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PSYCHOPHARMACOLOGICAL IMPLICATIONS OF DOPAMINE AND DOPAMINE ANTAGONISTS: A CRITICAL EVALUATION OF CURRENT EVIDENCE

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> Theories which combine correct and false facts are more dangerous to science than complete errors; and hypotheses which are only "justified in a certain sense" always create confusion because the necessary reservations cannot always be stated. Clearcut concepts can only be formed if we ruthlessly reject everything that does not belong to them, regardless of whether we are dealing with simple problems or with entire theories.
>
> Eugen Bleuler (1)

INTRODUCTION

The unusual attention that brain dopamine (DA) has received in the 20 years since its identification in the mammalian brain (2) is due mainly to two factors: (*a*) the discovery that in Parkinson's disease there is a specific deficit of nigro-striatal DA (3) [this discovery formed the basis for the successful application of DAs precursor L-DOPA in the treatment of Parkinson's disease (4–6)]; and (*b*) evidence implicating brain DA in psychotic disorders, especially the schizophrenic syndrome.

Whereas the role of the nigro-striatal DA in the pathophysiology, symptomatology, and treatment of Parkinson's disease can be regarded as established (7, 8), the evidence implicating brain DA in psychotic disorders is mainly pharmacological, that is to say, indirect in nature; therefore, it has to be considered at present as largely hypothetical.

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Since several excellent recent reviews dealing with the role of DA in psychotic disorders, especially schizophrenia, are available (9–11), the purpose of this essay is to examine critically only the most crucial evidence and, where possible, to introduce new elements into the discussion of this complex research field. Taking into account the nature of the available evidence, the discussion concentrates on the following points: (*a*) the possible relationship between the special distribution pattern of brain DA and the anatomical substrate(s) of disturbed behavior; (*b*) the possible anatomical substrates of the schizophrenic disorders; and (*c*) the relationship between drugs mimicking or blocking DA effects respectively, their possible mechanisms of action, and their effects in patients suffering from the schizophrenic disorders.

BRAIN DA AND THE NEUROPATHOLOGY OF BEHAVIOR

There are three major DA neuron systems in the mammalian brain [for review and references cf (12)]. These are (*a*) the nigro-striatal system, which originates in the (melanin-containing) neurons of the compact zone of the substantia nigra and terminates diffusely in the caudate nucleus and putamen (the corpus striatum or striatum), and probably also in the nucleus accumbens (13); (*b*) the mesolimbic system, which originates in the ventromedial tegmentum of the mesencephalon just dorsal and lateral to the interpeduncular nucleus (area A10 of Dahlström and Fuxe, nucleus paranigralis in the human brain) and projects to the nucleus accumbens, olfactory tubercle, and the central amygdaloid nucleus [recently, a projection system probably originating in area A10 has been described as terminating in several limbic cortical regions (14–16)]; (*c*) a system consisting of short neurons, arising mainly in the anterior part of the arcuate nucleus of the hypothalamus and terminating in the external layer of the median eminence (the tubero-infundibular DA system).

There is evidence from animal experiments to show that each of these three DA systems may be involved in a variety of behavioral reactions which, by way of analogy, may be assumed to have some relevance to the behavioral disturbances seen in psychotic patients.

Over the past ten years a great deal of information has accumulated related to the role of the subcortical DA systems in the functioning of the basal ganglia (mainly corpus striatum) as well as certain structures belonging to the limbic forebrain (cf 17). The majority of these studies deals with the behavioral pharmacology of the corresponding DA systems. In this respect, it is important to stress that despite many attempts, at present the work on the role of the subcortical DA in behavior does not seem to permit a clear-cut functional distinction to be made between the striatal and the limbic DA systems. On the whole, the results of the pertinent studies suggest that the role of the subcortical structures such as the striatal complex, the nucleus accumbens, and the olfactory regions, in the elaboration of patterns of locomotor as well as stereotyped behavior is critically dependent on the intactness of their dopaminergic innervation. Similarly, various forms of conditioned avoidance behavior have been shown to depend predominantly on the activity of these dopaminergic forebrain systems. [For comprehensive review and references, cf (17).]

Recent experimental evidence also suggests that the subcortical dopaminergic systems may be critically involved in reward-seeking behavior (18) as well as mechanisms controlling memory consolidation and retention (19). The role of the recently described mesocortical (limbic) DA system has not yet been established. There is, however, preliminary evidence suggesting that this system may participate in responses of the central nervous system to stress because it seems to react to stressful procedures much more sensitively than the coritcal norepinephrine or any of the subcortical monoamine systems do (20).

The relation of the median eminence DA to behavior is suggested by the finding that, on one hand, this DA system takes part in the control of secretion of hypophyseal hormones (especially prolactin and luteinizing hormone) (cf 21); on the other hand, hypophyseal hormones recently have been postulated to exert significant actions on several behavioral parameters (22). However, details as to the behavioral consequences of disturbed functioning of the median eminence DA have not yet been worked out.

The above observations in laboratory animals on the role of brain DA in behavior furnished the basis for the notion that, by analogy, at least certain behavioral abnormalities that regularly recur in psychotic patients may in fact be related to a disturbed functioning of brain DA systems. It is obvious, however, that the question as to a possible involvement of brain DA in psychiatric disorders, particularly schizophrenia, is ultimately nothing less than the repeatedly posed question as to the neuroanatomical substrate of these disorders.

NEUROANATOMICAL SUBSTRATES OF THE SCHIZOPHRENIC DISORDER

The question whether the schizophrenic condition has an underlying cerebral neuropathology has as yet remained unanswered. At the beginning of this century, Eugen Bleuler expressed the view (1) that "complete justice to all these factors (i.e. in schizophrenia) can only be done by a concept of the disease which assumes the presence of (anatomical or chemical) disturbances of the brain." As the primary disturbance in schizophrenia Bleuler saw a disturbance of "association" and "tension." Bleuler seems to have favored a rather widespread disturbance mainly at the neocortical level since he firmly rejected all "focal" hypotheses such as those of Kleist or Wernicke as well as Berze's suggestion of a lowered or defect "energy flow" to the cortex from subcortical structures (cf 23). A detailed discussion of the various hypotheses related to a possible neuropathology of mental illness is outside the scope of this article. It is, however, relevant in this context to note that, more recently, dysfunction of two of the most important DA-rich brain parts, namely the corpus striatum and the limbic system, has been discussed in relation to a possible pathophysiology of psychotic disturbances.

Corpus Striatum and the Schizophrenic Disturbance

In 1955, Mettler (24) proposed the hypothesis that in schizophrenia there might exist a disturbed function of the striatum. He based his hypothesis on observations

obtained in experimental animals showing that lesions of the striatum produced a form of physiological deficit which included, as one of its principal features, a disorder of perception. Specifically, Mettler (25–27) observed in cats with striatal lesions (which were added to a frontal cortex removal) a profoundly vacuous appearance of the animals; a visual, auditory, and labyrinthine disregard; paucity of eye movements; failure to react adaptively to situations and objects in the field of vision as well as a tendency to push forward into objects and fall down declivities. Furthermore, the animals displayed a great deal of stimulus binding (for example, they tended to follow rigidly moving objects placed directly before their eyes), cursive and essential hyperkinesias, pushing, leaping, resistance to superimposed postures, and passive movement. Also, cats with large, bilateral striatal lesions lost their ability to perform as well as to relearn tasks previously learned (28).

From these observations Mettler concluded that the striatum may be importantly involved in the organism's ability to relate itself to its environment by coordinating the shifting of attention from one source of sensory input to another. These "monitoring comparisons" of the striatum Mettler conceived of as necessary in order to maintain contact with, and make an adequate interpretation of, the source of exogenous stimuli, as well as to reinforce memory and sustain an adequate level of intellectuality. Since according to Mettler the striatum also supresses the thalamopallidal circuits concerned with deep afferents and vision, its overall role was to free the organism from proprioceptive dominance, thus putting it in a position to react to alternative stimulus configuration, that is, to make choices. Mettler proposed that the primary defect in schizophrenia may consist of an analogous disturbance of perception, that is, inability to shift attention from one source of sensory input to another, caused by a dysfunction of the striatal nuclei.

While Mettler's concept has to be regarded as highly speculative, recent work on the role of the caudate nucleus in complex behavior seems to furnish a certain degree of experimental basis for such a possibility. Thus, it has been convincingly demonstrated [for review and references, see (20)] that localized lesions of the caudate nucleus result in disturbances of such complex behaviors as retention of delayed responses and delayed alternation, spatial reversal, visual and auditory "go–no go" discrimination, delayed successive discrimination, object reversal, as well as bar pressing extinction, and various activity measures. Most importantly, however, the existence of a functional relation between the caudate nucleus and the prefrontal cortex has been demonstrated (cf 29); thus, lesions of the prefrontal cortex produce analogous disturbances of complex behavior like those produced by caudate lesions (see above). In the light of these experimental findings, it is conceivable that a disturbed relationship between the prefrontal cortex and the corpus striatum may produce complex behavior disturbances not dissimilar to those seen in psychotic patients.

Limbic System and the Schizophrenic Disturbance

Recently, attention has been drawn to a possible involvement of the brain's limbic system in at least some forms of schizophrenia [for review, cf (30)]. The notion that the limbic forebrain system may be relevant to psychic functions can be traced back

to the concept, proposed by Papez (31) in 1937, that this forebrain system may "constitute a harmonious mechanism which may elaborate the functions of central emotion, as well as participate in emotional expression." From the anatomical point of view the limbic system, like the striatum, is unique insofar as it is mainly interconnected with the reticular formation of the fore- and midbrain, to which it sends and from which it receives all of its noncortical connections. (The connections with the thalamoneocortical apparatus are phylogenetically a more recent addition.) In particular, the strong connections between the limbic system and the hypothalamus suggest that the functional state of the latter is inseparably related to the patterns of neuronal activity in the limbic-reticular formation system as a whole (32).

In his fundamental work on the limbic system, MacLean (33, 34) has appropriately pointed out that the anatomical situation of the limbic system within the forebrain is such as to enable it to correlate and integrate every form of internal and external perception. On the experimental level, a great number of studies have convincingly demonstrated that laboratory animals with experimentally induced damage to the limbic forebrain structures exhibit a series of disturbances such as inappropriate behavior, changes in sexual drives as well as changes in emotion and affect, and impairment in the ability to screen out multiple visual stimuli [for references, see (30)]. In the light of this experimental evidence it is interesting to note that some of the early symptoms in patients with schizophrenia seem to correlate with functions of the limbic system. Specifically, disturbance of visual perception, namely, difficulty in synthesizing the incoming visual stimuli into a whole picture, has been suggested as representing a common early symptom of the disease (35). In addition, studies with implanted recording electrodes have detected electrical abnormalities specifically from limbic structures in schizophrenic patients (cf 30). Finally a relationship between the limbic system and the schizophrenic disturbance seems to be suggested by observations showing that cases with known limbic system pathology—such as temporal lobe epilepsy, as well as encephalitis and brain tumors involving limbic structures—frequently occur with schizophrenia-like symptoms (30).

In connection with the above concepts implicating the corpus striatum and the limbic system respectively, in the pathophysiology of psychotic disorders, it is important to stress that these concepts are by no means mutually exclusive. As Nauta (32) has pointed out, despite their differing anatomical structure and functional significance, the corpus striatum and the limbic forebrain system have a very important characteristic in common: they both are virtually devoid of afferent fibers from the phylogenetically more recent lemniscus systems, receiving a large part of their afferent systems directly from the reticular formation of the brain stem. Thus, Nauta visualizes the striatum and the limbic forebrain system as representing jointly the brain's "analyzer-integrator system of the second order," being interposed between the first and third order analyzer-integrator systems of the brain stem reticular formation and the thalamoneocortical apparatus respectively. The possible interrelation between the striatum and the limbic forebrain system is further underlined by the mentioned difficulty in distinguishing neurochemically and neuropharm-

macologically between the functional roles played by the dopaminergic systems innervating these two structures. A good example in point is afforded by the limbic area of the nucleus accumbens whose morphology as well as neurochemistry makes it in many respects nearly indistinguishable from the striatal nuclei (cf 36).

BRAIN DOPAMINE AND SCHIZOPHRENIA

The hypotheses relating the striatum and/or limbic forebrain structures with the pathophysiology of the schizophrenic disorder have provided for an obvious link between this psychotic condition and brain DA which, as discussed above, plays an important role in the functioning of these two brain regions. However, judged merely on the basis of the anatomical-functional evidence, the relation between schizophrenia and brain DA is by no means compelling. Both the striatum and the limbic structures are rich in several other important neurohumoral factors such as acetylcholine, serotonin, norepinephrine, γ-aminobutyric acid, and substance P; each of these could play an important role in normal and disturbed functioning of these brain regions. That the DA hypothesis has attracted special attention is due mainly to a number of significant pharmacological as well as pharmacological-clinical observations that favor this particular thesis. In this respect, two observations are of special importance: (*a*) amphetamine's action on brain DA in relation to the drug's ability to induce a psychotic state in man; and (*b*) the psychotherapeutic (antischizophrenic) activity of neuroleptics that have been found to possess strong DA antagonist properties.

Amphetamine Psychosis

A psychotic state,the so-called amphetamine psychosis (37), frequently develops in subjects taking amphetamine chronically. Occasionally the amphetamine psychosis may also be precipitated with a large single dose of the drug. This toxic state presents features quite similar to ("indistinguishable" from) those seen especially in paranoid schizophrenia (37–39). Amphetamine is know to release DA from its storage sites in the nerve terminals as well as to prevent its inactivation by synaptic re-uptake [for reviews, see (40)]. Thus, the idea appears attractive (41, 42) that the psychotic state produced by amphetamine abuse may be related to a dopaminergic overstimulation taking place in the DA-rich brain regions, especially the striatum and/or the limbic system regions. This possibility seems supported by clinical experience showing that both amphetamine as well as other drugs known to act on brain DA, such as L-DOPA, and several amphetamine-like compounds (e.g. methylphenidate), will produce an exacerbation of the schizophrenic symptomatology in diseased patients (43–45).

Besides its effect on brain DA, amphetamine is known to act in an analogous manner on brain norepinephrine (i.e. increased release, inhibition of re-uptake) [for reviews and references, see (40)]. Thus, the alternate possibility has to be considered that the psychotic state produced by amphetamine in man may be due to the drug's effect on brain NA mechanisms rather than brain DA or that both DA and NA are important in this respect. To resolve this dilemma, the D- and L-isomers of ampheta-

mine have been utilized. However, the results of the corresponding studies produced confusion rather than clarification of this issue (cf 45). There seems to exist agreement regarding the observations that in inducing the psychotic state in healthy volunteers as well as exacerbating the schizophrenic symptomatology in diseased patients D- and L-amphetamine are nearly equipotent; also, both isomers seem to be nearly equipotent in inducing stereotyped behavior in laboratory animals. [This has led to the concept that the animal model of amphetamine-induced stereotypy is analogous to the amphetamine psychosis in man, representing, by inference, a model of the behavioral disturbance in schizophrenia (cf 42)].

When the amphetamine isomers were compared as to their relative potency in inhibiting the synaptosomal uptake of DA (in striatal homogenates) and NA (in homogenates of the cortex), Coyle & Snyder (46) found that both isomers were about equipotent on DA uptake; on the NA uptake D-amphetamine was ten times more potent than the L-isomer. From this the authors concluded that the psychotogenic activity of amphetamine (as well as its ability to induce stereotypies in animals) was due to an action on brain DA. In contrast to Coyle & Snyder, however, three other research groups (47–49) found that D-amphetamine was about equipotent with the L-isomer in inhibiting NA uptake (cortex) and four to five times more potent than the latter in inhibiting the striatal DA uptake. Thus, in contradistinction to Snyder's data, these data would seem to favor the opposite view, namely that rather than DA, brain NA may be involved in the amphetamine-induced psychotic disturbance. It is not even certain whether doses of amphetamine that produce all the typical behavioral effects in laboratory animals are high enough to inhibit DA or NA uptake in vivo; rather, in these (low) doses amphetamine probably has predominantly a releasing effect on the synaptically stored amines (cf 50). Likewise, it has been argued (51) that the observation that physostigmine attenuates the methylphenidate-induced psychosis but not the schizophrenic condition (52) may indicate that these two conditions are qualitatively different as to their neurochemical basis.

Although there is reason to assume that the amphetamine-induced stereotypy in laboratory animals—the animal model of amphetamine psychosis and, by inference, schizophrenia—is due to the drug's action on brain DA, it is difficult at present to decide on the precise anatomical substrate of this effect. Based on experiments with apomorphine it was suggested (53) that the DA in the limbic forebrain regions was closely related to stereotyped behavior. This was in agreement with the suggestion that several important features of amphetamine psychosis were limbic in origin (54). In contrast, recent evidence suggests that the striatal DA may be the substrate of the amphetamine stereotypy, with the limbic DA being primarily responsible in the amphetamine-induced locomotor activation (55). However, it has also been claimed that an intact striatum is not required for amphetamine to produce the typical stereotypies (56). Thus, even if the biochemical basis for the amphetamine-induced stereotyped behavior were assumed to reflect the biochemical disturbance in schizophrenia (an assumption that cannot be accepted at present without strong reservations), available experimental data would not allow a precise anatomical localization of such a hypothetical neurochemical disturbance.

In conclusion, although the animal model of amphetamine-induced stereotypy may represent a valid model of the amphetamine-induced psychosis in man, whether the latter represents a model of the schizophrenic dysfunction remains quite doubtful (57). Thus, conclusions drawn from the animal model cannot, at present, be applied directly to the problem of schizophrenia. This applies both to the biochemical as well as to the anatomical-localizational aspects of this psychotic disturbance.

Neuroleptic Drugs (DA Antagonists)

At present, the DA antagonist properties of antipsychotic drugs (i.e. the neuroleptics) probably represent the strongest argument in favor of an involvement of brain DA in schizophrenia.

With only a few exceptions, i.e. compounds with significant affinity for muscarinic receptors in the brain, such as thioridazine, clozapine, pimozide (58–60), neuroleptics of the phenothiazine and buytrophenone series in antipsychotic doses induce a parkinsonism-like syndrome in a large number of cases (cf 61). Since Parkinson's disease has been shown to be accompanied by a deficiency of DA in the nigro-striato-pallidal system (and nucleus accumbens) (3, 7, 8, 36), a relation between the parkinsonism-inducing activity of neuroleptics and a possible interference with brain DA systems suggested itself. In additon, since the relative potency of neuroleptics (with the exception of thioridazine, clozapine, pimozide; see above) for the induction of Parkinsonism correlates well with their antipsychotic activity (cf 61), involvement of brain DA in the antipsychotic effect of these drugs seemed possible.

The interference by neuroleptic drugs with brain DA mechanisms has been well established experimentally. The available evidence suggests at least three major possibilities: (*a*) blockade of the DA-sensitive adenylate cyclase, (*b*) blockade of the synaptic release of DA, and (*c*) blockade of DA receptors.

BLOCKADE OF THE DA-SENSITIVE ADENYLATE CYCLASE The striatum as well as the dopaminergically innervated limbic forebrain structures (nucleus accumbens, olfactory tubercle) contain an adenylate cyclase that is specifically activated by DA (62,63). This DA-sensitive adenylate cyclase has been postulated to represent the immediate receptor molecule involved in the chain of events triggered by DA at the postsynaptic membrane, eventually resulting in a physiologic effect (62). Neuroleptics are, on the whole, strong inhibitors of the DA stimulation of the striatal and limbic adenylate cyclase. However, there seems to be a lack of a complete correlation between the inhibitory potency of the neuroleptics on the DA stimulation of this enzyme and their clinical potency in producing extrapyramidal effects (catalepsy in experimental animals, parkinsonism in man) as well as their antipsychotic activity (64). Specifically, the neuroleptically potent group of butyrophenones (e.g. haloperidol, pimozide) has proved conspicuously weak in blocking the DA effect on the enzyme (62, 62). Thus, at present, it is difficult to relate the antipsychotic activity of neuroleptics as a group with their ability to block the DA-sensitive adenylate cyclase in the DA-rich areas (striatum and/or limbic brain areas). Since neuroleptics inhibit both the striatal and limbic adenylate cyclase equally well, no conclusion can be reached as to the possible site of the drugs' antipsychotic activity.

BLOCKADE OF SYNAPTIC RELEASE OF DA Recently, Seeman & Lee (65) provided evidence showing a striking correlation between the clinical potency of the neuroleptics (including the butyrophenones) and their ability to inhibit the stimulus-induced DA release in rat striatal slices. This action of neuroleptic compounds may be related to their well-known high efficacy in stabilizing cell membranes in general, with the brain DA neurons displaying a selective sensitivity in this respect. Thus the possibility exists that the blockade of the presynaptic coupling between nerve impulse and DA release may account for both the extrapyramidal and antipsychotic effects of all neuroleptic drugs presently available. It appears difficult, however, to reconcile this possibility with the finding obtained in vivo using the push-pull cannula technique showing that administration of neuroleptics produced an increase rather than decrease of DA release within striatal and limbic structures (66).

BLOCKADE OF DA RECEPTORS It is reasonable to assume that in order to exert their specific (i.e. antipsychotic) actions, neuroleptics (like other drugs) have to bind in the brain to a specific site at which to exert the specific effect; this site can be called conveniently the *receptor site.* This logical proposition has prompted studies that have resulted in the demonstration that membrane fractions of brain homogenates possess "receptor binding" properties when labeled with (^{3}H)haloperidol (67, 68). Most significantly the order of affinity of a large series of neuroleptics for the (^{3}H)haloperidol binding sites (tested in preparations of calf striatal membranes) showed a highly significant correlation with the clinical (antipsychotic) potency of these drugs (69, 70). This strongly suggests that the sites in cell membranes that bind (^{3}H)haloperidol may indeed be the sites of the antipsychotic activity of the neuroleptic drugs. It is, however, important to note that the (^{3}H)haloperidol binding (as expressed in fmol/mg protein) was highest in the caudate nucleus, with the putamen and nucleus accumbens showing much lower levels; in fact, the latter two regions had values no higher than the globus pallidus (64). Thus, there seems to be little correspondence between the number of the (^{3}H)haloperidol binding sites and the density of DA terminals, the latter being (as judged from the DA levels) much higher in the putamen and nucleus accumbens (where the DA concentration is comparable to that in the caudate nucleus) than in the globus pallidus (cf 8). This poor correlation is further borne out by the observation that the order of affinity of neuroleptic drugs for (^{3}H)dopamine binding sites [tested under conditions analogous to those for (^{3}H)haloperidol binding] did not show any statistically significant correlation with the drugs' antipsychotic activity (69, 70).

The above observations would then suggest that although the clinical effect of neuroleptic drugs is produced, as would be expected, through an action on (probably) specific receptors in the brain, and these receptors may be identical with the haloperidol binding sites, the available evidence does not favor the hypothesis that the drugs' antipsychotic activity is due to brain DA receptor blockade.

ALTERNATE POSSIBILITY FOR THE MODE OF ACTION OF ANTIPSYCHOTIC DRUGS Kornetsky (cf 57, 71, 72) has presented evidence showing that the core deficit in (at least some) schizophrenic patients involves an impairment in attention. This attentional deficit has been postulated to result from a dysfunction in those

brain regions concerned with maintainence of arousal and attention, that is the brain stem reticular activating system. Thus, Kornetsky & Eliasson (72) have formulated the hypothesis that the schizophrenic patient is in a continuous state of central excitation or hyperarousal. Further, the authors proposed that the beneficial effect of neuroleptic drugs in schizophrenic patients is brought about by a suppression of the state of hyperarousal to levels consistent with optimum performance of the subject (57, 72). In this respect, the level of arousal may be related to the efficiency of performance (in experimental situations); maximum performance of which a subject is capable is usually attained with medium levels of arousal, with both under- or over-arousal eliciting poorer performance (cf "inverted U model") (73, 74).

Neuroleptic drugs have been known for a long time to inhibit effectively the behavioral as well as EEG arousal reaction produced by sensory stimulation in laboratory animals [for references see (75)]. A large body of electrophysiological evidence points to the reticular activating system of the brain stem as the site of action of this anti-arousal effect of the neuroleptic drugs. As to the mechanism(s) of the arousal-inhibiting effect of neuroleptics, the following possibilities have been considered in the literature (cf 75): (*a*) direct blocking effect on those mechanisms of the reticular formation that are responsible for the arousal reaction, (*b*) blockade of afferent impulses in the sensory collateral fibers to the brain stem reticular formation, and (*c*) facilitation of inhibitory "filtering" mechanisms of the reticular formation, resulting in a reduction of the sensory load reaching the cortex.

Irrespective of which of the above possibilities is given preference, the experimental neurophysiological results are consistent with Kornetsky's hypothesis that the therapeutic efficacy of neuroleptics may be due to their suppressing action on the reticular activating mechanisms. From a neurochemical point of view, it is interesting to note that the monoamine most frequently implicated as an important neurohumoral factor in the functioning of the reticular mechanisms is norepinephrine (cf 76, 77). Thus, it may be significant that, in addition to amphetamine and L-DOPA (that is, drugs that increase both dopaminergic and noradrenergic activity in the brain) tricyclic antidepressants have been observed to both activate anergic patients and exacerbate the schizophrenic symptomatology (78, 79); the latter drugs prevent the inactivation of norepinephrine (but not DA) by inhibiting its synaptic re-uptake, thereby potentiating noradrenergic effects [for reviews and references, see (40)]. Furthermore, neuroleptics, especially those of the phenothiazine series, have been known to exert antiadrenergic effects in the periphery (cf 75), and several of them have been shown to affect brain norepinephrine metabolism in a way analogous to that of brain DA (cf 80), thus suggesting a possible blockade of central norepinephrine receptors. However, the effectiveness of neuroleptics on brain norepinephrine metabolism (increase in synthesis rate) does not parallel their clinical antipsychotic potency nor do the α-adrenergic blockers (such as phenoxybenzamine or phentolamine) exert any known antischizophrenic activity. On the other hand, it is interesting to note that recently antischizophrenic activity has been claimed for propranolol (81; see also 82), a potent β-adrenergic receptor blocker. Also, the experimental data concerning the effect of neuroleptics on brain norepinephrine refer mostly to acute effects produced by single-dose administration

whereas the antipsychotic effect in the schizophrenic patient typically is a function of an "irreducible minimum" of treatment time; that is to say, it is essentially chronic in nature. In this context it seems appropriate to mention the clinical observation (83) that the antipsychotic potency of neuroleptics can be increased by simultaneous administration of α-methyltyrosine, a drug known to inhibit synthesis of the catecholamines. This observation has often been quoted as supporting the DA hypothesis of antipsychotic effect of neuroleptic drugs. However, this argument rests on the assumption of a satisfactory correlation between the antipsychotic activity and the DA blocking activity of these drugs. Failing this, the above clinical observation may equally well be quoted in support of an involvement of norepinephrine; being an inhibitor of the tyrosine hydroxylase, α-methyltyrosine inhibits not only the formation of DA but also that of norepinephrine (84).

CONCLUSION

By evaluating the presently available information in a synthetic manner, the following concept seems to emerge: Accepting the premise that the schizophrenic disorder has an anatomical substrate in the brain, the corresponding neuropharmacological and behavioral studies seem to implicate three major brain systems as the most likely sites of this dysfunction: the reticular formation of the fore- and midbrain, the limbic forebrain system, and the corpus striatum. In this respect it appears significant that there exists a phylogenetically old anatomical-functional interrelationship between these three major subcortical systems (including their more recent thalamoneocortical connections); this fact underlines the crucial role of these subcortical mechanisms as important "analyzer-integrator" systems of the brain. This close anatomical-functional interrelation also makes it likely that a dysfunction of any one of these subcortical systems will find its corresponding expression in altered functioning of the other systems as well as the related thalamoneocortical mechanisms. Thus, assuming that one of these three systems may in fact be the primary "focus" of the schizophrenic disturbance, it would not be surprising to find that in the fully developed syndrome all three systems are involved. This complex relationship may explain the difficulty we face when trying to understand the pathophysiology of the schizophrenic disturbance; similarly, it makes the existence, in the fully developed syndrome, of a malfunction of a single neurohumoral factor unlikely, suggesting the possibility of a multineurohumoral disturbance as the overall biochemical feature of this disease. Specifically, the neurochemical correlate of such an anatomically extensive malfunction could be a combination of changes in the noradrenergic mechanisms in the reticular formation and dopaminergic forebrain mechanisms, especially those in the limbic-striatal systems. Moreover, disturbed functioning of the brain stem reticular formation may involve such important neurohumours as serotonin (especially in the mesencephalic-limbic subdivision) and possibly (secondarily) neuronal systems utilizing acetylcholine or γ-aminobutyric acid as their neurohumoral agents.

However, the likelihood of a multineurohumoral disturbance in schizophrenia should not be taken as a reason for evading the all-decisive question as to the

primary lesion which, by definition, has to be at the root of all other biochemical alterations. Therefore, the crucial question still remains: Which of the above possibilities represents the primary anatomical and neurochemical lesion in schizophrenia? At present we do not have an answer to this question.

Although the possible existence of a multineurohumoral disturbance does not help to answer the more decisive question as to the primary neurochemical lesion, it has an important bearing on the evaluation of the current neurochemical hypotheses of mental illness in general, and schizophrenia in particular. As discussed in the preceding pages, these hypotheses are based mainly on pharmacological evidence. However, since from the pharmacological point of view beneficial or aggravating effects could be actually expected in the instance of any given drug acting on one or more of the possibly deranged neurohumoral systems, no valid hypothesis as to the underlying primary biochemical disturbance can be deduced from such clinical effects. At present, no specific drug—which would exert its antipsychotic effect by acting solely on a single specific neurochemical factor or anatomical site in the brain—seems to be available. This clearly indicates that rather than being at the endpoint of its development, the present state of the chemotherapy of psychoses is actually only in its very beginnings, thus holding some promise for further fruitful developments in this area.

Returning, at the end of this essay, to the quotation placed at the beginning, it becomes obvious that if we were to adopt, as we probably should, Eugen Bleuler's uncompromising view as to the scientific value of the current hypotheses of schizophrenia (1), the present essay would have to be replaced by nearly complete silence.

Literature Cited

1. Bleuler, E. 1911. *Dementia Praecox or the Group of Schizophrenias.* Trans. J. Zinkin, 1950, p. 465. New York: Int. Univ. 548 pp.
2. Carlsson, A., Lindqvist, M., Magnusson, T., Waldeck, B. 1958. On the presence of 3-hydroxytyramine in brain. *Science* 127:471
3. Ehringer, H., Hornykiewicz, O. 1960. Verteilung von Noradrenalin und Dopamin (3-Hydroxytyramin) im Gehirn des Menschen und ihr Verhalten bei Erkrankungen des extrapyramidalen Systems. *Klin. Wochenschr.* 38: 1236–39
4. Birkmayer, W., Hornykiewicz, O. 1961. Der L-Dioxyphenylalanin (=L-DOPA) —Effekt bei der Parkinson-Akinese. *Wien. Klin. Wochenschr.* 73:787–88
5. Barbeau, A., Sourkes, T. L., Murphy, G. 1962. Les catecholamines dans la maladie de Parkinson. In *Monoamines et Systeme Neurveux Central,* ed. J. de Ajuriaguerra, 247–62. Geneva & Paris: Georg & Masson
6. Cotzias, G. C., Van Woert, M. H., Schiffer, L. M. 1967. Aromatic amino acids and modification of parkinsonism. *N. Engl. J. Med.* 276:374–79
7. Bernheimer, H., Birkmayer, W., Hornykiewicz, O., Jellinger, K., Seitelberger, F. 1973. Brain dopamine and the syndromes of Parkinson and Huntington. *J. Neurol. Sci.* 20:415–55
8. Lloyd, K. G., Davidson, L., Hornykiewicz, O. 1975. The neurochemistry of Parkinson's disease: Effect of L-dopa therapy. *J. Pharmacol. Exp. Ther.* 195:453–64
9. Snyder, S. H., Banerjee, S. P., Yamamura, H. I., Greenberg, D. 1974. Drugs, neurotransmitters, and schizophrenia. *Science* 184:1243–53
10. Snyder, S. H. 1974. Catecholamines as mediators of drug effects in schizophrenia. In *The Neurosciences. Third Study Program,* Eds-in-Chief, F. O. Schmitt, F. G. Worden, 721–32. Cambridge, Mass.: MIT Press. 1107 pp.
11. Matthysse, S. 1974. Schizophrenia: Relationships to dopamine transmission,

motor control, and feature extraction. See Ref. 10, pp. 733–37
12. Fuxe, K., Hökfelt, T., Ungerstedt, U. 1970. Morphological and functional aspects of central monoamine neurons. *Int. Rev. Neurobiol.* 13:93–126
13. Moore, R. Y., Bhatnagar, R. K., Heller, A. 1971. Anatomical and chemical studies of a nigro-neostriatal projection in the cat. *Brain. Res.* 30:119–35
14. Thierry, A. M., Blanc, G., Sobel, A., Stinus, L., Glowinski, J. 1973. Dopaminergic terminals in the rat cortex. *Science* 182:499–501
15. Hökfelt, T., Ljungdahl, A., Fuxe, K., Johansson, O. 1974. Dopamine nerve terminals in the rat limbic cortex: Aspects of the dopamine hypothesis of schizophrenia. *Science* 184:177–79
16. Lindvall, O., Björklund, A., Moore, R. Y., Stenevi, U. 1974. Mesencephalic dopamine neurons projecting to neocortex. *Brain Res.* 81:325–31
17. Laverty, R. 1974. On the role of dopamine and noradrenaline in animal behavior. *Prog. Neurobiol.* 3:31–70
18. Crow, T. J. 1972. Catecholamine-containing neurons and electrical self-stimulation: 1. A review of some data. *Psychol. Med.* 2:414–21
19. Routtenberg, A., Holzman, N. 1973. Memory disruption by electrical stimulation of substantia nigra, pars compacta. *Science* 181:83–86
20. Tassin, J. P. 1977. Qualitative and quantitative distribution of dopaminergic terminals in various areas of rat cerebral cortex. In *Symp. Non-Striatal Dopaminergic Neurons*, ed. E. Costa, G. L. Gessa. New York: Raven. In press
21. Ganong, W. F. 1972. Pharmacological aspects of neuroendocrine integration. *Prog. Brain. Res.* 38:41–57
22. DeWied, D. 1974. Pituitary-adrenal system hormones and behavior. See Ref. 10, pp. 653–66
23. Frey, T. S. 1973. A review of some important studies on schizophrenic thought disorders and their implications. *Acta Psychiatr. Scand.* 49:213–29
24. Mettler, F. A. 1955. Perceptual capacity, functions of the corpus striatum and schizophrenia. *Psychiatr. Q.* 29:89–111
25. Mettler, F. A., Mettler, C. C. 1940. Labyrinthine disregard after removal of the caudate. *Proc. Soc. Exp. Biol. Med.* 45:473–75
26. Mettler, F. A., Mettler, C. C. 1941. Role of the neostriatum. *Am. J. Physiol.* 133:594–601
27. Mettler, F. A., Mettler, C. C. 1942. The effects of striatal injury. *Brain* 65: 242–55
28. Thompson, R. L., Mettler, F. A. 1963. Permanent learning deficit associated with lesions of the caudate nuclei. *Am. J. Ment. Defic.* 67:526–35
29. Divac, I. 1972. Neostriatum and functions of prefrontal cortex. *Acta Neurobiol. Exp.* 32:461–77
30. Torrey, E. F., Peterson, M. R. 1974. Schizophrenia and the limbic system. *Lancet* II:942–46
31. Papez, J. W. 1937. A proposed mechanism of emotion. *Arch. Neurol. Psychiatry* 38:725–43
32. Nauta, J. H. 1963. Central nervous system organization and the endoctrine motor system. In *Advances in Neuroendocrinology*, ed. A. V. Nalbandov, 5–21. Urbana: Univ. Illinois. 525 pp.
33. MacLean, P. D. 1949. Psychosomatic disease and the "visceral brain." *Psychosom. Med.* 11:338–53
34. MacLean, P. D. 1952. Some psychiatric implications of physiological studies on frontotemporal portion of limbic system (visceral brain). *Electroencephalogr. Clin. Neurophysiol.* 4:407–18
35. Chapman, J. 1966. The early symptoms of schizophrenia. *Br. J. Psychiatry* 112:225–51
36. Farley, I. J., Price, K. S., Hornykiewicz, O. 1977. Dopamine in the limbic regions of the human brain: normal and abnormal. See Ref. 20
37. Connell, P. H. 1958. *Amphetamine Psychosis.* London: Chapman & Hall
38. Griffith, J. D., Cavanaugh, J., Held, J., Oates, J. A. 1972. Dextro-amphetamine. *Arch. Gen. Psychiatry* 26:97–101
39. Angrist, B. M., Gershon, S. 1970. The phenomenology of experimentally induced amphetamine psychosis—preliminary observations. *Biol. Psychiatry* 2:95–107
40. Costa, E., Garattini, S., eds. 1970. *Int. Symp. Amphetamines Related Compounds.* New York: Raven. 962 pp.
41. Randrup, A., Munkvad, I. 1972. Evidence indicating an association between schizophrenia and dopaminergic hyperactivity in the brain. *Orthomolecular Psychiatry* 1:2–7
42. Snyder, S. H. 1973. Amphetamine psychosis: A model schizophrenia mediated by catecholamines. *Am. J. Psychiatry* 130:61–67
43. Janowsky, D. S., El-Yousef, M. K., Davis, J. M., Sekerke, H. J. 1973. Provocation of schizophrenic symptoms by in-

travenous administration of methylphenidate. *Arch. Gen. Psychiatry* 28: 185–94
44. Preston West, A. 1974. Interaction of low-dose amphetamine use with schizophrenia in outpatients: 3 case reports. *Am. J. Psychiatry.* 131:321–23
45. Matthysse, S. 1974. Dopamine and the pharmacology of schizophrenia: The state of the evidence. In *Symp. Catecholamines Enzymes Neuropathol. Schizophrenia, J. Psychiatr. Res.* 11: 107–13. Oxford: Pergamon. 364 pp.
46. Coyle, J. T., Snyder, S. H. 1969. Catecholamine uptake by synaptosomes in homogenates of rat brain: Stereospecificity in different areas. *J. Pharmacol. Exp. Ther.* 170:221–31
47. Ferris, R. M., Tang, F. L. M., Maxwell, R. A. 1972. A comparison of the capacities of isomers of amphetamine, deoxypipradol and methylphenidate to inhibit the uptake of tritiated catecholamines into rat cerebral cortex slices, synaptosomal preparations of rat cerebral cortex, hypothalamus and striatum and into adrenergic nerves of rabbit aorta. *J. Pharmacol. Exp. Ther.* 181: 407–16
48. Thornburg, J. E., Moore, K. E. 1973. Dopamine and norepinephrine uptake by rat brain synaptosomes: Relative inhibitory potencies of l- and d- amphetamine and amantadine. *Res. Commun. Chem. Pathol. Pharmacol.* 5:81–88
49. Harris, J., Baldessarini, R. J. 1973. Effects of amphetamine analogs on the uptake of (^{3}H) catecholamines by homogenates of rat corpus striatum and cerebral cortex. *Neuropharmacology* 12:669–79
50. Carlsson, A. 1974. Discussion. See Ref. 45, p.55
51. Hornykiewicz, O. 1974. Discussion. See Ref. 45, p. 53
52. Davis, J. M. 1974. A two factor theory of schizophrenia. See Ref. 45, pp. 25–29
53. McKenzie, G. M. 1972. Role of the tuberculum olfactorium in stereotyped behavior induced by apomorphine in the rat. *Psychopharmacologia* 23: 212–19
54. Ellinwood, E. H. Jr. 1968. Amphetamine psychosis. II. Theoretical implications. *Int. J. Neuropsychiatry* 4:45–54
55. Iversen, S. 1976. Behavioral implications of dopaminergic neurons in the mesolimbic system. See Ref. 20
56. Marcus, R. J., Villablanca, J. R. 1974. Is the striatum needed for amphetamine induced stereotyped behavior? *Proc. West Pharmacol. Soc.* 17:219–22
57. Kornetsky, C., Markowitz, R. 1975. Animal models of schizophrenia. In *Model Systems in Biological Psychiatry,* ed. D. J. Ingle, H. Schein. 26–50. Cambridge, Mass.: MIT Press. 196 pp.
58. Miller, R. J., Hiley, C. R. 1974. Antimuscarinic properties of neuroleptics and drug-induced Parkinsonism. *Nature* 248:596–97
59. Snyder, S. H., Greenberg, D., Yamamura, H. I. 1974. Antischizophrenic drugs and brain cholinergic receptors. *Arch. Gen. Psychiatry* 31:58–61
60. Yamamura, H. I., Manian, A. A., Snyder, S. H. 1976. Muscarinic cholinergic receptor binding: Influence of pimozide and chlorpromazine metabolites. *Life Sci.* 18:685–92
61. Hornykiewicz, O. 1975. Parkinsonism induced by dopaminergic antagonists. In *Adv. Neurol., Dopaminergic Mechanisms,* ed. D. B. Calne, T. N. Chase, A. Barbeau, 9:155–64. New York: Raven. 445 pp.
62. Kebabian, J. W., Petzold, G. L., Greengard, P. 1972. Dopamine-sensitive adenylate cyclase in caudate nucleus of rat brain and its similarity to the "dopamine receptor." *Proc. Natl. Acad. Sci. USA* 69:2145–49
63. Clement-Cormier, Y. C., Kebabian, J. W., Petzold, G. L., Greengard, P. 1974. Dopamine-sensitive adenylate cyclase in mammalian brain: A possible site of action of antipsychotic drugs. *Proc. Natl. Acad. Sci. USA* 71:1113–17
64. Snyder, S. H., Creese, I., Burt, D. R. 1975. The brain dopamine receptor: Labelling with (^{3}H) dopamine. *Psychopharmacol. Commun.* 1:663–73
65. Seeman, P., Lee, T. 1975. Antipsychotic drugs: Direct correlation between clinical potency and presynaptic action on dopamine neurons. *Science* 188: 1217–19
66. Lloyd, K. G., Bartholini, G. 1975. The effect of drugs on the release of endogenous catecholamines into the perfustate of discrete brain areas of the cat brain *in vivo. Experientia* 31:560–61
67. Seeman, P., Chau-Wong, M., Tedesco, J., Wong, K. 1975. Brain receptors for antipsychotic drugs and dopamine: Direct binding assays. *Proc. Natl. Acad. Sci. USA* 72:4376–80
68. Burt, D. R., Enna, S. J., Creese, I., Snyder, S. H. 1975. Dopamine receptor binding in the corpus striatum of mam-

malian brain. *Proc. Natl. Acad. Sci. USA* 72:4655–59
69. Creese, I., Burt, D. R., Snyder, S. H. 1976. Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. *Science* 192:481–83
70. Seeman, P., Lee, T., Chau-Wong, M., Wong, K. 1976. Antipsychotic drug doses and neuroleptic/dopamine receptors. *Nature* 261:717–18
71. Kornetsky, C., Mirsky, A. F. 1966. On certain psychopharmacological and physiological differences between schizophrenic and normal persons. *Psychopharmacologia* 8:309–18
72. Kornetsky, C., Eliasson, M. 1969. Reticular stimulation and chlorpromazine: An animal model of schizophrenic overarousal. *Science* 165: 1273–74
73. Duffy, E. 1957. The psychological significance of the concept of "arousal" or "activation." *Psychol. Rev.* 64:265–75
74. Malmo, R. A. 1959. Activation: A neuropsychological dimension. *Psychol. Rev.* 66:367–86
75. Brücke, F. Th. v., Hornykiewicz, O., Sigg, E. B. 1969. *The Pharmacology of Psychotherapeutic Drugs.* New York: Springer. 157 pp.
76. Bradley, P. B., Key, B. J. 1968. The effects of drugs on arousal responses produced by electrical stimulation of the reticular formation of the brain. *Electroncephalogr. Clin. Neurophysiol.* 10:560–71
77. Boakes, J., Bradley, P. B., Candy, J. M. 1972. A neuronal basis for the alerting action of (+)-amphetamine. *Br. J. Pharmacol.* 45:391–403
78. Feldman, P. E. 1959. The treatment of anergic schizophrenics with imipramine. *J. Clin. Exp. Psychopathol.* 20: 235–42
79. Gershon, S., Angrist, B. M. 1973. Effects of alterations of cholinergic function on behavior. In *Psychopathology and Psychopharmacology,* ed. J. D. Cole, A. M. Freedman, A. J. Friedhoff, 15–36. Baltimore: John Hopkins Univ. Press. 290 pp.
80. Sedvall, G., Fyrö, B., Nybäck, H., Wiesel, F.-A. 1975. Actions of dopaminergic antagonists in the striatum. See Ref. 61, pp. 131–40
81. Jefferson, J. W. 1974. Beta-adrenergic receptor blocking drugs in psychiatry. *Arch. Gen. Psychiatry* 31:681–91
82. Yorkston, N. J., Zaki, S. A., Malik, M. K. U., Morrison, R. C., Havard, C. W. H. 1974. Propranolol in the control of schizophrenic symptoms. *Br. Med. J.* 4:633–35
83. Carlsson, A., Roos, B.-E, Walinder, J., Skott, A. 1973. Further studies on the mechanism of antipsychotic action: Potentiation by alpha-methyltyrosine of thioridazine effects in chronic schizophrenia. *J. Neural Transm.* 34:125–32
84. Udenfriend, S., Zaltzman-Nirenberg, P., Gordon, R., Spector, S. 1966. Evaluation of the biochemical effects *in vivo* by inhibitors of the three enzymes involved in norepinephrine synthesis. *Mol. Pharmacol.* 2:95–105