbic system than in the striatum. Both investigators found that this effect was antagonized by anticholinergic drugs, the striatum being more sensitive to inhibition than the limbic region.

The interpretation of these findings is problematic at the present time. Both Andén (1974) and Bartholini, Keller, and Pletscher (1975) have made attempts to do so, but a discussion of their explanations is beyond the scope of this review. It is not clear how far these mechanisms could be extrapolated to man. Suffice it to say that the striatum and limbic system may reasonably be believed to have different receptor sensitivities to neuroleptic, cholinomimetic, and anticholinergic drugs as well as different patterns of cholinergic-dopaminergic interregulation. This may open the possibility for new antipsychotic drugs such as clozapine with a relatively high antipsychotic, low EPS ratio. Until further clarification of the DA-ACh balance in the limbic region is available, along with a complete understanding of a drug's interactions on these structures, it seems premature to challenge the theory that hyperactivity of the mesolimbic DA system is relevant to schizophrenia on the basis of lack of correlation between animal studies and antipsychotic properties.

Scatton, Garret, and Julou (1975) recently demonstrated that neuroleptics increase DA synthesis in rat
mesocortical DA neurons. They found that these neurons required higher doses of neuroleptics than the nigrostriatal system to produce a comparable effect on DA synthesis.

**Phencyclidine: A Psychotomimetic That Disrupts the DA-ACh Balance?**

Phencyclidine (Sernyl, PCP) is a general anesthetic that was dropped from clinical use because a significant percentage of subjects who received it experienced disturbing thoughts and feelings during the period of emergence from anesthesia. Careful study by Luby et al. (1962) and others demonstrated that PCP may produce an altered state of consciousness that more closely resembles schizophrenia than that produced by LSD-25. In particular, it produces disorders in thinking that resemble those seen in schizophrenia: concreteness, bizarre content, and delusions (Luby et al. 1962 and Meltzer et al. 1972). In this regard, it may even be superior to amphetamine as a model for schizophrenia. Like amphetamine, PCP can also cause a reactivation or intensification of symptoms in schizophrenics (Rosenbaum et al. 1959).

PCP may well produce its effects on mental functioning via a unique combination of increased dopaminergic and decreased cholinergic activity. PCP significantly increases the depletion of DA by AMPT in rats, suggesting an increase in DA turnover (Leonard and Tonge 1969). It is a more potent blocker of DA uptake by rat caudate synaptosomes than is d-amphetamine (Smith et al. 1975). Ketamine, an analog of PCP with similar but weaker effects on cognitive processing in man, also increases rat brain DA turnover (Sung, Frederickson, and Holtzman 1973). Both PCP and ketamine block the reuptake of NE into the terminals of postganglionic adrenergic nerves (Nedergaard 1973) but potentiate the peripheral sympathomimetic effects of epinephrine and NE (Hitner and DiGregorio 1974). PCP may block the reuptake of NE and DA in mouse brain (Hitzemann, Loh, and Domino 1973). Haloperidol, a DA blocker, inhibits the increase in corticosterone that normally occurs after ketamine administration to rats (Fahringer, Foley, and Redgate 1974). Both PCP and ketamine have potent anticholinergic properties, both central and peripheral antimuscarinic action (Kalir et al. 1969), and weak antinicotinic properties (at the neuromuscular junction; Paster et al. 1974). Molecular properties that lead to blockade of the acetylcholine receptor have been related to PCP's psychotomimetic effects (Weinstein et al. 1973).

Kanner, Finnegan, and Meltzer (1975) have used the Ungerstedt (1971b) rotational model to demonstrate a functional effect of PCP on dopaminergic and/or cholinergic transmission. As discussed previously, drugs such as amphetamine that release DA and block its reuptake cause rotation of rats with unilateral lesions of the nigrostriatal pathway toward the lesioned side. This effect is not, however, solely dependent on DA activity. There is also considerable evidence that ACh influences the extent of rotation in this model by modifying the DA-ACh balance (Andén and Bédard 1971, Costall, Naylor, and Olley 1972, and Mueller and Seeman 1974). Anticholinergic drugs such as scopolamine also cause ipsilateral rotation but less effectively than amphetamine (Kelley, Miller, and Sahakian 1974). PCP produces a dose-dependent ipsilateral rotation in rats with unilateral substantia nigra lesions. This ipsilateral turning is decreased 40 percent by pretreatment with AMPT and 81 percent by prior administration of haloperidol. Both AMPT and haloperidol completely inhibit amphetamine-induced rotation. Ipsilateral turning elicited by PCP can also be slightly but significantly enhanced by anticholinergic agents and inhibited by cholinomimetic drugs (Kanner, Finnegan, and Meltzer 1975). Taken together, this evidence suggests the possibility that both an increased dopaminergic and a decreased cholinergic effect of PCP contribute to ipsilateral rotation in the rats with unilateral substantia nigra lesions.

It is not yet certain whether the dopaminergic or the anticholinergic properties of PCP, or a combination of these properties, are actually responsible for the psychotomimetic effects of PCP. If this hypothesis should be substantiated, it would mean that the two best drug models of schizophrenia may be mediated by effects on DA or ACh or both in a manner that potentiates dopaminergic over cholinergic activity.

**Presynaptic and Postsynaptic Effects of Neuroleptics**

The probable existence of presynaptic DA receptors that are important to the regulation of DA synthesis has been discussed previously. We indicated that Aghajanian and Bunney (1973) did not find that iontophoretically applied chlorpromazine or haloperidol affected the firing rate of substantia nigra DA neurons or prevented the inhibitory effects of DA. However, this does not mean
there are no presynaptic effects of neuroleptics that might be relevant to their antipsychotic action.

For some years, Seeman and his colleagues have been proposing that the antipsychotic drugs may act mainly presynaptically, by any one of a number of mechanisms, to interfere with the release of DA after an electrical impulse reaches the nerve terminal (Seeman 1972, Seeman, Staiman, and Chau-Wong 1974, and Seeman and Lee 1974). The basic mechanism of action is believed to be local anesthetic in nature. The impulse-coupling block produced by the neuroleptics leads to increased DA levels in the DA neuron that can then be activated by a feedback mechanism from postsynaptic receptors that are relatively deprived of DA because of the impulse-coupling block. Thus, even though the frequency of impulse-coupled DA release is diminished, there is more DA released per impulse, and DA turnover is increased (Seeman and Lee 1974).

Seeman and Lee (1975) recently studied the effect of a large series of neuroleptics of diverse chemical structure on the electrically stimulated release of $^3$H-dopamine from rat neostriatal slices. The release was Ca$^{2+}$-dependent, inhibited by tetrodotoxin and proportional to the frequency and voltage of stimulation. The neuroleptics were much better inhibitors of electrically stimulated DA release than the release of choline, GABA, glutamic acid, or their metabolites. Seeman and Lee (1975) reported an extraordinary correlation between the inhibitory effect of neuroleptics on stimulated DA release and clinical potency. The means of deriving the relative clinical potency was not explicitly described, however, and inspection reveals some surprising conclusions—for example, that the average clinical dose of fluphenazine is a 8 mg/day, and of clozapine, is 300 mg/day. Both figures are quite low. A few other figures are also questionable; for example, spiroperidol and haloperidol and many of the other drugs they cite have been used relatively rarely clinically, so average clinical dose data are not very reliable. In any event, interference with DA release was detectable at a sufficiently low concentration of the neuroleptics to indicate this effect may be significant, and it is probable that this important study will trigger much more investigation along these lines.

**Receptor Supersensitivity**

Receptor supersensitivity is a concept of growing importance in neuropharmacology; it refers to variations of receptor response in accordance with the availability of its neurotransmitter. That is, in the absence of a neurotransmitter, a receptor becomes supersensitive so as to respond maximally to any remaining transmitter. Conversely, when a neurotransmitter exists in excess, the receptor sensitivity is diminished. The fluctuation of receptor sensitivity has been demonstrated most elegantly for the adrenergic receptors of the cat nictitating membrane (Langer and Trendelenburg 1966).

Recently, many investigators have demonstrated changes in the sensitivities of central DA receptors after various pharmacologic agents or brain lesions. We have mentioned previously that the turning behavior that develops in rats after unilateral destruction of the substantia nigra has been attributed to a form of “behavioral supersensitivity” presumably due to supersensitivity of postsynaptic DA receptors that develops after structural denervation (Ungerstedt 1971b). We have also mentioned that stereotypy can be induced by DA receptor agonists and interrupted by blockers of DA receptors. When DA receptors are chronically blocked by neuroleptic drugs (i.e., pharmacologically denervated), the stereotypy resulting from DA agonists is much enhanced (Schelkunov 1967). However, a similar supersensitivity of stereotyped motor behavior develops as well after chronic stimulation of DA receptors (Klawans 1975). These and other complexities in interpreting behavioral assays of DA function make it difficult to equate behavioral supersensitivity to postsynaptic neuronal receptor supersensitivity. Behavioral aspects of drug-induced dopaminergic supersensitivity are fully discussed by Moore and Thornburg (1975) and Ungerstedt et al. (1975).

More direct investigation of neuronal sensitivity has been made by studying the depression of neuronal firing caused by DA. A microiontophoretic study of the caudate nucleus depleted of DA by intraventricular 6-OHDA showed an increase in the ability of DA to depress neuronal firing that was induced by excitant amino acids in animals under general anesthesia (Siggins, Hoffer, and Ungerstedt 1974).

We have previously discussed the possibility that supersensitivity may be mediated by increased responsiveness of DA-sensitive adenylate cyclase. It does not appear that this is the mechanism. Neurochemical evidence for supersensitivity of denervated neurons is the finding that the normal inhibition of DA turnover produced by the DA-receptor-stimulating agent apomor-
Phine is significantly enhanced after chronic pharmacological denervation by haloperidol (Gianutsos, Hynes, and Lal 1975). Similarly, apomorphine causes a significantly greater increase in ACh levels in the denervated caudate nucleus than in the intact caudate nucleus (Fibiger and Grewaal 1974). These data could represent an increased inhibitory effect of DA on denervated cholinergic neurons in the caudate nucleus.

Supersensitivity of DA receptors may be relevant to dopaminergic hyperactivity in schizophrenia, and has been discussed by Bowers (1974a) on the basis of a lack of increase in CSF HVA. Klawans (1975) has also advocated this concept as the basis of schizophrenia as well as amphetamine psychosis based on the reports of Janowsky et al. (1973) and Connell (1958). Johnson and Milner (1966) and West (1974) found that schizophrenics are unusually sensitive to methylphenidate or amphetamine. Dose-response curves for selected effects of a DA agonist such as apomorphine or a DA-releasing agent such as amphetamine will be needed in untreated schizophrenics and controls to test this hypothesis.

Inactivation of Dopamine

Functional inactivation of DA can occur by several different processes including 1) neuronal reuptake, 2) enzymatic breakdown, and 3) storage. We will briefly discuss the biochemistry of these processes and the relevance of each to schizophrenia.

**Dopamine Uptake and Adenosine Triphosphatase**

The major mechanism for terminating the action of catecholamines once they have been released from nerve endings in the peripheral sympathetic nervous system is via transport directly back into the nerve ending in a process called neuronal reuptake (Iversen 1967). Comparable processes are believed to occur in the CNS for catecholaminergic and serotonergic neurons. This reuptake process is an active, energy-dependent process rather than passive diffusion. It proceeds against a concentration gradient, is stereochemically specific, and is temperature dependent. The uptake process also appears to depend on the activity of the sodium pump (the Na⁺-K⁺-Mg²⁺-dependent adenosine triphosphatase (Na⁺,K⁺-ATPase)) which is crucial to maintaining a high intracellular potassium concentration and a low intracellular sodium concentration. Tricyclic antidepressant drugs, anticholinergic drugs, and ouabain can inhibit the reuptake of DA in brain slices or brain nerve endings (Nose and Segawa 1974 and Ross and Renyi 1975a, 1975b, and 1975c). If this effect occurred in vivo, it would lead to an increased availability of DA at postsynaptic receptor sites. Such an effect has been proposed as the basis for the antiparkinsonian action of the anticholinergic drugs (Coyle and Snyder 1969a). Conceivably, such a mechanism might contribute to the exacerbation of schizophrenic symptoms sometimes seen with tricyclic antidepressant drugs (Pollack et al. 1965) and the anticholinergic drugs (Singh and Kay 1975a and 1975c). Chlorpromazine can inhibit the uptake of catecholamines in peripheral sympathetic neurons, but the effect is present at such high concentrations that it is doubtful that this action is relevant to its antipsychotic effect (Gey and Pletscher 1964 and Thoenen, Hurlimann, and Haefely 1965). In any event, this effect would tend to promote dopaminergic activity.

Recent investigations have called attention to the effects of catecholamines themselves on Na⁺,K⁺-ATPase activity (Kaack 1972, Schaeffer, Unyi, and Pfeifer 1972, and Yoshimura 1973). Although very high concentrations of the catecholamines were required to demonstrate an effect, it is possible that the Na⁺,K⁺-ATPase in schizophrenics' brain may be more sensitive to DA.

There have been numerous efforts to relate the antipsychotic effect of the neuroleptic drugs to their capacity to inhibit Na⁺,K⁺-ATPase. The neuroleptics are relatively poor inhibitors of brain Na⁺,K⁺-ATPase, however, and the nonantipsychotic neuroleptics are generally as effective as the antipsychotic neuroleptics in producing this effect (Davis and Brody 1966). Gubitz, Akera, and Brody (1973) proposed that the free-radical form of the phenothiazines, which can be formed in vivo, may be the active species that inhibits Na⁺,K⁺-ATPase. There is as yet no study of the relative potencies of the free-radical forms of phenothiazines as inhibitors of human brain Na⁺,K⁺-ATPase. Perhaps the capacity of phenothiazine free radicals to inhibit the Na⁺,K⁺-ATPase from brain tissue of unmedicated schizophrenics, should it be obtainable, would correlate better with antipsychotic potencies.

**Enzymatic Breakdown**

The enzymatic breakdown of DA can be divided into two independent pathways, namely deamination by MAO (Rosengren 1960) and O-methylation by COMT.
(Axelrod, Albers, and Clemente 1959). These two enzymes can act consecutively on DA or the ensuing catabolite and in either order (figure 9).

COMT is a soluble enzyme and ubiquitous throughout the brain. The physiologic role of COMT is uncertain; it may serve to increase tyrosine hydroxylase activity by reducing the concentration of deaminated catecholamines that can inhibit tyrosine hydroxylase (Jarrot 1973). COMT is located in glial cells, suggesting it may serve to inactivate the DA and NE taken up from the synaptic cleft by glial cells (Katz, Goodwin, and Kopin 1969). Mathyse and Baldessarini (1972) studied the activity of this enzyme in the red blood cells of schizophrenics and controls and found no significant difference. This, of course, may not be true of the enzyme in dopaminergic brain regions in some schizophrenics.

Dill and Campbell (1973) reported that 3-methoxytyramine (O-methyl dopamine; figure 9), the product of O-methylation of DA, can produce effects on the basal ganglia similar to those of known hallucinogens (such as mescaline) and proposed that 3-methoxytyramine could be an endogenous psychotoxin in schizophrenia. No direct evidence for this hypothesis has been presented. O-methyl dopamine might be likely to accumulate in some cases of schizophrenia if there is indeed a deficiency in the MAO that inactivates DA in some areas of schizophrenia (see Wyatt and Murphy, p. 77 of this issue). Studies on the role of methylated amines in the etiology of schizophrenia have been reviewed by Rosenstein and Friedhoff (p. 90 of this issue).

MAO is located in the outer membrane of mitochondria. Recent evidence suggests that MAO may exist in multiple forms (Costa and Sandier 1972 and Usdin 1974). The physiologic role of MAO is to inactivate unbound intracellular amines, especially within neurons. The products formed by MAO may not all be inactive, however, since the aldehyde metabolites (figure 9) may have biological activity (Barondes 1962 and Sabelli et al. 1969).

The demonstration of low blood platelet MAO activity in some schizophrenic patients (Wyatt and Murphy, p. 77 of this issue) has raised the possibility that diminished brain MAO activity might contribute to excessive dopaminergic activity in schizophrenia. Recent postmortem studies of schizophrenic brains have failed to show any such deficit (Schwartz et al. 1974); but the problems of postmortem studies are such that this cannot be accepted as a definitive demonstration that MAO activity in some areas of the schizophrenic brain is not significantly diminished. Because of the possible heterogeneity of MAO in different areas of the brain, determination of MAO activity with DA as substrate in small groups of neurons from areas of the brain relevant to schizophrenia in untreated schizophrenics and controls would be required to test this hypothesis definitively; it is well-nigh impossible, however, to conceive of the circumstances under which such a study could be carried out. There is some indirect evidence that inhibition of MAO is not relevant to schizophrenia in that potent MAO inhibitors that inhibit all forms of MAO and that should nearly completely suppress the oxidative catabolism of DA have little capacity by themselves to produce an exacerbation of schizophrenia and may even have some therapeutic benefits (Hedberg, Houck, and Glueck 1971, Lauer et al. 1958, and Spaide et al. 1969). The failure of MAO inhibitors routinely to exacerbate schizophrenia could be the result of alternative routes of DA metabolism or the possibility that even though DA accumulates under such conditions, other amines also accumulate and might antagonize the effects of increased DA. These alternatives seem somewhat strained; thus, these MAO studies may be considered as significant negative evidence against both the MAO and DA hypotheses.

**Dopamine Metabolites in Cerebrospinal Fluid of Schizophrenic Patients**

HVA, the major metabolite of DA, is formed as a result of both O-methylation and deamination (figure 9). It can be measured in the CSF by fluorometric, gas chromatographic, or mass spectroscopic methods. DOPAC is an intermediate in the formation of HVA, the product of deamination without O-methylation. Under some circumstances, DOPAC may be a better index than HVA of the functional activity of nigrostriatal DA neurons (Roth, Walters, and Aghajanian 1973). There are as yet no studies of DOPAC levels in the CSF of schizophrenics. It is believed that the major contributor to CSF HVA is the caudate nucleus and other dopaminergic structures that border on the lateral ventricles (Garelis et al. 1974, Papeschi et al. 1971, and Sourkes 1973). The increase in DA turnover that occurs when DA receptors are blocked with neuroleptic drugs is reflected in an increase in lumbar CSF HVA levels (Fyro et al. 1974 and Persson and Roos 1969). HVA, as well as other acid metabolites, can be actively transported from...
Figure 9. Enzymatic breakdown of dopamine.

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DOPAMINE
  MAO
  COMT

ALDEHYDE
  ALDEHYDE DEHYDROGENASE (ADH)

O-METHYL-DOPAMINE
  MAO

DOPAC
  DI-HYDROXY PHENYL ACETIC ACID
  COMT

HVA
  HOMOVANILLIC ACID
  ALDEHYDE DEHYDROGENASE (ADH)
```

the CSF to the blood via the choroid plexus (Ashcroft, Dow, and Moir 1968). This transport can be inhibited by high concentrations of the drug probenecid (Gulberg, Ashcroft, and Crawford 1966). Recent studies of CSF HVA have included, therefore, pretreatment with probenecid to diminish the efflux of HVA from CSF and thereby abolish the 5:1 concentration gradient that exists from ventricular to lumbar CSF. The probenecid technique requires that probenecid levels be measured in CSF since the degree of inhibition of acid metabolite efflux varies as a function of probenecid concentration (Cohen et al. 1974), especially at low concentrations of probenecid (Perel, Levitt, and Dunner 1974). HVA from the blood is believed ordinarily not to enter the CSF (Pletscher, Bartholini, and Tissot 1967) but may do so when blood HVA levels are increased, as after L-dopa administration (Prockop, Fahn, and Bailour 1974).

If schizophrenia were associated with a generalized increase in brain DA turnover, HVA in unmedicated schizophrenics should be increased. The absence of an increase would not, however, rule out the possibility of increased DA turnover in dopaminergic neurons that do not significantly contribute to the CSF HVA. For example, the contribution of HVA to CSF by the mesolimbic and limbic cortical dopaminergic neurons (which as mentioned previously may be the critical ones for the pathophysiology of schizophrenia) may be too small, in part because these neurons may be too far from the lateral ventricles to contribute much HVA to the CSF relative to that of the caudate.

Chase, Schnur, and Gordon (1970) found normal HVA levels in six chronic schizophrenic patients who had been drug-free for at least 2 weeks. No probenecid was employed. The fact that these patients had recently been receiving neuroleptics diminishes the significance of this finding. Rimon et al. (1971) compared CSF HVA levels (no probenecid) in 31 untreated, acute schizophrenics and 27 nonschizophrenic psychiatric patients. Although there were no significant differences in the groups as a whole, patients with paranoid schizophrenia or paranoid states had significantly higher CSF HVA levels than nonparanoid schizophrenics plus a small control group. The basis for selecting the small control group (9 out of a possible 27) was not stated.
Bowers and Van Woert (1972), using relatively low doses of probenecid, found levels of CSF HVA in acute schizophrenics that were not different from those found in controls. Bowers (1972) studied CSF levels of HVA and the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) after probenecid administration in three different groups: twelve patients who developed psychotic episodes following self-administration of psychotomimetic drugs (probably LSD), 18 nondrug-induced schizophrenic patients, and 15 prison inmate controls. He found that CSF HVA was not significantly different in the three groups. However, 5-HIAA levels were decreased in the drug-induced psychotic patients, a finding that was attributed to a direct effect of LSD on the activity of serotonergic neurons. In a later study, Bowers (1973) measured CSF HVA and 5-HIAA in 18 untreated acute psychotics (with probenecid, but without measuring probenecid in CSF) and compared the levels with depressive patients and with prison inmates. For all psychotics, HVA and 5-HIAA levels were not significantly different from either control group. However, when the schizophrenics were subdivided into Schneider-positive or -negative (i.e., presence or absence of one or more of Schneider's (1959) first-rank symptoms of schizophrenia), 5-HIAA tended to be high and HVA low in the Schneider-positive group. The ratio of 5-HIAA to HVA was significantly elevated in Schneider-positive psychotics when compared to Schneider-negative psychotics, depressed patients, and inmates. Specific psychotic symptoms were better correlated with 5-HIAA levels than with HVA levels.

In a fourth study, Bowers (1974a) used high doses of probenecid and corrected for the amount of probenecid in CSF. When patients were subdivided on the basis of Stephens-Astrup prognostic ratings, nine poor prognosis schizophrenics had significantly lower mean HVA levels (95±standard error 12 nanograms per milliliter) than did eight good prognosis schizophrenics (142±standard error 20 nanograms per milliliter). Eleven patients with affective psychosis had mean CSF HVA levels (142±standard error 14 nanograms per milliliter) that were significantly higher than those in poor prognosis schizophrenics but not in good prognosis schizophrenics. There were no differences in 5-HIAA levels or probenecid values of the three groups.

Sedvall et al. (1974) found normal levels of HVA in CSF of 34 untreated schizophrenics, some of whom were included in the Fyro et al. (1974) study. This group consistently finds that CSF HVA levels are higher in females than males.

Post et al. (1975) studied 5-HIAA and HVA in 20 acutely psychotic unmedicated schizophrenics, patients with affective psychoses, and controls, with and without probenecid. No significant differences in 5-HIAA and HVA levels in the acute schizophrenics, affective psychoses, and controls were found. Patients with more Schneider-positive symptoms had lower 5-HIAA accumulations and lower HVA accumulations. The latter finding is in agreement with Bowers (1973), but the former is the opposite of Bowers' findings. Following recovery from the acute episode, probenecid-induced accumulations of HVA were reduced compared to those in the acute stage in schizophrenics but not in patients recovered from acute mania. Patients who had been ill more than 1 month before hospitalization tended to have lower HVA levels after recovery than those ill for less than 1 month. Although it was taken as preliminary evidence that DA turnover might be reduced in the preschizophrenic phase and relatively increased in the acute stage, this finding is difficult to evaluate. Only 12 of 17 schizophrenic patients and 6 of 16 manic patients were studied in the recovered phase; yet the mean levels were compared to the entire sample of schizophrenic and manic patients. Nevertheless, this lead is a most important one and points up the need for longitudinal studies in unmedicated patients, through as many cycles of health and illness as possible, with collection of a variety of behavioral data to correlate with the biological data.

Van Praag and Korf (1975) studied CSF HVA with probenecid pretreatment and measurement of CSF probenecid in 33 psychotic patients, most of whom would be diagnosed as schizophrenic, and controls (number not specified). Van Praag and Korf (1975) divided the psychotic patients into those with 1) motor agitation and anxiety, 2) anxiety but no motor agitation, or 3) neither motor agitation nor anxiety. They found that HVA levels were significantly increased in the group with motor agitation when compared to the controls or to the other two psychotic groups and postulated that increased DA turnover must be related to motor activity and not to "true" psychiatric symptoms. It is not possible to evaluate this report fully since the differences in HVA levels between the motor agitation group and the others were relatively small, the standard deviation was rather large, and an inappropriate statistical test (a Student's t test uncorrected for the number of comparisons performed rather than an analysis of variance) was used. Sedvall et al. (1974) found no relationship between motor activity and CSF HVA in manic patients.
With the exception of the studies of Post et al. (1975) and Van Praag and Korf (1975), all other studies of lumbar CSF HVA in unmedicated acute schizophrenics (total N > 100) have found low-normal HVA levels. Thus, it seems likely that there is no increase in DA turnover, at least in the caudate nucleus of acute schizophrenic patients. As stated previously, this result should not be used to reject the hypothesis of increased DA turnover in schizophrenia since the functional activity of DA relevant to schizophrenia may not be measured by the method. Furthermore, Bowers (1974a) has cited unpublished data demonstrating that initial HVA levels in untreated schizophrenics are negatively correlated with the dose of a phenothiazine necessary to produce remission. This could indicate that increased transmission in DA pathways, such as the mesolimbic or mesocortical systems, is associated with decreased turnover of DA in the striatum. Bowers (1974a) and Curzon (1975) have pointed out that supersensitivity of DA receptors might permit an increased DA activity in the face of low or normal HVA levels.

**Neuroendocrine Studies of the Dopamine Hypothesis**

The major determinant of prolactin secretion from the pituitary gland appears to be the tonic inhibitory influence of DA released from the tubero-infundibular DA neurons of the hypothalamus. DA may promote the release of a prolactin inhibitory factor (PIF) into the pituitary portal vessels, which in turn inhibits prolactin release. Alternatively, DA itself, after gaining access to the pituitary-portal circulation, may reach the pituitary portal vessels, which in turn inhibits prolactin release. Sachar (in press) did not observe any increase in serum prolactin in untreated schizophrenics. As stated previously, this result should not be used to reject the hypothesis of increased DA turnover in schizophrenia since the functional activity of DA relevant to schizophrenia may not be measured by the method. Furthermore, Bowers (1974a) has cited unpublished data demonstrating that initial HVA levels in untreated schizophrenics are negatively correlated with the dose of a phenothiazine necessary to produce remission. This could indicate that increased transmission in DA pathways, such as the mesolimbic or mesocortical systems, is associated with decreased turnover of DA in the striatum. Bowers (1974a) and Curzon (1975) have pointed out that supersensitivity of DA receptors might permit an increased DA activity in the face of low or normal HVA levels.

**Serum Prolactin Levels in Schizophrenics**

Serum prolactin levels in schizophrenics are elevated within 15-30 minutes after an intramuscular injection of chlorpromazine (H. Y. Meltzer, D. J. Goode, and W. W.
Meltzer, Sachar, and Frantz (1975) found serum prolactin to be elevated 12 hours after the first oral dose of several phenothiazines in 12 of 20 schizophrenics. Possible reasons for lack of an increase in all patients include the possibility of patients not taking medication, problems in absorption, rapid metabolism, or failure of the tubero-infundibular neurons to respond. After several days of phenothiazine administration, serum prolactin levels were elevated in all subjects studied by Meltzer, Sachar, and Frantz (1974a and 1974b) and Meltzer and Fang (1976), but in only 11 of 14 subjects studied by Kolakowska et al. (1973).

Longitudinal study of serum prolactin levels in schizophrenics following phenothiazine treatment has demonstrated that in the majority of patients whose serum prolactin levels were determined 12 hours after the last dose, the levels rose to a plateau within less than a week providing dosage was not increased (Meltzer and Fang 1976). If dosage was increased, serum prolactin levels usually but not always increased further.

There was no decline in serum prolactin levels in 20 subjects studied over a 3-month period, indicating that no tolerance to this effect of the phenothiazines develops. There is some evidence that tolerance to the effects of neuroleptic drugs on neostriatal DA receptors develops in man in that the capacity of these drugs to induce extrapyramidal side effects diminishes within several months of continuous use in most patients (Klein and Davis 1969). Since tolerance to the antipsychotic effects of the neuroleptic drugs does not usually develop, this suggests that the tubero-infundibular neurons and the hypothalamic-pituitary DA receptors are more similar to those relevant to the antipsychotic effects of the neuroleptics than are those of the neostriatum.

Discontinuation of neuroleptic drugs in eight patients who had been receiving neuroleptics at doses of 200 to 800 mg chlorpromazine or its equivalent for 2-3 months led to a rapid fall in serum prolactin (Meltzer and Fang 1976). By 24 hours, serum prolactin had decreased 30-70 percent; by 48-72 hours, it was within normal limits (Meltzer and Fang 1976). Thus, the blockade of tubero-infundibular DA receptors is readily reversible just as its onset is rapid. By contrast, clinical antipsychotic improvement after initiation of treatment is slower by at least several days and frequently weeks; similarly, relapse after stopping neuroleptics in an acute schizophrenic in remission may also not take place for days, weeks, or months. Conceivably, this could represent a major difference between the tubero-infundibular DA system and the dopaminergic system relevant to psychosis in terms of time of onset and time of decrease in phenothiazine effects. A more likely possibility is that dopaminergic blockade or inhibition of DA release is only the initial event in a much more complex sequence of neuronal events. Perhaps events with a comparatively long half-life, such as slow axoplasmic transport, induction of synthesis of new enzymes, or axonal sprouting that might be dependent on dopaminergic neuronal activity, must be altered before the antipsychotic effect is manifest.

In any event, the rapid decay of the effect of neuroleptic drugs on serum prolactin suggests that for some pharmacologic studies in man, it may be appropriate to wait only brief intervals after discontinuing medication to be free of a drug effect, particularly if the subject has been receiving medication for only a brief time. This might be especially true for studies involving DA receptors. Other effects of neuroleptics might be much more persistent.

Meltzer, Sachar, and Frantz (1974a and 1974b) and Meltzer and Fang (1976) studied serum prolactin levels in unmedicated schizophrenic patients. Levels in 8 a.m. samples were within normal limits, even in the most severely disturbed patients. As acute stress increases serum prolactin in man (Noel et al. 1972), this finding was surprising. Conceivably, chronic stress might not elevate serum prolactin. Alternatively, pathologically increased dopaminergic activity in the tubero-infundibular tract in schizophrenic patients might inhibit the effect of stress on serum prolactin. L-dopa and apomorphine block the effect of restraint stress on serum prolactin in rats (H. Y. Meltzer, S. Daniels, and V. S. Fang, unpublished data).

Major future uses of serum prolactin levels in schizophrenic patients receiving neuroleptic drugs are to attempt to correlate the prolactin levels achieved after several days' administration with blood levels of the phenothiazines, EPS, or clinical response. Sachar (in press) noted that the time course and individual variation in extent of increase in serum prolactin after a single oral or intramuscular dose of chlorpromazine or thioridazine was suggestive that prolactin levels might parallel drug levels and be more useful than drug levels that are technically more difficult to assay. It is
conceivable that measurement of the duration of the serum prolactin increase after administration of depot neuroleptic drugs may be useful in determining the frequency of need for such injections. Kolakowska et al. (1975) did in fact find a significant correlation between blood levels of chlorpromazine and serum prolactin levels in a small group of schizophrenic patients. No relationship between prolactin levels and EPS was found in this study.

Meltzer and Fang (1976) found a significant correlation between improvement in psychotic behavior and the magnitude of serum prolactin levels after prolonged treatment with 400 mg chlorpromazine or its equivalent in 12 male schizophrenic patients (Spearman \( r = .532, p < .05 \)) but not in 11 female schizophrenics (Spearman \( r = .150, p > .025 \)). In some patients, serum prolactin levels did not significantly correlate with the highest dosage of phenothiazine prescribed when the dosage was translated to chlorpromazine or its equivalent. This may have been due to the fact that there was evidence that thioridazine tended to produce higher serum prolactin than chlorpromazine or trifluoperazine (Meltzer and Fang 1976). Kolakowska et al. (1975) also found slight evidence of a direct relationship between serum prolactin levels following phenothiazine treatment and clinical response. Prospective studies of this relationship with multifaceted assessment of clinical response and concomitant measurement of blood levels of drugs are needed.

Utilization of serum prolactin levels as an index of the activity of tubero-infundibular DA neurons and the DA receptors of these neurons should be of additional value in exploring many problems relative to schizophrenia. For example, stimulation by apomorphine could determine if there is a supersensitivity to dopaminergic agonists, in which case the decrease in serum prolactin levels should be greater than in controls. Such studies carried out in patients medicated with neuroleptics could demonstrate supersensitivity that might be useful in predicting patients vulnerable to the development of tardive dyskinesia, which as stated before, is possibly the result of supersensitivity in the neostriatial dopaminergic system.

**GABA and Schizophrenia**

Roberts (1972) has hypothesized that the inhibitory neurotransmitter GABA may be deficient in schizophrenia. He has theorized that there may be pacemaker or command neurons that use GABA as a neurotransmitter and that inhibit complex preprogrammed neuronal circuits that regulate discrete bits of behavior. A decrease in the activity of these GABA neurons might initiate hyperactivity of dopaminergic neurons. There is accumulating evidence that GABA-minergic neurons with cell bodies in the globus pallidus, and possibly the putamen, synapse on the dopaminergic neuronal cell bodies in the substantia nigra and inhibit the activity of these neurons (Kim et al. 1971, McGee et al. 1971, and Yoshida and Precht 1971). There is as yet only limited but intriguing pharmacologic evidence for a GABA-minergic influence on mesolimbic dopaminergic neurons. Stevens, Wilson, and Foote (1974) postulated that the ventral tegmental area (VTA) in the rat might receive GABA efferents from limbic dopaminergic tracts—that is, from nucleus accumbens septi, olfactory tubercle, and the nucleus of the stria terminalis. They injected the putative GABA-blocking agent bicuculine into the VTA or the substantia nigra of freely moving cats with stereotactically implanted cannulas. Bicuculine in the VTA rapidly produced hypervigilance, followed by staring, crouching, and the appearance of intense fear. This reaction was followed by behavior that was cautiously and tentatively characterized as catalepsy, stereotypy, waxy flexibility, and possible hallucinations. Injection of bicuculine into the substantia nigra produced grooming, circling, and hyperesthesia. Amphetamine potentiated and haloperidol inhibited the effects of bicuculine injected into the VTA. The authors favored the conclusion that bicuculine in the VTA blocked GABA inhibition of mesolimbic dopaminergic units that mediate dopaminergic stereotyped behavior. However, they point out the possibility of a cholinergic influence on the VTA and of nonspecific synaptic excitant effects of bicuculine. These GABA studies require verification and extension of the investigation of the role of GABA in mesocortical and mesolimbic dopaminergic activity.

Because GABA levels in brain increase rapidly after removal or death, direct measurement of GABA in brain is not likely to be a useful test of the GABA hypothesis of schizophrenia. However, the activity of glutamic acid decarboxylase (GAD), the enzyme that controls the synthesis of GABA, can be measured in postmortem material. It has been repeatedly demonstrated that GABA levels and GAD activity are markedly decreased in the brains of deceased Huntington’s chorea patients (McGeer, and Fibiger 1973 and Perrin, Hansen, and Kloster 1973), a disease that sometimes presents...
with schizophrenic symptoms (Garron 1973) and that is partially responsive to neuroleptic drugs (Fahn 1973 and Ringel, Guthrie, and Klawans 1973) and GABAnergic agents (Andén, Dalen, and Johansson 1973 and Mattsson and Boman 1974). GAD activity has not been found to be decreased in a pilot study of schizophrenic brains (McGeer, McGeer, and Fibiger 1974), but further studies should be carried out since it is extremely difficult to interpret results in postmortem studies of psychiatric patients who had been treated for many years with high doses of neuroleptic drugs, who may have had intercurrent illnesses at the time of death, and who may not even have been adequately diagnosed in the first place. Even if no definitive decrease in total GAD activity is found in specific brain regions, the role of GABA would not be definitively disproven because the functional activity of the enzyme might still have been reduced in vivo, or conceivably GABA inactivation might have been enhanced. Determination of GABA levels in the CSF of untreated and neuroleptic-treated schizophrenics could also be of interest.

Frederiksen (1975) has recently reported that baclophen, a phenyl GABA derivative that can cross the blood-brain barrier, produced a significant and rapid enhancement of the effects of neuroleptics in treatment-resistant schizophrenics. Core symptoms of schizophrenia such as thought disorder and autism cleared. Eventually, the need for neuroleptic medication ceased (Frederiksen 1975). In commenting on this work, has proposed that baclophen increases GABA activity, which in turn inhibits dopaminergic activity. This important clinical study needs documentation.

Dopamine and Neuromuscular Dysfunction

As summarized elsewhere (Meltzer, p. 106 of this issue), there is considerable evidence for neuromuscular dysfunction in some patients with schizophrenic or affective psychoses. This evidence includes increased release of muscle enzymes during an acute psychotic period, morphological abnormalities of skeletal muscle fibers and subterminal motor nerves, and physiologic abnormalities of motor nerves and spinal cord reflexes. A link between the DA hypothesis and neuromuscular functioning would be of interest.

DA has been demonstrated to have a direct effect on neuromuscular transmission (Blum 1969, Capetola, Ferko, and Calesnick 1974, and Gallagher and Karczmar 1973). Gerald and Hsu (1975) demonstrated complex, dose-dependent effects of amphetamine on neuromuscular transmission. Administration of high dose methamphetamine to rhesus monkeys via indwelling jugular catheters for periods of 3 weeks to 3 months produced pathological changes in the morphology of a small proportion of muscle fibers (H. Y. Meltzer, C. R. Schuster, and M. W. Fischman, unpublished data). Similar findings have been demonstrated in rats given d-amphetamine in the drinking water for 2 weeks (H. Y. Meltzer, unpublished data). Skeletal muscle biopsies have been obtained from eight chronic amphetamine abusers who were not also alcohol abusers. In six of eight subjects, there were morphological abnormalities in muscle fibers similar to those in psychotic patients. As previously indicated, PCP, like amphetamine, may produce its psychotomimetic effects by dopaminergic mechanisms. PCP, in conjunction with restraint stress, can produce remarkable increases in rat plasma creatine phosphokinase (CPK) activity as well as extensive muscle pathology (Meltzer 1972). Increases in serum CPK activity have been found in acutely psychotic patients (Meltzer, p. 106 of this issue).

Parkinsonian patients, known to have diminished dopaminergic function in their basal ganglia, also show pathological changes in skeletal muscle fibers similar to the abnormalities present in schizophrenia, that is, fiber-type grouping and scattered atrophy (Edström and Nystrom 1969). Kanner and Meltzer (1974) reported that electrolytic lesions in the rat substantia nigra and knife cuts underneath the globus pallidus can produce pathological changes in skeletal muscle structure. These pathological fibers include scattered atrophic fibers such as those found in schizophrenic patients.
Dopaminergic influences upon alpha-motor neuron excitability may be increased in schizophrenic and manic patients. There is considerable evidence for a descending dopaminergic system that reduces alpha-motor excitability. For example, neuroleptic drugs decrease alpha-motor neuron excitability in rats while L-dopa augments it (Andén, Jukes, and Lundberg 1971). Alpha-motor neuron excitability can be studied in many by means of "H-reflex" testing (Magladery and McDougal 1950). The H-reflex is the electrically evoked counterpart of the spinal monosynaptic or "tendon" reflex. It is elicited by stimulation of the posterior tibial nerve in the popliteal fossa and recorded from surface electrodes placed over the soleus muscle. The H-reflex recovery curve is generated by plotting the ratio of a test reflex response to a preceding conditioning response at varying delays between the conditioning and test stimuli. There are two studies of the H-reflex recovery curve in schizophrenics (Crayton, Meltzer, and Goode 1975 and Glotzner and Mattke 1972). In both studies, about two-thirds of the psychotic patients studied had delayed recovery curves, indicating decreased alpha-motor neuron excitability, and hence possibly increased dopaminergic activity. In both studies, the neuroleptics enhanced recovery, possibly as the result of decreased dopaminergic activity following treatment with these agents.

Whether excessive descending dopaminergic activity could contribute to any of the neuromuscular abnormalities found in psychotic patients is still under investigation. Patients with the largest increases in serum CPK activity or the greatest extent of scattered small angular fibers have usually had decreased H-reflex recovery curves (Crayton, Meltzer, and Goode 1975).

6-OHDA-Induced Damage of the Noradrenergic Reward System: DBH and Schizophrenia

Stein and Wise (1971) have proposed that schizophrenia may be due to endogenous production of the neurotoxin 6-OHDA within the noradrenergic neurons of the medial forebrain bundle, which leads in turn to the destruction of these neurons. On the basis of the theory that noradrenergic neurons of the medial forebrain bundle are believed to mediate rewarded or goal-directed behavior in rats (Stein 1971), Stein and Wise (1971) proposed that damage to this system in man could produce deficits in human goal-directed behavior and in the human capacity to experience pleasure, both of which are said to be characteristic of schizophrenia. However, the medial forebrain bundle is not the only brain tract that will support electrical self-stimulation. Breese, Cooper, and Hollister (1974) presented evidence that self-stimulation in the lateral hypothalamus of the rat can be mediated by DA rather than NE. Fibiger and Phillips (1974) demonstrated that both dopaminergic and noradrenergic pathways in the rat brain can support electrical self-stimulation. Both the nigrostriatal and mesolimbic dopaminergic pathways supported self-stimulation in their studies.

Numerous investigations have shown that 6-OHDA causes a selective and long-lasting depletion of NE from noradrenergic nerve terminals of the sympathetic nervous system, presumably due to a selective neurotoxic action of 6-OHDA on catecholamine-containing neurons (Thoenen and Tranzer 1968; for review, see Malmfors and Thoenen 1971). However, the specificity of its neurotoxic actions for catecholamine neurons has been questioned, especially in the CNS (Poirier et al. 1972). It appears that the effects of 6-OHDA are dose dependent, with neurotoxic actions specific for catecholamine-containing neurons occurring at low concentration of 6-OHDA, and nonspecific histopathology occurring at high concentrations of this drug (Agid et al. 1973 and Stahl et al. 1975). Depending on the dose of 6-OHDA or pretreatment with desipramine, selective depletion of noradrenaline or DA can be produced (Breese and Traylor 1971 and Uretsky and Iversen 1970).

Rats treated with 6-OHDA show a decrease in the rate of self-stimulation of the medial forebrain bundle (Stein and Wise 1971). However, their methodology was strongly criticized by Antelman et al. (1972), who pointed out the possibility of nonspecific drug toxicity and reversibility of the 6-OHDA effect by experimenter priming of the medial forebrain bundle. Stein and Wise (1971) also reported that pretreatment with chlorpromazine antagonized the effect of 6-OHDA on self-stimulation, presumably because chlorpromazine might prevent the NE depletion by blocking neuronal uptake of 6-OHDA. These investigators have speculated that chlorpromazine exerts its antipsychotic effects by inhibiting the uptake of endogenously produced 6-OHDA and thereby preventing destruction of the schizophrenic's noradrenergic reward system.
clinical efficacy of antipsychotic phenothiazines with their ability to inhibit amine uptake, as well as by the fact that many drugs that are potent amine uptake blockers have no clinical effectiveness in the treatment of schizophrenia and may even produce an exacerbation (Pollack et al. 1965).

Stein and Wise (1971) proposed that 6-OHDA could be formed endogenously from DA in the synaptic cleft by auto-oxidation or by enzymatic reaction. They hypothesized that DBH might be diminished, on a genetic basis, in schizophrenia, which might lead to release of DA rather than NE into the synaptic cleft where conversion of DA to 6-OHDA would occur. They also noted that other means of formation of 6-OHDA might be present in schizophrenia. Adams (1972) proposed that 6-OHDA and other related compounds that are toxic to catecholamine neurons might be produced by DBH through the formation of dopamine-o-quinone as an intermediate.

Wise and Stein (1973) assayed postmortem brain specimens from 18 schizophrenic patients and 12 controls and found significant reductions in DBH activity in all regions studied, particularly the hippocampus and diencephalon. Some studies were carried out to determine the effects of postmortem changes, drug treatment, duration of hospitalization, cause of death, and age. These factors were felt not to be sufficient to explain the differences. Subsequently, Wise, Baden, and Stein (1974) reported that the activities of lactic dehydrogenase, MAO, and superoxide dismutase (the latter enzyme being the one that catalyzes the decay of superoxide anions such as those produced by the auto-oxidation of 6-OHDA) were not significantly different in the brains of schizophrenics and controls. There was some evidence for decreased activity of catechol-O-methyltransferase and choline acetyltransferase (the enzyme that catalyzes the synthesis of acetylcholine). The selective decrease in activity in three out of six enzymes was proposed as evidence that nonspecific causes of enzyme inactivation were not present.

Laduron (1975) severely criticized the biochemical method used by Wise and Stein (1973) for DBH assay on several grounds including the fact that the curve presented by Stein and Wise that related DBH activity to substrate concentrations was probably invalid. Wyatt et al. (1975) studied DBH activity in postmortem brains from nine schizophrenic patients and nine controls. There was a tendency for DBH activity to be lower in schizophrenic brain, but this did not reach statistical significance and could be related to drug dosage and the elapsed time between death and freezing the brain for study. However, Laduron's criticism of the assay technique of the Wise and Stein (1973) study could also be leveled against Wyatt et al. (1975). More adequate biochemical studies, including one of the radioimmunoassay for DBH, in brains from young, untreated schizophrenics will be needed to test the DBH hypothesis.

DBH activity may be determined in other tissues. Rosenblatt, Leighton, and Chanley (1973) found that two schizophrenic patients had increased DBH activity in the sympathetic nerves of the salivary gland as judged by conversion of infused tritiated DA to NE. This interesting study needs further attention to methodologic issues and larger numbers of subjects.

Serum DBH activity is believed to result from the exocytosis of NE storage granules by sympathetic nerves (Weinshilboum and Axelrod 1971). Its activity varies widely in man and is under genetic control. Serum DBH activity was studied longitudinally in schizophrenic patients and found not to vary from the acute phase to the remission phase (Meltzer, Cho, and Russo 1975). The distribution of DBH activities is not significantly different in schizophrenics and normals (Dunner et al. 1973. Meltzer et al., in press, Shopsin et al. 1974, and Wetterberg et al. 1972). Since serum DBH activity is under genetic control (Ross, Wetterberg, and Myrhed 1973), if there were a genetic basis for low serum DBH activity in the brains of schizophrenics, one might expect low serum DBH as well. It would appear that at the present time there is little firm evidence for the Stein and Wise theory of schizophrenia.

**Dopamine in Mania, Following Lysergic Acid Diethylamide, and in Depression**

The focus of this review on the role of relative dopaminergic hyperactivity in schizophrenia does not preclude the possibility that dopamine is involved in other psychiatric illnesses or altered states of consciousness. Sack and Goodwin (1974) have reviewed the evidence implicating increased DA in mania. Some recent studies have demonstrated that lysergic acid diethylamide is a
DA agonist (Da Prada et al. 1975, Von Hungen, Roberts, and Hill 1974, and Pieri, Pieri, and Haefely 1974) and suggested that this may be related to its psychotomimetic effects. Halaris, Belendiuk, and Freedman (1975) have proposed that the ability of tricyclic antidepressants to block the reuptake of DA may be relevant to their antidepressant effects, implying that decreased DA is important to the pathophysiology of depression. The fact that the neuroleptics are effective treatments for some types of psychotic depression (Cole and Davis 1975 and Overall et al. 1964) suggests the possibility that increased dopaminergic activity may be relevant to some types of depression. Van Praag et al. (1975) have proposed that changes in DA physiology are related to motor disturbances in the psychoses rather than any disease-specific process.

It is not critical to the dopamine hypothesis of schizophrenia that dopamine only be involved in schizophrenia. It is probable that there are a number of biological abnormalities common to the psychoses (Meltzer 1975). Specificity may emerge from involvement of particular subgroups of dopamine neurons and from other abnormalities that are unique to the psychoses. As will be pointed out in the concluding section of this review, it is our belief that dopaminergic hyperactivity is a secondary phenomenon in schizophrenia.

Conclusions

The evidence for a role for DA in the pathophysiology of schizophrenia is compelling but not irrefutable; the “smoking gun” has not yet been discovered. Evidence consistent with the hypothesis still cannot be transformed into basic principles of the etiology of schizophrenia that could conceivably become the theoretical framework into which the majority of clinical as well as biochemical data that concern schizophrenia might be comprehended.

At the present stage of its evolution, the hypothesis can be tested via clinical pharmacologic studies with 1) a therapeutic intent (e.g., administration of AMPT, GABA-mimetic drugs), 2) the intent of transiently exacerbating symptomatology (e.g., amphetamine, methylphenidate), or 3) a major focus on neuroendocrine indicators of central dopaminergic activity (prolactin). Because of the heterogeneity of schizophrenia and the fact that many state, as opposed to trait, factors are likely to modify clinical response, investigators must be alert to the likelihood of large variances in results and the need to identify subpopulations who respond in a consistent fashion to repeated trials. As morphologic and biochemical techniques of ever-increasing sophistication are developed, postmortem studies of more discrete components of the schizophrenic brain have the potential to yield great breakthroughs; but the possibility of obtaining the appropriate samples, whatever they might be, seems remote because of the near universal use of neuroleptic drugs in diagnosed schizophrenics who are likely to come to autopsy quickly enough after death to be usable for research purposes. Nevertheless, the potential fruits of such studies are so great it would seem that there should be an international effort made to collect such brains, with specimens made available to laboratories throughout the world that have the technical skills to carry out relevant analyses. Spinal fluid metabolite studies in schizophrenics have not yet been especially productive of basic information about the pathophysiology of DA or balancing neurotransmitters, but more work, including the development of methods of measuring brain GABA turnover by CSF studies, might be informative. One of us has reviewed other aspects of the strategy for clinical research in schizophrenia that are applicable for further study of the DA hypothesis in schizophrenia (Meltzer, pp. 10-18 of this volume).

The DA hypothesis is exceptional in the history of biological studies in schizophrenia in the extent to which it has used immediately relevant basic research studies (e.g., investigations of animal models involving amphetamine or PCP administration) and an anatomical basis for the locus of dysfunction (e.g., the limbic DA system) to generate clinical information and to test further elaborations of the hypothesis. It is already clear that investigators, either alone or in interdisciplinary groups, are working concomitantly with humans and laboratory animals, with in vivo and in vitro techniques, to pursue the goal of determining the relevance of DA and related neurotransmitters to schizophrenia. From this flexible research strategy, it is clear that much good science has already emerged and will continue to do so at an increasing rate. As we stated in the introduction, by the criteria of promoting a large variety of attempts at experimental rejection or elaboration of the hypothesis, the DA hypothesis has been an extraordinary success. It is our opinion that it will prove to be functionally correct—that is, some, perhaps even most, schizophrenics, at least at some stages of their illness, will have
the equivalent of hyperactivity of some DA neurons. However, we also believe dopaminergic hyperactivity is probably secondary to some other basic defect that allows for dopaminergic activity to be transiently increased during periods of increased CNS arousal created by excessive environmental demands. It is probable that this core defect is only partially suppressed by decreasing DA activity and, in any event, is suppressed at a slower rate than DA neurons. Direct evidence for the secondary role of DA is the comparison of the rate of increase or decrease in serum prolactin after the initiation or discontinuation of phenothiazines and the rate of clinical change in schizophrenics (Meltzer and Fang 1976). The cause of the biologic defect, or possibly defects, in schizophrenia may not even be defects in any of the known neurotransmitters such as NE, serotonin, or acetylcholine, except possibly GABA (this exception is based only on the very limited clinical report of Frederiksen 1975). Conceivably, the core defect might be viral, autoimmune, cell-mediated toxicity, maintenance of neuronal integrity so as to prevent inappropriate branching or sprouting of central neurons, or an almost limitless possibility of neurochemical processes. The DA hypothesis may, however, provide the guide to this core process as the causes of the apparent increase in dopaminergic activity in schizophrenics are identified.

How could increased dopaminergic activity produce the abnormal behavior associated with schizophrenia? In discussing this issue, it is generally assumed that hyperactivity of the dopaminergic tract itself must generate the psychopathology via some more or less direct output to the motor system. Thus, Snyder (1972) and Stevens (1973) nominate the mesolimbic system and Thierry et al. (1973) and Hokfelt et al. (1974) add the mesocortical dopaminergic tracts. While this may be the case, it could also be that the brain areas that actually generate the psychopathology via some more or less direct output to the motor system. Thus, Snyder (1972) and Stevens (1973) nominate the mesolimbic system and Thierry et al. (1973) and Hokfelt et al. (1974) add the mesocortical dopaminergic tracts. While this may be the case, it could also be that the brain areas that actually generate the psychopathology via some more or less direct output to the motor system.

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