Antipsychotic drug actions: a clue to the neuropathology of schizophrenia?[1]

STEVEN MATTHYSSE[2]

Department of Psychiatry, Harvard Medical School and Massachusetts General Hospital, Boston, Massachusetts 02114

ABSTRACT

Some actions of antipsychotic drugs (electron donor ability, inhibition of oxidative phosphorylation, "stabilization" of membranes) are nonspecific properties of the phenothiazine group. Unlike these effects, enhancement of dopamine turnover in the brain seems to characterize only the antipsychotic subgroup of the phenothiazines. Antipsychotic drugs of the butyrophenone and diphenylbutylpiperidine classes also have this property. It is not yet clear whether the effects of these drugs on dopamine metabolism are related to their effects on mental state, or only to their extrapyramidal side effects. The enhancement of turnover is probably a consequence of blockade of dopamine receptors. *Nucleus accumbens septi* and several other limbic dopamine-containing nuclei are plausible candidates for the site of action of antipsychotic drugs.—MATTHYSSE, S. Antipsychotic drug actions: a clue to the neuropathology of schizophrenia? *Federation Proc.* 32: 200–205, 1973.

Research in schizophrenia has made slow progress, compared to the brilliant insights into Tay-Sachs disease and parkinsonism, reviewed in this symposium by Dr. O'Brien and Dr. Hornykiewicz, but I think the cause is easy to find: there has been no place to start. There is no demonstrable neuropathological change, no definitive mode of genetic transmission, no acceptable animal model. It is true that many agents produce catatonialike posturing in animals, but schizophrenia is, above all, a disorder of thought and of the most subtle aspects of interpersonal relations. At least in depression, some of the cardinal features, such as motor retardation, apathy, and withdrawal from the social group, can be observed in animals. What we do have to guide us in schizophrenia is a plentiful array of psychoactive drugs, whose mental effects—even on the most subtle features of thought and interpersonal relations—can be studied in man, and whose biochemical and physiological properties can be studied in animals.

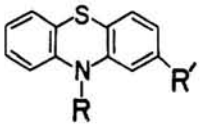
Among our tools we have agents that attenuate the schizophrenic condition (neuroleptics), and agents that exacerbate it (psychotomimetics). There are some advantages to studying neuroleptics. It is arguable that they act more directly to attenuate schizophrenic behavior, than the psychotomimetics act to produce it. In many cases the psychotomimetics produce only the accessory phenomena of schizophrenia, such as hallucinations; the thought content is rarely as regressive and infantile as it is in schizophrenia. A further advantage of the neuroleptics is that there are far more controlled experiments in man, establishing the effectiveness of different ring substitutions. Structure-activity relations of neuroleptics are provided without charge by drug companies, whereas in the case of psychotomimetics, the experiments are generally conducted far from the eyes of reviewers.

When we begin to study the phenothiazines, we encounter an unexpected embarrassment of riches. The phenothiazines have a notoriously wide spectrum of actions, from protozoan motility to the pecking behavior of pigeons. In Europe chlorpromazine is even known by the ubiquity of its effects: it is called "Largactil." A method is needed for selecting, for further study, the effects that may be relevant to schizophrenia. Figure 1 depicts a group of phenothiazines that are commonly judged to be *not* antipsychotic. They are used as antihistaminics, antiemetics, sedatives, or in the treatment of Parkinson's disease. We decided to reject, as not relevant to schizophrenia, those actions shared equally by phenothiazines with and without antipsychotic actions. On the other hand, the relevance of a biochemical or biophysical effect of the antipsychotic phenothiazines is enhanced if antipsychotic drugs of nonphenothiazine structures, such as the butyrophenone haloperidol, have the same property. This criterion leads us to reject several well-known effects of chlorpromazine, as not relevant to the action of this drug in schizophrenia. Among them are electron donor ability, inhibition of oxidative phosphorylation, and "stabilization" of membranes. Typical experiments will be briefly illustrated.

Foster and Fyfe (21) used nuclear magnetic resonance to measure the binding of 1,4-dinitrobenzene, an electron acceptor, with various phenothiazines. Promazine was the strongest donor; chlorpromazine the weakest; and the nonantipsychotics diethazine, trimeprazine, promethazine and ethopropa-

[1] From the symposium on *Contributions of Neurochemistry to Neurology and Psychiatry* presented at the 3rd meeting of the American Society for Neurochemistry, Seattle, Wash., March 23, 1972.

[2] Supported by the Benevolent Foundation of Scottish Rite Freemasonry, Northern Jurisdiction, U.S.A., and Public Health Service Grant MH-16674 from the National Institute of Mental Health.



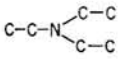
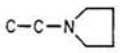
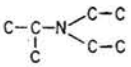
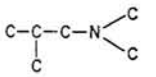
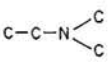
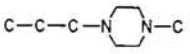
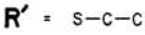
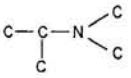
DRUG	R	DRUG	R
DIETHAZINE		PYRATHIAZINE	
ETHOPROPAZINE		TRIMEPRAZINE	
FENETHAZINE		THIETHYLPERAZINE	
METHDILAZINE		R′ =	
PROMETHAZINE			

Figure 1. Nonantipsychotic phenothiazines.

zine were in the middle. Medina (40) studied the coefficient of respiratory control (the ratio of oxygen consumption under conditions of ADP-stimulation to the unstimulated ratio), an index developed to estimate the efficiency of oxidative phosphorylation, using isolated sarcosomes from guinea pig heart. Chlorpromazine inhibited this ratio 40%; but promethazine also inhibited it 40%. "Stabilization" of membranes can be estimated by the degree to which a drug protects red cells against lysis in distilled water. The 50% effective dose is 1.9×10^{-5} molar with chlorpromazine; this dose is right in the middle, higher than the 50% effective molarity of thiethylperazine but lower than the effective molarity of pyrathiazine (both nonantipsychotics) (17). Surface activity can also be estimated by the lowering of surface tension of a Ringer's solution. Seeman and Bialy (53) found that chlorpromazine and ethopropazine had an identical effect on surface tension, although they did not realize at that time how much the two drugs differ in antipsychotic potency. Nearly all the studies that are comparative fail to show a clear differentiation between antipsychotic and nonantipsychotic phenothiazines. Our Ockham's razor is almost too sharp: from an embarrassment of riches we arrive at a scarcity of promising effects.

One reported effect, however, does seem to differentiate the subgroups successfully: neuroleptics increase the rate of dopamine turnover (synthesis and destruction) in the brain. This phenomenon has been found using each of the five major methods of estimating turnover of amines: *1*) accumulation of dopamine after monoamine oxidase inhibition; *2*) depression of dopamine by α-methyltyrosine; *3*) tissue concentrations of homovanillic acid; *4*) radioactive dopamine appearance after intravenous infusion of radioactive tyrosine; *5*) disappearance of radioactive dopamine after previously labeling brain storage sites. Since each method has its pitfalls, it is encouraging that they all give the same result.

Carlsson and Lindquist (8) found that chlorpromazine and haloperidol, *but not promethazine*, increased *O*-methyldopamine in mouse brain after monoamine oxidase inhibition. Anden et al. (2) reported that chlorpromazine, haloperidol and spiroperidol increased homovanillic acid in rabbit corpus striatum, whereas *promethazine did not.* Trimeprazine had a small effect, which is contrary to the hypothesis, because it is not an antipsychotic phenothiazine. Nyback et al. (42) measured accumulation of dopamine-^{14}C in mouse brain after tyrosine-^{14}C tail vein infusion, and also disappearance of dopamine-^{14}C formed prior to drug administration. Chlorpromazine, haloperidol, levomepromazine, perphenazine and chlorprothixene all increased synthesis and disappearance; *promethazine did not.*

Extrapyramidal symptoms (tremor, peculiar gait, writhing movements) are a prominent side effect of the phenothiazines. Since dopamine is a neurotransmitter in the extrapyramidal system, it is possible that the dopamine turnover effect is only related to the motor side effects of these drugs. Fortunately, the antipsychotic and motor effects of the phenothiazines can be dissociated. Cole and Clyde (11) found that the incidence of parkinsonian side effects with thioridazine is 3%, whereas with other antipsychotic phenothiazines, like fluphenazine, it is as high as 36%. Thioridazine assumes special importance, since using it we can see if the dopamine turnover effect is really characteristic of antipsychotic phenothiazines, or only of those with prominent extrapyramidal effects. Roos (52) found that thioridazine increases homovanillic acid in rabbit corpus striatum. Laverty and Sharman (34) reported that single doses of thioridazine, like chlorpromazine, increased caudate homovanillic acid in the cat, but chronic administration of thioridazine failed to have an effect, although chlorpromazine continued to do so under these conditions. In mice, however, both drugs increased striatal homovanillic acid to an identical extent, as well as the disappearance of dopamine after α-methyltyrosine (44). In man there are two interesting though inconclusive reports of homovanillic acid increases after thioridazine: Gerbode and Bowers (24) observed a value of twice the upper limit of normal, in a patient who had been taking therapeutic doses of thioridazine 4–5 days prior to the tap, and Chase et al. (10) also reported an homovanillic acid elevation after thioridazine in one case. The thioridazine results are puzzling, being consistent with the hypothesis for rabbits and mice, but not for cats.

We chose cerebrospinal fluid homovanillic acid to estimate turnover, in order that we could study monkeys (since species differences in the response to thioridazine have been reported); observe the time course of effects with long-term drug administration; and use each animal as his own control, to facilitate comparison of antipsychotic and nonantipsychotic drugs. More meaningful results can be obtained, in studies of cerebrospinal fluid biogenic amine metabolites, if ventricular rather

TABLE 1. Mean concentrations of 5-hydroxyindolylacetic acid and homovanillic acid in lateral ventricular and cisternal CSF of dog before and during treatment with probenecid.[a]

	5HIAA		HVA	
	Control period	During probenecid treatment	Control period	During probenecid treatment
Mean ventricular concentration (v)	291	434	1309	1995
Mean cisternal concentration (c)	41	274	51	424
Mean of the ratios (v/c) ± standard error	7.23 ± 0.85	1.63 ± 0.08	28.8 ± 10.7[a]	4.90 ± 0.52
(no. of ratio estimates)	(8)	(9)	(5)	(9)

[a] The mean concentration of 5HIAA, 5-hydroxyindolylacetic acid, and HVA, homovanillic acid, are expressed in ng/ml. Data are from Guldberg et al. (27).

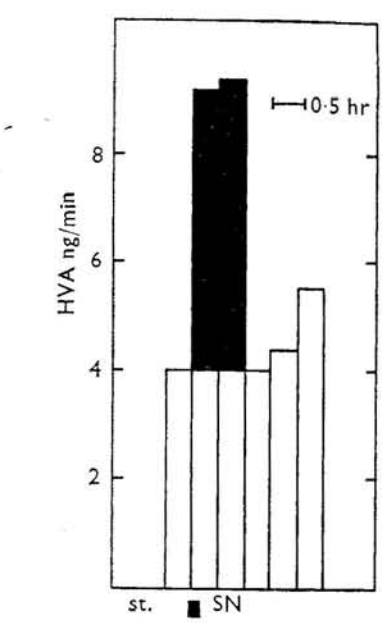
than cisternal or lumbar cerebrospinal fluid is sampled. As shown in Table 1, reproduced from data of Guldberg et al. (27), a very large concentration gradient exists from the lateral ventricle to the cisterna magna, especially for homovanillic acid. Since the gradient diminishes after probenecid treatment, it is thought to reflect active uptake of the amine metabolites along the walls of the third ventricle, cerebral aqueduct and fourth ventricle. Indeed, introduction of 5-hydroxyindoleacetic acid into the cisterna magna of cats was reported not to cause any demonstrable increase in its lumbar cerebrospinal fluid concentration (6). The concentration of homovanillic acid in lateral ventricular cerebrospinal fluid is only indirectly related to the rate of dopamine turnover in surrounding structures, but, as shown in Fig. 2, Portig and Vogt (48) were able to demonstrate a marked increase in the concentration of homovanillic acid in a ventricular perfusate shortly after electrical stimulation of the substantia nigra. It appears, therefore, that functional synaptic release and metabolism are reflected in cerebrospinal fluid homovanillic acid concentrations.

Our operative procedure involves placement of a blunt-tipped cannula in the lateral ventricle, just anterior to the foramen of Monro, using pneumoencephalographic and stereotaxic control (see Fig. 3). If time must elapse before the sampling is begun, the cannula is withdrawn and only a guide tube is left in place; the device is covered with a tight-fitting cap to help prevent infection. In order to begin sampling cerebrospinal fluid, the cannula is inserted through the guide tube into the lateral ventricle, and a small amount of fluid is withdrawn by suction into a small diameter tube. The tubing is inverted below the level of the lateral ventricle, and fluid begins to flow. In order to avoid draining the ventricular system completely, a valve device is used that permits one drop of cerebrospinal fluid to flow every four minutes into a fraction collector. Fluid is sampled continuously for 30–60 days.

In Fig. 4 are combined the results of administering five drugs, and a saline control, to a single monkey over a 30-day period. The overall time period of the measurements is 36 hours, to permit determination of the magnitude and duration of the rise. All drugs were injected intramuscularly, in procaine solution to prevent pain, at a dose of 10 mg/kg. A marked elevation resulted from chlorpromazine treatment, as was previously observed in anesthetized dogs (26); saline, promethazine and methdilazine had no effect. The effect of trimeprazine was small. The negative findings with these three nonantipsychotics support the hypothesis. The rise following thioridazine is rather small, considering that its antipsychotic potency is generally regarded as equivalent to chlorpromazine; the possibility cannot be excluded, on the basis of this first comparative experiment, that the dopamine turnover effect is more closely related to motor system side effects than to antipsychotic actions. Extension of the comparison to other nonantipsychotic phenothiazines, and further investigation of the relative magnitude of the thioridazine effect are in progress.

We have emphasized studies of dopamine in preference to noradrenaline because in previous experiments, increases in noradrenaline turnover seemed to be nonspecific phenothiazine effects, shared equally by promethazine and antipsychotic phenothiazines (42). Although the phenothiazines and butyrophenones have actions on both noradrenaline and dopamine turnover, it appears that a new neuroleptic, pimozide (a diphenylbutylpiperidine), augments dopamine turnover without affecting the metabolism of noradrenaline (43). Pimozide is said to be an effective antipsychotic drug (32), but it is believed to be without sedative properties and to be useful primarily in patients whose overactivity and agitation have been controlled by other means (56). Its lack of sedative action is consistent with the view that arousal and activity level are influenced primarily by the noradrenaline system. It seems unlikely to be a coincidence that three distinct classes of neuroleptic compounds—phenothiazines, butyrophenones and diphenylbutylpiperidines—all affect the synthesis and destruction of dopamine. Another set of observations connecting dopamine and psychosis is the repeated finding of psychosis arising as an unwanted consequence of L-dopa treatment. Yaryura-Tobias et al. (61) reported that dopa exacerbates psychoses when it is used to treat extrapyramidal symptoms in schizophrenics; 4 out of 5 schizophrenics are said to have developed hallucinations. Jenkins and Groh (33) reported that 7 out of 90 patients with Parkinson's disease developed psychotic symptoms after dopa,

Figure 2. Release of homovanillic acid (HVA) after stimulation of the substantia nigra (SN). (From Portig and Vogt (48).)



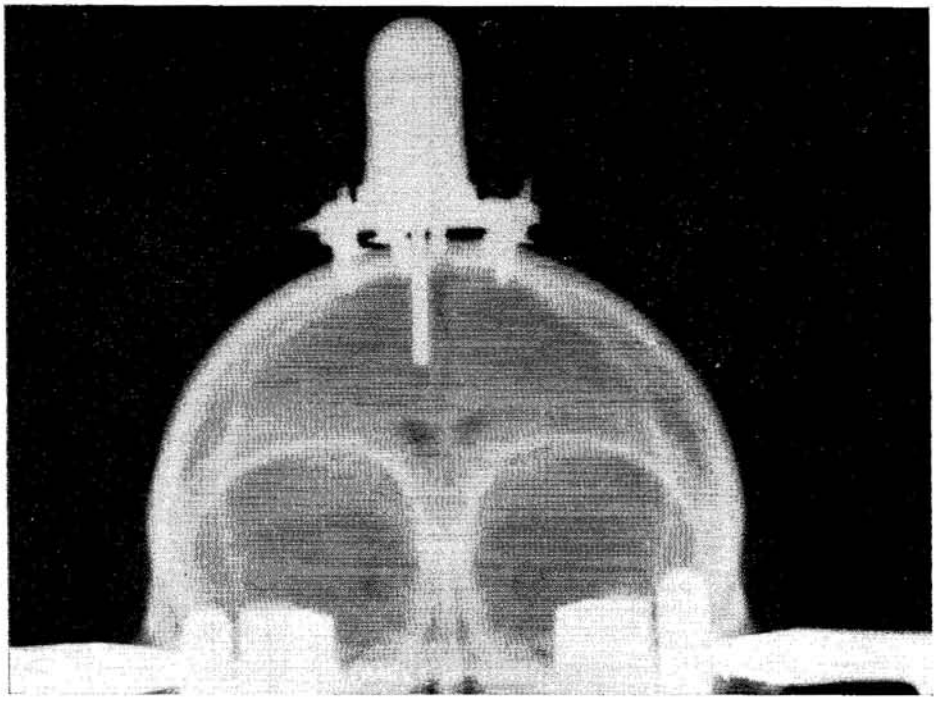


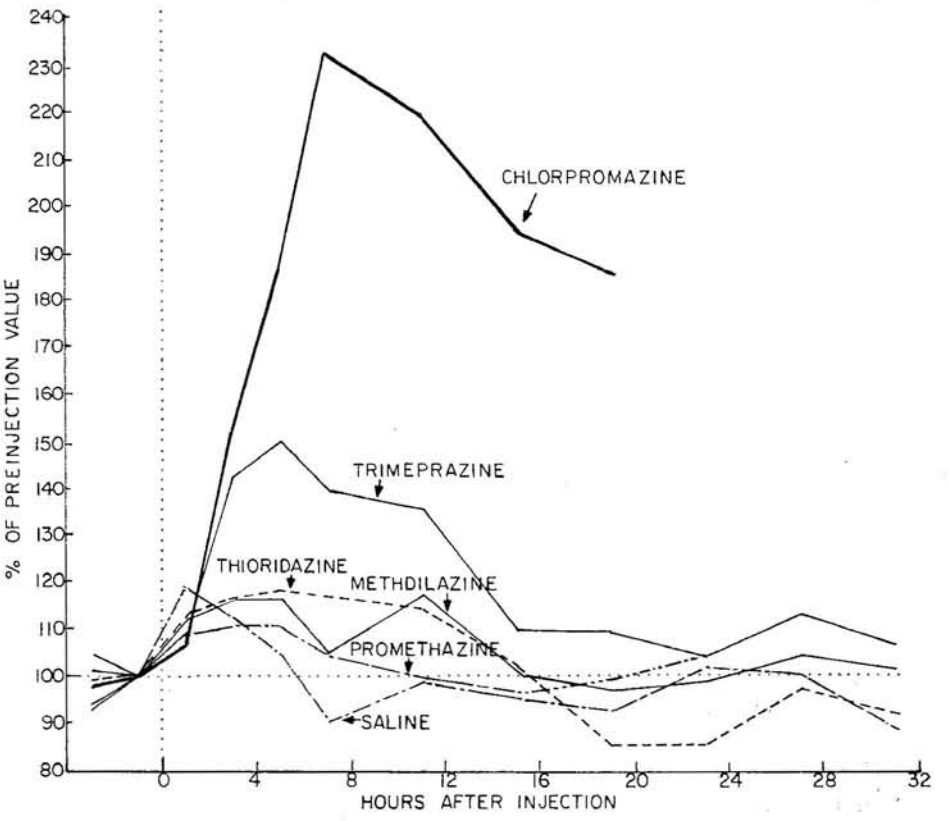
Figure 3. Pneumoencephalographic implantation of ventricular cannula.

and Celesia and Barr (9) found the incidence to be 8 out of 45. Bunney et al. (7) observed increased psychotic behavior in 4 out of 10 depressives receiving L-dopa.

It is thought that the primary action of the neuroleptics is blockade of dopamine transmission, and that the increased turnover is a compensatory mechanism in which the presynaptic dopamine neuron is released from negative feedback inhibition. Direct evidence for blockade of dopamine synapses by neuroleptics is scarce, but the results so far obtained are consistent with this interpretation. Feltz (19) observed that excitatory responses in the caudate nucleus to stimulation of the substantia nigra were blocked by local application of haloperidol. The blocked cells did not, however, respond to dopamine, and the possibility of a local anesthetic action could not be ruled out. Similarly, iontophoretic chlorpromazine has been observed to suppress caudate responses to nigral stimulation, but local anesthetic activity of the drug could not be excluded (Connor, personal communication). In the putamen, however, iontophoretic chlorpromazine does appear to antagonize dopamine actions, even after its local anesthetic effect has worn off (62). Neurons in the nucleus solitarius (which contains dopamine nerve terminals) are accelerated by apomorphine, a dopamine receptor stimulant; chlorpromazine blocks the stimulation by apomorphine, and in this case a local anesthetic effect is unlikely, because chlorpromazine alone had no effect (58).

Suppose we now assume that the hypothesis of specific blockade of dopamine transmission by neuroleptic drugs is true, even though all doubts have not been laid to rest; does the theory give us any clues to the neuropathological basis of schizophrenia? The most well-known dopamine pathway is the nigrostriatal tract, which is not likely to be related to psychosis. The retinal dopamine cells are not likely candidates either, nor is the hypothalamic tubero-infundibular dopamine system. There are also dopamine terminals in what is called the "mesolimbic" dopamine system: the nucleus accumbens septi, the centralis nucleus of the cortico-medial amygdaloid group, the anterior perforated substance (or tuberculum olfactorium), the nucleus of the diagonal band of Broca, and the interstitial nucleus of the stria terminalis. The cell bodies of this system lie in the region surrounding the interpeduncular nucleus (22, 23, 60). In a general way, the importance of these regions of the limbic system for emotional behavior is obvious, but information is scarce about the specific functions of the limbic dopamine nuclei.

Figure 4. Comparison of phenothiazine effects on lateral ventricular homovanillic acid.



Nucleus accumbens septi, although embryologically an extension of the caudate, seems to be functionally related to the septum. Lesions cause increased irritability, as evidenced by hyperactivity and a lower threshold for jumping in response to shock. Possibly because they are more irritable, the lesioned animals acquire conditioned avoidance responses more rapidly (35). The nucleus accumbens septi is also an important self-stimulation site. Despite its reinforcing properties, accumbens stimulation does not produce the generalized arousal found with stimulation of the medial forebrain bundle (51). Electrodes implanted in regions of the mesencephalon that contain cell bodies of dopamine neurons, such as the substantia nigra and the area surrounding the interpeduncular nucleus, give high rates of self-stimulation (16, 45).

Nucleus centralis of the amygdala has rarely been studied separately from the rest of the amygdaloid complex. One electrophysiological study suggests multisensory convergence on centralis units, perhaps with a special sensitivity to sexual stimulation and to novelty (15). It may also play a role in the suppressant effects of punishment on operant behavior. Stereotaxic implantation of norepinephrine abolishes the suppressant effect of punishment (dopamine, however, was without effect) (36, 37).

Anterior perforated substance lesions cause rage reactions, hyperactivity, and excitation (54). Apomorphine-induced stereotyped gnawing behavior (which can be blocked by haloperidol (18)) can be prevented by lesions in the anterior perforated substance but not by lesions in the striatum or nucleus accumbens (38).

Nucleus of the diagonal band, dorsal part, is of interest because it controls the "theta rhythm" of the hippocampus (a 4–7 cycle per second rhythm that appears following sensory stimulation, and seems to be associated with arousal) (47). Chlorpromazine prevents the appearance of the theta rhythm (55). Its relevance to the dopamine system is somewhat obscure, because the dopamine nerve terminals appear to be concentrated in the ventromedial part of the nucleus rather than the dorsal part (23). Stimulation of the hippocampus in man produces changes in imagery and thought processes not unlike schizophrenia; the change has been described as "an altered mental state in which thought regresses from secondary to primary process, from word representations to imagery, and from dim thought images to hallucinations" (30).

It is not possible at present to specify whether the action of the dopamine system on these limbic structures is excitatory or inhibitory. Iontophoretic dopamine is generally inhibitory in the caudate, but excitatory responses have been observed both to nigral stimulation and to local dopamine application (12, 13, 19, 31, 39). Apomorphine, which stimulates dopamine receptors, has an excitatory action on nucleus solitarius neurons (58). It seems likely that the dopamine system modulates activity in the limbic structures that it innervates, rather than directly transmitting information. According to histofluorescence data, the nigro-neostriatal system in the rat contains only about 3,500 neurons on each side (23); the mesolimbic system presumably has even fewer, and this number seems too small to convey information, although it could have a major influence on the excitability of limbic system nuclei.

From the blocking action of neuroleptics on dopamine synapses, it is a relatively small step to postulate overactivity of dopaminergic transmission in schizophrenia, whether generalized or confined to one nuclear group. This simple hypothesis is by no means the only possible interpretation. It is not even the most plausible, since cerebrospinal fluid homovanillic acid concentrations in schizophrenia appear to be essentially normal. Persson and Roos (46) observed no significant abnormality in CSF homovanillic acid in chronic schizophrenics (although homovanillic acid did increase after phenothiazine treatment, as the hypothesis of dopamine blockade by neuroleptics predicts); Rimon et al. (50) also found no difference between acute untreated schizophrenics and age-matched acute psychiatric patients with other diagnoses.

It may be that a system inhibited by, or inhibiting, dopamine neurons is deficient in schizophrenia, and the dopamine blocking action of antipsychotic drugs restores a balance. For example, Purkinje cells, which are inhibitory γ-aminobutyric acid (GABA) neurons, are themselves inhibited by noradrenaline neurons from the locus ceruleus (29). More relevant to the dopamine system, neurons in the substantia nigra are inhibited by an input arising in the caudate (25, 57, 63, 64); this inhibition is thought to be transmitted by GABA since it is blocked by picrotoxin (49). A deficiency in GABA transmission might cause nigral cells to fire excessively, an imbalance alleviated postsynaptically by dopamine blockade.

The possibility that inadequate serotonin transmission is the relevant deficiency is suggested by observations on psychotomimetic drugs. Even if the neuroleptics are a better clue to disturbed functioning in schizophrenia, as I have suggested, it would certainly be desirable to have a theory in which the actions of both types of drugs could be synthesized. As in the case of the phenothiazines, the hallucinogens are potent compounds that may be expected to have many effects unrelated to their psychotomimetic actions. Comparison of effective and ineffective members of a series is, as in the phenothiazine case, a useful way of distinguishing relevant from irrelevant effects. The serotonin blocking actions of lysergic acid diethylamide (LSD) on smooth muscle have led many observers to a fascination with the possible role of central serotonin blockade in its psychotomimetic actions, but bromolysergic acid diethylamide (BOL) is an even more potent peripheral antagonist than LSD, although it does not have hallucinogenic activity. It has been shown that iontophoretic or intravenous administration of LSD suppressed excitatory actions of serotonin on brainstem neurons, whereas the effect of BOL was very weak (53; but see 4a for cautions in interpretation); LSD also reduces the firing rate of raphe neurons, BOL having no effect (1a).

Transmission deficiency in a system whose relations with the dopamine system are inhibitory would fall within the category of "system degenerations" of the nervous system, such as motor system disease (in which lower motor neurons degenerate (1)) or parenchymatous cerebellar degeneration (in which Purkinje cells are specifically affected (41)). Degenerative diseases of neurons utilizing a particular transmitter are known: Parkinson's disease, in which dopaminergic nigroneostriatal neurons degenerate (as reviewed by Dr. Hornykiewicz at this symposium), and Huntington's chorea, in which it is likely that there is selective degeneration of GABA neurons in the putamen, globus pallidus and sub-

stantia nigra (T. L. Perry, unpublished communication).

Several factors cooperate to create a rather favorable situation for experimental study of the dopamine and serotonin systems as they affect limbic system structures, interact with each other, and are modified by neuroleptic and psychotomimetic drugs. *1*) There is a very convenient packaging, as it were, of the dopamine and serotonin cell bodies (near the interpeduncular fossa, and in the raphe nuclei, respectively). *2*) A clear differentiation exists between effective and ineffective members of both classes of drugs (e.g., chlorpromazine versus promethazine, and LSD versus BOL). *3*) The dopamine system (unlike noradrenaline, GABA, or acetylcholine) is restricted to a relatively few nuclear groups, rather than being diffusely scattered throughout the brain. *4*) In view of the functions and neural connections of these nuclei, it is plausible that they may contribute to the pathogenesis of schizophrenia. For these reasons, I think we can look forward to physiological and biochemical studies of psychoactive drugs with some optimism.

Grateful thanks are due to Professor S. S. Kety, Drs. M. Ebert, F. Schnass and P. Siegel, Mr. R. Denning, and Mss. E. Howell and S. Ferre, for their collaboration and assistance in many aspects of this work.

REFERENCES

1. Adams, R. D., and R. L. Sidman. *Introduction to Neuropathology*. New York: McGraw-Hill, 1968, pp. 280–281.
1a Aghajanian, G. K., H. J. Haigler and F. E. Bloom. *Life Sci.* 11: Part I, 615, 1972.
2. Anden, N. E., B. E. Roos and B. Werdinius. *Life Sci.* 3: 149, 1964.
3. Angrist, B. M., and S. Gershon. *Pharmakopsychiat. Neuro-Psychopharmatol.* 4: 64, 1971.
4. Angrist, B. M., B. Shopsin and S. Gershon. *Nature* 234: 152, 1971.
4a Bloom, F. E., B. J. Hoffer, G. R. Siggins, J. L. Barker and R. A. Nicoll-*Federation Proc.* 31: 97, 1972.
5. Boakes, R. J., P. B. Bradley, I. Briggs and A. Dray. *Brit. J. Pharmacol.* 40: 202, 1970.
6. Bulat, M., and B. Zivkovic. *Science* 173: 738, 1971.
7. Bunney, W. E., D. L. Murphy, H. Keith, H. Brodie and F. K. Goodwin. *Lancet* 1: 352, 1970.
8. Carlsson, A., and M. Lindquist. *Acta Pharmacol. Toxicol.* 20: 140, 1963.
9. Celesia, G. G., and A. N. Barr. *Arch. Neurol.* 23: 193, 1970.
10. Chase, T. N., J. A. Schnur and E. K. Gordon. *Neuropharmacology* 9: 265, 1970.
11. Cole, J. O., and D. J. Clyde. *Rev. Can. Biol.* 20: 565, 1961.
12. Connor, J. D. *Science* 160: 899, 1968.
13. Connor, J. D. *Recent Publ. Assoc. Res. Nervous Mental Diseases* In press.
14. Coyle, J. T., and S. H. Snyder. *J. Pharmacol. Exptl. Therap.* 170: 221, 1969.
15. Creutzfeldt, O. D., F. R. Bell and W. R. Adey. *Progr. Brain Res.* 3: 31, 1963.
16. Crow, T. J. *Experientia* 27: 662, 1971.
17. Despopoulos, A. *Biochem. Pharmacol.* 19: 2907, 1970.
18. Ernst, A. M. *Acta Physiol. Pharmacol. Neerl.* 15: 141, 1969.
19. Feltz, P. *European J. Pharmacol.* 14: 360, 1971.
20. Ferris, R. M., and R. A. Maxwell. *Federation Proc.* 31: 601 1972.
21. Foster, R., and C. A. Fyfe. *Biochim. Biophys. Acta* 112: 490, 1966.
22. Fuxe, K. *Acta Physiol. Scand. Suppl.* 247: 39, 1965.
23. Fuxe, K., T. Hokfelt and U. Ungerstedt. Distribution of Monoamines in the Mammalian Central Nervous System by Histochemical studies. In: *Metabolism of Amines in the Brain*, edited by G. Hooper. London: Macmillan, 1969, p. 10–22.
24. Gerbode, F. A., and M. B. Bowers. *J. Neurochem.* 15: 1053, 1968.
25. Goswell, M. J., and E. M. Sedgwick. *J. Physiol., London* 218: 84P, 1971.
26. Guldberg, H. C., and C. M. Yates. *Brit. J. Pharmacol.* 36: 535, 1969.
27. Guldberg, H. C., G. W. Ashcroft and T.B.B. Crawford. *Life Sciences* 5: 1571, 1966.
28. Harris, J. In press.
29. Hoffer, B. J. *Brain Res.* 30: 425, 1971.
30. Horowitz, M. J., and J. E. Adams. Hallucinations on Brain Stimulation: Evidence for Revision of the Penfield Hypothesis. In: *Origins and Mechanisms of Hallucinations*, edited by W. Keup. New York: Plenum, 1970, p. 13–22.
31. Hull, C. D., G. Bernardi and N. A. Buchwald. *Brain Res.* 22: 163, 1970.
32. Janssen, P., J. Brugmans, J. Dony and V. Schuermans. *J. Clin. Pharmacol. J. New Drugs* 12: 26, 1972.
33. Jenkins, R. B., and R. H. Groh. *Lancet* 2: 177, 1970.
34. Laverty, R., and D. F. Sharman. *Brit. J. Pharmacol.* 24: 759, 1965.
35. Lorens, S. A. *J. Comp. Physiol. Psychol.* 73: 284, 1970.
36. Margules, D. L. *Brain Res.* 35: 177, 1971.
37. Margules, D. L. *European J. Pharmacol.* 16: 21, 1971.
38. McKenzie, G. M. *Psychopharmacologia* 23: 212, 1972.
39. McLennan, H., and D. H. York. *J. Physiol. London* 189: 393, 1967.
40. Medina, H. *Biochem. Pharmacol.* 13: 461, 1964.
41. Netsky, M. G. Degenerations of the Cerebellum and its Pathways. In: *Pathology of the Nervous System*, edited by J. Minckler. New York: McGraw-Hill, 1968, vol. 1, p. 1163–1185.
42. Nyback, H., Z. Borzecki and G. Sedvall. *European J. Pharmacol.* 4: 395, 1968.
43. Nyback, H., J. Schubert and G. Sedvall. *J. Pharm. Pharmacol.* 22: 622, 1970.
44. O'Keeffe, R., D. F. Sharman and M. Vogt. *Brit. J. Pharmacol.* 38: 287, 1970.
45. Olds, M. E., and J. Olds. *J. Comp. Neurol.* 120: 259, 1963.
46. Persson, T., and B. E. Roos. *Brit. J. Psychiat.* 115: 95, 1969.
47. Petsche, H., C. Stumpf and G. Gogolak. *Electroencephalog. Clin. Neurophysiol.* 14: 202, 1962.
48. Portig, P. J., and M. Vogt. *J. Physiol., London* 204: 687, 1969.
49. Precht, W., and M. Yoshida. *Brain Res.* 32: 229, 1971.
50. Rimon, R., B. E. Roos, V. Rakkolainen and Y. Alanen. *J. Psychosomatic Res.* 15: 375, 1971.
51. Rolls, E. T. *Brain Res.* 31: 275, 1971.
52. Roos, B. E. *J. Pharm. Pharmacol.* 17: 820, 1965.
53. Seeman, P. M., and H. S. Bialy. *Biochem. Pharmacol.* 12: 1181, 1963.
54. Spiegel, E. A., H. R. Miller and M. J. Oppenheimer. *J. Neurophysiol.* 3: 538, 1940.
55. Stumpf, C. *Intern. Rev. Neurobiol.* 8: 77, 1965.
56. Sugerman, A. A. *Current Therap. Res. Clin. Exptl.* 13: 706, 1971.
57. Sutin, J., and J. McNair. *Physiologist* 14: 241, 1971.
58. Takaori, S., N. Fukuda and Y. Amano. *Japan J. Pharmacol.* 20: 424, 1970.
59. Taylor, K. M. and S. H. Snyder. *Science* 168: 1487, 1970.
60. Ungerstedt, U. *Acta Physiol. Scand. Suppl.* 367: 1, 1971.
61. Yaryura-Tobias, J. A., B. Diamond and S. Merlis. *Current Therap. Res. Clin. Exptl.* 12: 528, 1970.
62. York, D. H. *Brain Res.* 37: 91, 1972.
63. Yoshida, M., and W. Precht. *Brain Res.* 32: 225, 1971.
64. Yoshida, M., A. Rabin and M. Anderson. *Brain Res.* 30: 235, 1971.