in Florence showed some symptomatic improvement with only minor side effects, but this requires confirmation in a controlled trial. Cyclosporin A does not cause bone marrow depression; but reports of the development of lymphoma in patients treated with the drug after transplantation,[6] and indeed in patients treated with other immunosuppressive drugs,[7] mean that immunosuppression should be used circumspectly.

Another approach is based on the finding that suppressor lymphocyte activity is depressed during acute relapses in multiple sclerosis.[8] This has raised the possibility of enhancing suppressor cell activity therapeutically, and is yet another potentially promising line of investigation.

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Regular Review

Molecular pathology of schizophrenia: more than one disease process?

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The social effects of schizophrenia may be devastating, but the nature of the disease process remains obscure. Indeed, we are not even certain that there is a single pathological process. The diagnosis is made partly by the presence of certain psychological symptoms and partly by exclusion of other syndromes and disease processes. Thus hallucinations which are not due to a primary affective disturbance and for which there is no "organic" cause may well be described as schizophrenic. The use of stricter criteria, such as the presence of Schneider's first-rank symptoms (certain types of auditory hallucination, delusions of passivity and interference, thought alienation, and delusional perception), can increase the reliability of diagnosis, but it also restricts the definition of schizophrenia to a smaller group of illnesses than is implied by current usage—without improving the accuracy of prediction of outcome.

The belief that the primary disturbance in schizophrenia is chemical has long been plausible; that it is a disturbance of neurohumoral function is supported by observations that schizophrenic symptoms can be exacerbated in patients and provoked in non-psychotic individuals by drugs that act on specific transmitters. The psychosis seen in some amphetamine abusers may be indistinguishable from acute paranoid schizophrenia.[1 2] The psychotic changes, like those in schizophrenia, occur in clear consciousness (that is, in the absence of disorientation), and can include first-rank symptoms. In animals many of the behavioural effects of the amphetamines have been shown to be due to increased dopamine release from central dopamine pathways,[3] and the psychotic changes in man seem likely also to be associated with increased dopaminergic transmission.

Mechanism of the antipsychotic effect.—Both schizophrenic symptoms and those of the amphetamine psychosis are reduced by neuroleptic drugs. Carlsson and Lindqvist[4] found that these drugs increase dopamine turnover and suggested this was secondary to blockade of the dopamine receptor. Dopamine-induced activation of adenylate cyclase in the corpus striatum is inhibited by neuroleptic drugs; this inhibition correlates well with antipsychotic potency[5] for a range of drugs, though the butyrophenone compounds are somewhat less active than would be predicted from their clinical effects. Nevertheless, while blockade of the dopamine receptor is an obvious explanation of the extrapyramidal actions of neuroleptic drugs some controversy exists about the extension of that mechanism to explain their antipsychotic effect. The principal argument to the contrary[6] is that the correlation between extrapyramidal and therapeutic effects is not perfect. Some drugs (such as thioridazine) have fewer Parkinsonian effects than would be expected from their clinical efficacy. These same drugs, however, have high anticholinergic potency[7]—in other words, they have "inbuilt" antiparkinsonian activity. When this is taken into account the relation between dopamine antagonism and therapeutic effectiveness becomes more compelling. In the corpus striatum, where there is an interaction between acetylcholine and dopamine, drugs with a low incidence of side effects have relatively weak effects on dopaminergic transmission. This interaction does not occur in the mesolimbic dopamine system (the nucleus accumbens and related structures), and here dopamine blockade correlates well with therapeutic effectiveness.[8 9] Moreover, when dopamine antagonism is assessed not in the adenylate cyclase system but as inhibition of butyrophenone binding (an assay that probably identifies a second type of dopamine receptor) the relative lack of potency of the butyrophenones disappears.[10 11]

TABLE I—*Neurohumoral hypotheses of schizophrenia*

Authors	Theory	Principal arguments	Evidence from postmortem studies	
			For	Against
Gaddum, 1954[19]; Woolley and Shaw, 1954[20]	Serotonin deficiency	LSD psychosis resembles schizophrenia LSD blocks serotonin receptors		Serotonin turnover not decreased[21]; Serotonin receptors unchanged[17];
Randrup and Munkvad, 1965[22]	Dopamine neurone overactivity	Amphetamine psychosis resembles acute paranoid schizophrenia Amphetamines increase dopamine release Antipsychotic drugs block dopamine receptors		Dopamine turnover not increased[15]
Bowers, 1974[13]; Crow, Deakin, Johnstone, and Longden, 1976[23]	Dopamine receptor supersensitivity	As above	Dopamine receptors increased [15 16]	
Stein and Wise, 1971[27]	Noradrenaline neurone degeneration	Reward processes are mediated by central noradrenergic systems; anhedonia is a core feature of chronic schizophrenia		Dopamine-β-hydroxylase not reduced[28]
Murphy and Wyatt, 1972[24]	Monoamine oxidase deficiency	Platelet monoamine oxidase activity is reduced in some schizophrenic patients		Monoamine oxidase activity not reduced[25]

TABLE II—*Two syndromes in schizophrenia*

	Type I	Type II
Characteristic symptoms	Hallucinations, delusions, thought disorder (positive symptoms)	Affective flattening, poverty of speech, loss of drive, (negative symptoms)
Type of illness in which most commonly seen	Acute schizophrenia	Chronic schizophrenia, the "defect" state
Response to neuroleptics	Good	Poor
Outcome	Reversible	? Irreversible
Intellectual impairment	Absent	Sometimes present
Postulated pathological process	Increased dopamine receptors	Cell loss and structural changes in the brain

A recent clinical study[12] showed that only the *cis*- or α-isomer of the thiaxanthene flupenthixol, which blocks the dopamine receptor, is effective in treatment; the β-isomer, which is very much less potent as a dopamine antagonist, is no more active than placebo. This result is hard to explain except on the basis that dopamine antagonism is necessary for the therapeutic effect. The dopamine blockade theory of neuroleptic action has, indeed, survived stringent tests; and antagonism of dopamine receptors, particularly those located within the mesolimbic system and the subset that is specifically labelled by butyrophenones, is most probably the critical element in diminishing schizophrenic symptoms.

Changes in the dopamine receptor.—Is there, therefore, a primary disturbance of dopaminergic transmission in schizophrenia? Probenecid blocks the elimination of the dopamine metabolite homovanillic acid (HVA) from cerebrospinal fluid and can be used to obtain an estimate of dopamine turnover in the central nervous system. Use of this technique[13 14] has produced no evidence of an increase in HVA that could be attributed to overactivity of dopamine neurones. Indeed, within the group of schizophrenic patients poor prognosis[13] and increasing severity of symptoms[14] are associated with decreased concentrations of HVA in the cerebrospinal fluid. Post-mortem studies[15] have also shown no evidence of increased dopamine turnover—a surprising finding, since many patients coming to necropsy have been on long-term medication; presumably (as in animal experiments) the acute effects of neuroleptic drugs on dopamine turnover disappear with continued administration. These studies give no support to the view that dopamine neurones are overactive in schizophrenia (table I).

By contrast, there is evidence[15 16] that the numbers of dopamine receptors are increased in the brains of a proportion (perhaps two-thirds) of patients with schizophrenia, as shown by receptor assay techniques.[15 16] In experiments on animals the numbers of receptors have been found to increase after administration of neuroleptics; but the size of the change (around 100%) in schizophrenic patients is relatively large, and there is an increase in some patients who had been free of medication for the year before death.[15] Moreover, two types of dopamine receptor can be identified by ligand-binding techniques, and only that type of receptor labelled by the butyrophenone antagonist drugs is increased in schizophrenia[17]; while receptors labelled by both antagonist and agonist compounds are increased after administration of neuroleptics.[18]

Other neurohumoral theories have been tested in post-mortem studies of the brains of schizophrenics. On the basis of the LSD psychosis and the pharmacological antagonism by LSD of some effects of serotonin Gaddum[19] suggested that serotonergic transmission might be deficient. Tryptophan metabolism (by way of the serotonin and other pathways), however, is not abnormal in the schizophrenic brain,[21] and serotonin receptors (assessed by binding of LSD and 5-hydroxytryptamine) are unchanged.[17] Reports have been conflicting on possible changes in the monoamine oxidase activity in platelets[24] in schizophrenia, but interest in this question has been diminished by the finding[25] that enzyme activity, assessed with several different substrates, is normal in the brain of schizophrenics. Finally, there is evidence[26] that certain central noradrenergic pathways (such as the locus coeruleus innervation of the cerebral cortex) play a part in reward mechanisms; Stein and Wise[27] suggested that these pathways degenerate in schizophrenia. A deficient response to rewarding stimuli is a plausible explanation for some features of the disease, but studies[28] of the enzyme dopamine-β-hydroxylase (a marker for noradrenergic neurones) have not shown a consistent reduction in the schizophrenic brain.

At present, therefore, the only change found consistently in the postmortem studies of the schizophrenic brain is an increase in the numbers of dopamine receptors. Since such a change implies an increased and perhaps maladaptive response of the system, this finding could explain the beneficial effects of dopamine antagonists. The time course of the therapeutic effect is, however, noteworthy: benefit follows blockade of the dopamine receptors only after an interval of at least two weeks.[29] This suggests that blockade of the receptors may be necessary only to allow some other change to occur. Furthermore the therapeutic effects of blockade of dopamine receptors, and presumably of neuroleptic drugs in general, are limited to positive symptoms (delusions, hallucinations, and thought disorder).[12] These are the symptoms that are characteristic of acute schizophrenic illnesses. Negative symptoms (flattening of affect, poverty of speech, and loss of drive) are more commonly seen in chronic schizophrenia, particularly in institutionalised patients; and these patients probably benefit much less from drug treatment.[30]

Two syndromes?—Several lines of evidence support the view that the fundamental defect in some chronic illnesses may be distinct from that underlying the acute disturbance. Thus chronic schizophrenics may be relatively resistant to the effects of amphetamine-like drugs,[31] which readily exacerbate the symptoms of acute schizophrenia. Moreover, cognitive changes (such as disorientation in time) that resemble those of organic states are seen[32 33] in some institutionalised patients; and four radiological studies [34–37] have suggested that there is a group of chronic patients, probably including those with the greatest deterioration, who have structural changes of the cerebral ventricles. In the first computed tomography study,[36] increased ventricular size was correlated with negative symptoms and evidence of intellectual impairment.

It seems that two syndromes can be distinguished in those diseases currently described as schizophrenic and that each may be associated with a specific pathological process (table II). The first (the type I syndrome, equivalent to "acute schizophrenia," and characterised by the positive symptoms—delusions, hallucinations, and thought disorder) is in some way associated with a change in dopaminergic transmission; the second process (the type II syndrome, equivalent to the "defect state," and characterised by the negative symptoms—affective flattening and poverty of speech) is unrelated to dopaminergic transmission but may be associated with intellectual impairment and, perhaps, structural changes in the brain. Type I symptoms are reversible; type II symptoms, which are more difficult to define, may indicate a component of irreversibility. The former predict a potential response to neuroleptics; the latter are more closely associated with a poor long-term outcome. Episodes of type I symptoms may be followed by development of the type II syndrome, and both may be present together. Type II symptoms, however, define a group of illnesses of graver prognosis. They occasionally occur in the absence of the type I syndrome (for example, in "simple" schizophrenia), but because these symptoms are not well defined the diagnosis in these cases is difficult to establish.

The cause of schizophrenic illness remains obscure. A genetic influence is undoubted, but the facts that the onset of symptoms is often in adult life and that concordance in monozygotic twins (about 50%) falls short of 100% suggest that genes may be relevant only in predisposing to some other factor. Infection with a slow virus may be relevant.[38–40] Some neurotropic viruses (for example, polio, herpes simplex, and zoster) are selective in the cells they attack. Conceivably a slow virus infection might be associated either with a primary chemical disturbance (for example, through an affinity for a receptor site) or with a more general disturbance of higher cognitive functions.

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