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The biology of schizophrenia*

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For a disease with a life-time prevalence of approximately 1% in contemporary cultures, descriptions of schizophrenia in the past are surprisingly few. One of the earliest probable cases was described by Willis[1] in 1683; accounts of the onset of a progressive personality deterioration in early adult life were offered by Haslam[2] and Pinel[3] in 1809. In the late 19th century the clinical picture of the organic dementias, including general paralysis of the insane, was recognized and interest quickened in the description and classification of the psychoses. From the work of Emil Kraepelin[4] and Eugen Bleuler[5], in the first decade of this century, the concept of the functional psychoses arose; it was held that schizophrenia and manic-depressive psychosis could be distinguished, on psychological grounds, from the organic psychoses.

Thus of 'dementia praecox' Kraepelin[4] wrote 'perception is not usually lessened' (p. 5), 'orientation is not usually disordered' and 'memory is comparatively little affected. The patients are able, when they like, to give a correct detailed account of their past life, and often know accurately to a day how long they have been in the institution' (p. 18). While Kraepelin qualified this view with the reservation that in some terminal states there might be a 'general decay of mental efficiency' and that patients might 'become impoverished in thought, monotonous in their mental activities', Bleuler[5], who refined the concept to the 'group of schizophrenias', was less equivoval: 'In contrast to the organic psychoses we find in schizophrenia ... that sensation, memory, consciousness and motility, are not directly disturbed' and 'memory as

* The 1981 Curran Lecture delivered at St. George's Hospital Medical School.

such does not suffer in this disease' (p. 59). Unlike Kraepelin he made no exceptions in the case of terminal states: 'consciousness ... is not altered in the chronic conditions of schizophrenia. In this respect the schizophrenics behave as do the healthy' (p. 62). Thus both Bleuler and, to a lesser extent, Kraepelin were attempting to distinguish the disease they were describing from the organic psychoses. In adopting Morel's[6] term 'dementia praecox' Kraepelin was not referring to the global impairment of memory and intellect that is implicit in the modern use of the term 'dementia'.

Conclusions open to question have been based on this premise. Thus whereas in the organic dementias intellectual impairment commonly has been found to be associated with structural changes in the brain, the assumed absence of intellectual loss in schizophrenia has been thought to imply that such structural changes do not occur. Sometimes the argument has been taken further: if such structural changes are found to be present it is suggested that the case is not one of 'true' schizophrenia.

The dementia of dementia praecox

Two lines of evidence challenge this interpretation of the views of Kraepelin and Bleuler: a) there is a group of patients in whom memory capacity and orientation are defective; and b) such defects are sometimes associated with structural changes in the brain.

Some 25% of institutionalized patients with a diagnosis of schizophrenia give their age as 5 or more years less than their true age[7,8]. These patients often believe themselves to be an age close to that at the time of their first admission even though this may have been 25 or more years earlier; they make corresponding errors in estimating the current year and the duration of their hospital stay[9]. They are unable to acquire new information; for them 'time stands still'. A similar form of temporal disorientation is observed in patients with Alzheimer-type dementia, but because of the high mortality among those with this condition, the discrepancy between subjective and true age is never so striking as that observed in some patients with schizophrenia. In schizophrenia the phenomenon is unrelated to past physical treatments; it contradicts Bleuler's statement that 'the integration of perceptions concerning spatial and temporal orientation is quite good; even delirious (deluded) schizophrenics are for the most part well orientated as to place and even to time' (Bleuler[5], p. 58). Within the population of schizophrenic patients temporal disorientation is strongly correlated with impaired performance on tests of intellectual function. For both functions there is a range of disability; patients with temporal disorientation represent but the extremity of a continuum of intellectual impairment which afflicts many patients suffering from the disease.

Structural changes in the brain

Also radiological surveys suggest that some chronic schizophrenic patients have structural changes in the brain. Pneumoencephalographic studies from the 1920's, onwards[10,11], provide a basis for such claims; however, the difficulty in obtaining appropriate con-

Table 1. Pneumo-encephalographic studies of schizophrenia - within patient group comparisons

Author	No. of patients	Age (years)	Sub-groups	Pneumo-encephalogram Normal	Abnormal
Haug[13]	91	< 60	Without deterioration (n = 45)	39	6
			With deterioration (n = 46)	9	37
					(p < 0.001)
Asano[14]	53	mean 29	'Peripheral' (n = 21)	12	9
			'Nuclear' (n = 32)	7	25
					(p < 0.01)

Table 2. Computerized tomography studies in schizophrenia

Author	Patient group	Controls	Main findings
Johnstone et al.[15,16]	18 chronic institutionalized subjects (age range 42 to 70 years)	Age and premorbid occupation matched normal subjects	Mean ventricular size increased in the schizophrenic group; within this group associated with intellectual impairment and presence of negative symptoms
Weinberger et al.[17]	58 chronic schizophrenic patients aged less than 50 years	56 volunteers (including 48 at genetic risk but free of symptoms of Huntington's chorea)	Mean ventricular size increased 240% in schizophrenic group by comparison with controls
Donnelly et al.[19]	15 chronic schizophrenic patients aged less than 50 years	-	Intellectual impairment (Halstead-Reitan battery) significantly related to increased ventricular size
Rieder et al.[18]	17 out-patients with chronic schizophrenia (age range 20 to 35 years)	-	Cortical sulci were prominent in 4 patients and these patients were intellectually impaired by comparison with other patients
Golden et al.[20]	42 patients and out-patients with chronic schizophrenia (age range 20 to 40 years)	-	Mean ventricular site size correlated with intellectual impairment (Lubria-Nebraska battery)

trol observations with a procedure with an associated morbidity, and some negative findings when such controls were introduced[12] has led to these claims being discounted. Nevertheless, in 2 studies[13,14] in which comparisons within the patient group were made, patients with greater deterioration or more typical and severe schizophrenic illnesses were more likely to show abnormalities of ventricular size and structure than were patients without these features (table 1).

The advent of computerized tomography (CT scanning) renewed interest in the question. In the first CT scan study[15,16] a group of institutionalized patients with chronic schizophrenia were found to have significantly larger mean ventricular area than an age and pre-morbid occupation-matched control group. Within the patient group ventricular size was related to intellectual impairment and the presence of so-called negative symptoms (flattening of affect and poverty of speech). Later studies have replicated the main finding. Thus enlarged ventricles have been found in some patients in their 20's and 30's as well as at later ages[17], and also in some non-hospitalized schizophrenics[18], and in these patients there was evidence of cognitive impairment. In 2 further in-patient studies[19,20] poor intellectual performance was found to be correlated with increased ventricular size (table 2).

From the studies on temporal disorientation the conclusion seems inescapable that there is a group of chronic schizophrenic patients who contradict Bleuler's dictum on the absence of disorders of orientation and memory; the now established association of more general intellectual deficits with evidence of structural changes in the brain suggests that the disease in these cases resembles dementia more closely than has previously been thought.

The neurochemical component

While schizophrenia, on the basis of these findings, might be considered to be the consequence of mild chronic brain disease (e.g. an encephalitis) the observation that symptoms sometimes respond to medication (and sometimes remit spontaneously) favors the concept of a 'functional' and reversible psychosis. Since the introduction of chlopromazine in 1952[21], schizophrenic symptoms have been known to be ameliorated by the group of drugs known as neuroleptics; more recently it has been established that symptoms can be exacerbated in patients[22] and induced in normal subjects by administration of the amphetamines and related compounds[23]. Both observations are consistent with the view that changes in the neurotransmitter dopamine are in some way related to the development of symptoms:

a) Deniker[24] suggested that the antipsychotic effects of neuroleptic drugs were related to their ability to induce a neurological syndrome closely resembling Parkinson's disease. The discovery that dopamine is depleted in the brains of patients dying with Parkinson's disease[25] suggested that this syndrome is due to a failure of dopaminergic transmission. Neuroleptic drugs increase dopamine turnover (interpreted as secondary to blockade of dopamine receptors)[26]. In 2 in vitro systems[27,28] dopamine antagonist potency of various neuroleptics correlates well with their therapeutic efficacy in schizophrenia.

b) The symptoms of the amphetamine psychosis closely resemble those of acute paranoid schizophrenia[23]. Amphetamine-induced abnormal behaviors in animal experiments are dependant on intact dopamine stores and are selectively reversed by administration of neuroleptic drugs[29].

On this basis the 'dopamine hypothesis' has been formulated - that schizophrenic symptoms are
- ameliorated by the dopamine receptor blockade induced by neuroleptic drugs;
- due to increased dopamine release.

The first part of this hypothesis concerning the mechanism of the antipsychotic effect is related to but not necessarily dependent upon the more ambitious second part concerning the nature of the neurohumoral disturbance.

The mechanism of the antipsychotic effect

The thiaxanthene group of neuroleptic drugs exhibits a stereoisomerism that is relevant to dopamine antagonist activity: the cis- or α-isomers are potent dopamine antagonists while the trans- or β-isomers are almost devoid of activity[27] although the series resemble each other with respect to certain other pharmacological actions. Flupenthixol is a thiaxanthene widely used in the treatment of schizophrenia; a comparison of the effectiveness of the α- and β-forms with placebo in the treatment of the symptoms of acute schizophrenia[30] provided a direct test of the role of dopamine antagonism in the antipsychotic effect. 45 patients

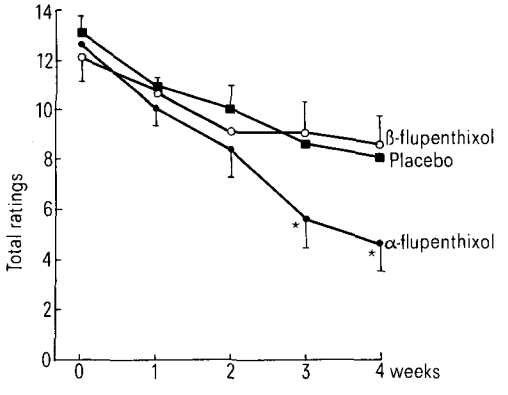

Figure 1. The effects of the 2 stereoisomers of flupenthixol in acute schizophrenia[30].

recently admitted with exacerbations of psychosis (including nuclear symptoms assessed by the 'present state examination') were randomly allocated to α-flupenthixol, β-flupenthixol or placebo; symptoms were assessed at weekly intervals by ratings based on a semi-structured interview (fig. 1).

Symptoms decreased in all treatment groups including placebo. Non drug-related changes are presumably attributable to admission to hospital, the ward environment or spontaneous remission. But there was also a drug effect. Patients on the α- but not the β-isomer had improved to a significantly greater extent by the 3rd and 4th weeks, consistent with the view that dopamine antagonism is a necessary element in the therapeutic effect. With current pharmacological knowledge it is difficult to otherwise explain this stereoisomer-specific effect.

Further, effects of neuroleptic drugs with respect to individual symptoms were more circumscribed than expected. 'Positive' symptoms (delusions, hallucinations and thought disorder) which signal 'pathology' by their presence can be distinguished from 'negative' symptoms (flattening of affect and poverty of speach), which signal 'pathology' through the diminution or absence of a normal function.

Positive symptoms diminished with time under treatment with the α-isomer to higher degree than under treatment with the β-isomer (fig. 2). Negative symptoms although infrequent showed little tendency to spontaneous improvement and no differential response to medication. Thus the beneficial effects of dopamine receptor blockade appear to be limited to the positive symptoms.

Is there a disturbance of dopaminergic transmission?

Possible abnormalities of dopamine neurone activity have been investigated in the post-mortem brain. Although concentrations of monoamine are maintained by feedback mechanisms in the face of changes in turnover, an increase in pre-mortem turnover should be revealed by an increase in the concentrations of the metabolites homovanillic acid (HVA) and dihydroxyphenylacetic acid (DOPAC). No evidence of an increase was obtained from a study of 45 schizophrenic brains[31] - this might be because the disturbance underlying the psychosis does not persist until just before death (although many patients have symptoms at this time). However, the findings are in agreement with earlier studies in acutely psychotic patients on the concentrations of dopamine metabolites in cerebro-spinal fluid[32a,b]. Thus there is no evidence that dopamine neurones are overactive.

But there is evidence for an increase in dopamine receptors. With butyrophenones (e.g. haloperidol or spiroperidol) as ligands, numbers of dopamine receptors have been found to be significantly increased in the brains of patients who have suffered from schizophrenia in each of the 3 major dopaminergically-innervated areas - caudate nucleus, putamen and nucleus accumbens[33]. The change is best reflected in the maximum binding values obtained from a Scatchard analysis (fig. 3).

In the patient group the range of maximum binding values is widened with a mean increase by approximately 100%, while values for some patients are within the normal range. When there is a change this is an increase in numbers rather than a change in affinity.

Is this change associated with the disease process or a secondary consequence of chronic neuroleptic administration? In animal experiments such drugs increase butyrophenone binding, but the former interpretation should be considered because

a) an increase in receptor numbers is found in some patients who have been drug-free during the year before death[33];

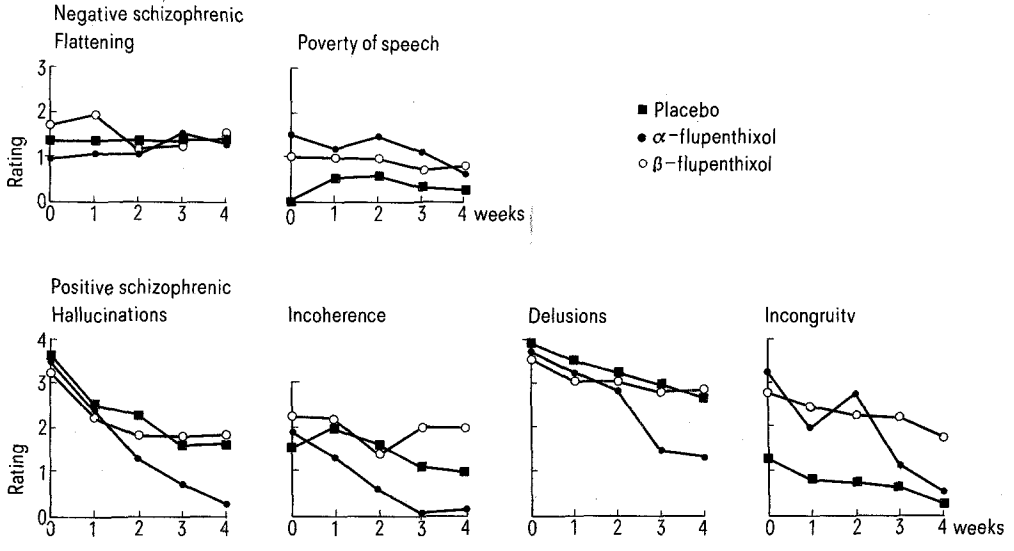

Figure 2. Differential effects of α-flupenthixol on the positive and negative symptoms of schizophrenia[30].

b) a similar increase is not seen in tissue samples from patients with Huntington's chorea who have received neuroleptic medication[35];
c) the increase is specific for one type of dopamine (the 'D^2') receptor. Analysis of the binding of flupenthixol[36], a ligand for both D_1 and D_2 receptors, revealed an increase only in the latter component; and binding of dopamine agonists (e.g. apomorphine and ADTN which may be ligands for a 3rd, the D_3, dopamine receptor) was not increased[34,37,38].
The binding of ligands to some other receptors, some enzymes associated with transmitter metabolism, the concentrations of transmitters themselves, their precursors and metabolites have been found to have similar values in schizophrenic and control brain tissue (table 3).

An increase in number of D_2-type dopamine receptors is thus the only consistent chemical difference established so far between the brains of patients suffering from schizophrenia and healthy brains. If this increase corresponds to an enhanced and excessive response of the post-synaptic neurone it could explain why dopamine antagonists are effective in treatment.

Two syndromes

What is the relationship between the structural brain changes seen in some schizophrenic patients, and the reversibility of symptoms that is seen with, and sometimes without, drug treatment in others? There is evidence that these features are associated respectively with negative and positive symptoms. It has been proposed[42] that the 2 symptom groups represent relatively independent dimensions of psychopathology and may reflect different underlying disease processes (table 4). The constellation referred to as the type I syndrome (of positive symptoms) is more characteristically seen in acute psychotic episodes and the type II syndrome (of negative symptoms) is more frequent in chronic illnesses and is equivalent to what is sometimes described as the 'defect state'. However, this is not an invariable rule, since positive symptoms may still be present after many years in an institution and negative symptoms are seen in some patients with acute shizophrenia particularly if there have been previous episodes (table 4).

A practical consequence of the separation of the 2 syndromes is the emergence of a predictor of potential drug response, the presence of positive symptoms being favorable and negative symptoms unfavorable. The latter symptoms (the type II syndrome) are at least sometimes associated with intellectual impairment. This may be because they are also associated with the structural changes in the brain. Presumably such changes reflect cell loss at some as yet unidentified site; this could account for the apparent irreversibility of the type II syndrome (the defect state) and its association with poor outcome. By contrast the type I syndrome represents a reversible and neurochemical

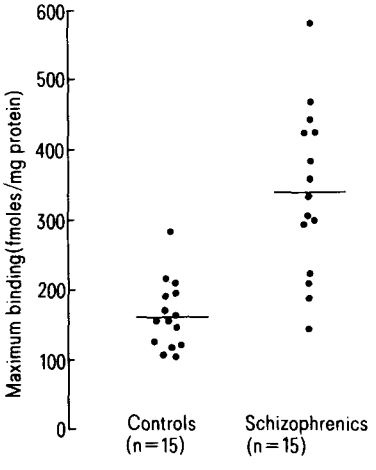

Figure 3. Maximum spiroperidol binding as an index of numbers of dopamine receptors in the brains of patients with schizophrenia[33].

Table 3. Chemical parameters investigated and found to have similar values in brain tissue from schizophrenics and controls[37-41]

Receptor ligands	Enzymes
LSD } for the	Tyrosine hydroxylase
5-HT } serotonin receptor	Dopa-decarboxylase
GABA	Dopamine-β-hydroxylase
Diazepam – for the benzo-diazepine receptor	Mono-amine oxidase
	Choline acetyl transferase
	Glutamic acid decarboxylase
QNB – for the muscarinic cholinergic receptor	
WB-4101 – for the α-adrenergic receptor	
Transmitters	**Transmitter precursors and metabolites**
Dopamine	5-HIAA (5-hydroxy-indole-acetic acid)
Noradrenaline	Kynurenine
Serotonin	Tryptophan
GABA	Homo-vanillic acid
	Dihydroxy-phenyl-acetic acid

Table 4. Two syndromes in schizophrenia[42]

	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
Response to neuroleptics	Good	Poor
Intellectual impairment	Absent	Sometimes present
Postulated pathology	?,increased dopamine receptors	?, cell loss and structural changes in brain
Outcome	Reversible	?, irreversible

component in some way related to a change in dopaminergic transmission. An increase in numbers of D_2 receptors is the only current finding which might be pathophysiologically significant.

Recent studies have tested the 2-syndrome hypothesis: 1. Positive symptoms were found to be exacerbated by amphetamine and diminished by neuroleptic administration, while negative symptoms (retardation and blunting of affect) were unchanged following either drug[43]. Thus the operations which modify the dopaminergic component influence only positive symptoms. 2. The presence of increased ventricular size, postulated as related to negative symptoms, has been found to be a predictor of non-response to neuroleptic drugs[44]. 3. In a large population of institutionalized patients negative symptoms were found to be significantly related to intellectual impairment and the presence of neurological signs, but none of these features was related to the presence of positive symptoms[45]. 4. Most recently in 14 patients who had been assessed before death the presence of positive but not negative symptoms was found to be significantly related to increased numbers of D_2 dopamine receptors[46].

While the 2 syndromes may represent independent dimensions of pathology, they do not constitute separate diseases. Patients may have symptoms of both types, either at the same time or sequentially. The relation between the syndromes is an overlapping one. Some patients have only type I and some only type II symtoms but many have both (fig. 4).

Changes with time (indicated by arrows) cast light on some diagnostic questions and also on prediction of outcome. Thus patients who experience only episodes of positive symptoms, and make a complete recovery, tend to be diagnosed as suffering from 'good-prognosis schizophrenia', 'schizophreniform' or 'cycloid' psychoses, 'reactive schizophrenia' or sometimes 'schizoaffective' psychoses with the implication that the diseases they suffer from differ from classical or 'Kraepelinian' schizophrenia. Also included in the group of 'pure' type I syndromes are those chronic paranoid illnesses (sometimes unresponsive to neuroleptics) in which the personality is well-preserved. In many patients, however, the passage of time and repeated episodes of psychosis lead to the emergence of type II symptoms. Such a development indicates progression to a classical or Kraepelinian form of illness. Some patients subsequently lose their positive symptoms, and may then be described as suffering from a 'pure defect' state. A particularly interesting, if rare, group includes those patients who acquire negative symptoms without ever having passed through episodes of acute psychosis, justifying a Bleulerian label of 'simple' schizophrenia. Other patients who have lost positive symptoms they had at an earlier stage may re-acquire them in further psychotic episodes. What seems to be unusual however is for patients who have once acquired negative symptoms to lose them. This may be because such symptoms are closely associated with a structural change in the brain. The presence of negative symptoms thus defines a group of illnesses of graver prognosis.

Genes and viruses

A contribution of genes to etiology has been firmly established by twin and adoption studies[47], but the genetic component is neither simple nor sufficiently explanatory. Concordance in monozygotic twin pairs is probably no more than 50%. Moreover illness onset in most cases of schizophrenia occurs in adult life rather than early in development as would be expected in a simple inherited metabolic disorder.

Other findings in family studies are difficult to explain using a simple genetic theory. Concordance for dizygotic twin pairs is higher than for siblings[48], although twins and siblings share genes to the same extent; and concordance rates in dizygotic twins and other pairs of relatives are higher for pairs of the same than of the opposite sex[49]. For these reasons the genetic component may represent not so much a determinant of a specific chemical aberration as a predisposition to an environmental pathogen[50].

The possibility that one or more viruses may be responsible for schizophrenia is supported by some intriguing findings. Seasonal influences have been demonstrated both for onset of illness, and for the month of birth of patients who later become schizophrenic[51]. Patients are more likely to become ill between the months of June and August of each year, and are more likely to have been born in January to March. Whether these effects are interrelated has yet to be established. The variation in season of onset suggests an infective agent with a high prevalence in the early summer (or earlier if an incubation period is involved). An alteration of procreative behavior with an increase in births of individuals predisposed to schizophrenia 9 months later could account for the season of birth effect. An alternative explanation is that an agent with a winter prevalence affects the neonate or foetus in utero in such a way that the

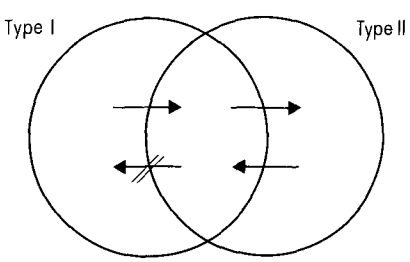

Figure 4. Relationships between type I and type II syndromes.

individual is rendered susceptible or tolerant to the same or a related agent when exposed in later life. In pairs of monozygotic twins discordant for schizophrenia the affected member was found to have had a lower birth weight, and a higher incidence of cyanosis, infantile colic, feeding problems and early illness[52], findings that are compatible with the presence of a pathogen in utero.

Although there is a lack of evidence for person-to-person transmission this possibility should not be too readily dismissed. Abe[53] examined the risk to the co-twin in the period following the onset of schizophrenic illness in one of monozygotic twins. After 6 months the risk was roughly constant i.e. the pattern of onset appeared to be the result of a random process. Within the first 6 months, however, there was a significantly increased risk to the 2nd twin. Moreover, when analyzed by whether the twins were together or apart at illness onset in the 1st twin all of the excess occurred in those pairs who were together. This can be accounted for either by the passage of an agent from one to the other twin, or by exposure of both twins to a single influence simultaneously.

Cerebro-spinal fluid from some patients with acute psychoses was found to induce cytopathic effects in human embryonic fibroblast cultures[54]. The effect could not be passaged but the fact that it was prevented by filters of size 50–100 nm suggested that the effect (which has been found reliable in fibroblast cultures) might reflect the presence of a virus. Such cytopathic effects are not limited to schizophrenia but are seen also with CSF's from patients with affective (manic-depressive) psychoses, Huntington's chorea and some neurological conditions[55]. If the effect reflects the presence of a virus which is not merely secondary to CNS disease one must consider whether more than one agent is present or whether one agent could cause a number of different neuropsychiatric diseases, the form of the disease being determined by genetic predisposition. With respect to this latter possibility it is particularly interesting that the season of birth and season of onset effects seen for mania are identical to those seen for schizophrenia[51].

The time course of the functional psychoses may be thought unusual for a viral illness. However slow virus diseases of the nervous system are now well recognized[56] and in some cases (e.g. subacute sclerosing panencephalitis, visna, progressive multifocal leucoencephalopathy) an agent has been identified. Moreover one class of conventional agents the herpes viruses, has an affinity for the nervous system, a propensity to become latent, and to cause recurrent episodes of illness thus providing a paradigm for CNS virus involvement in psychiatric disease. The nature of the virus interaction with specific neuronal pathways (e.g. sensory neurones in the case of herpes simplex and zoster) remains to be established, and the possibility that the interaction is the result of an affinity between the virus and a neurotransmitter receptor has possible therapeutic implications. Antibodies to cytomegalovirus (a herpes virus, known to cause foetal and neonatal disease) are increased in CSF relative to serum in some schizophrenic patients[57], a finding consistent with the view that this virus is responsible for some psychotic illnesses.

Conclusions

Genes may be relevant not only to predisposition but also to the type of schizophrenic illness which occurs, and determine whether symptoms of the type I or type II syndromes or a combination of the two are the major manifestations. Both syndromes, however, might be caused by a single agent, e.g. a virus. Thus, amongst the population of patients at risk there is a group who experience a primary neurochemical disturbance (e.g. of dopaminergic transmission). This becomes manifest in positive symptoms (delusions, hallucinations and thought disorder) and might result from an affinity of the virus for a particular neurochemical structure (e.g. the D_2 dopamine receptor or a molecule concerned in its regulation). Within this population however, is a sub-group that is predisposed to a more malignant and widespread disease. In these patients the virus gains further footholds in the nervous system, with the consequence that the disease acquires the characteristics of a chronic encephalitis. It is in these cases that there is evidence of structural change (although the site of the presumed cell loss has yet to be determined) and when present this change is associated with intellectual impairment and negative symptoms (the type II syndrome).

Thus the disturbance underlying the type I syndrome is a neurochemical one which accounts for the reversibility of some schizophrenic symptoms and illnesses, and their response to neuroleptic drugs. It is compatible with Bleuler's view of schizophrenia as a functional psychosis which can be clearly distinguished from dementia. The change underlying the type II syndrome is progressive and irreversible and accounts for poor long-term outcome. To this form of illness Kraepelin's term dementia praecox can be applied with the term dementia retaining its contemporary connotation of organic psychosis.

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