Structure and Function in Neurology and Psychiatry

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In the 19th century the triumphs of neuropathology and the clinico-anatomical method led to the evolution of neurology as a separate 'organically' based discipline associated with the concept of functional localisation. At the same time the growth of psychodynamic psychiatry contributed to the progressive separation of the two disciplines, with neuropsychiatry sitting uneasily in the middle. Psychiatrists are now showing increasing interest in the structure and function of the nervous system, but are having difficulty in integrating their findings into 'functional' diseases. This may be because disorder of function in the nervous system is much more complex than previously envisaged. The function of the nervous system is profoundly affected by psychological and social factors. The view that neurology is wholly 'organic' and synonymous with structural disease of the nervous system is fallacious. Neurological patients have complex dynamic disorders of function in the nervous system whether or not structural disease is present.

"The antithesis between 'organic' and 'functional' disease states still lingers at the bedside and in medical literature, though it is transparently false and has been abandoned long since by all contemplative minds."
(Kinnier Wilson, 1940)

Neurological practice is rooted in structure, in neuroanatomy and neuropathology. One of the primary objectives of the neurologist is to find the lesion. For this he has developed his skills in neurological examination and utilises increasingly sophisticated and costly investigative techniques. Neurological disorder is widely referred to as organic. Yet structural lesions produce their symptoms and signs by disturbing the function of the nervous system: by interruption, decrease, increase or release of function; by excitation, inhibition, instability or restoration of function. However, this disturbance of function in neurology is often taught and practised as though it were a static or almost wholly 'reflex' neurophysiology – fixed lesions producing fixed defects in function. The neurological textbooks are littered with diagrams, figures and tables showing how a lesion at this or that site produces a clear-cut constellation of symptoms and signs. The reality for the observant neurologist is often rather different. Not all the expected symptoms and signs are present. Those that are present, whether motor, sensory, reflex, cognitive or behavioural, come and go or fluctuate in intensity over minutes, hours or days under a variety of intrinsic or extrinsic influences. Some are very intermittent, such as the seizures associated with a cerebral tumour or scar, or the migrainous headaches associated with an arteriovenous malformation. Furthermore, the symptoms and signs of a fixed structural lesion may be indistinguishable from those of functional disorders in the nervous system, for example the hemiparesis of a stroke and the Todd's paralysis following seizures. Psychological and social factors frequently clearly influence and interact with neurological symptoms and signs, but are often overlooked or ignored as though this was somehow part of 'psychiatry'.

Psychiatrists in general adopt an uncertain, even confused, approach to structure and function. Individually they may belong to very different schools of thought depending whether they are orientated to the neuropsychiatric or psychodynamic wing of the discipline (Hill, 1964). Some are concerned that they may be overlooking a structural lesion, something that really belongs to neurology! All recognise that various types of cerebral pathology produce mental symptoms which form part of the practice of psychiatry, so-called 'organic psychiatry' or 'neuropsychiatry' (Lishman, 1978; Trimble, 1981), which clearly has close links with neurology. At the very least it is borderline territory, the interface or bridge between the two disciplines. The main corpus of psychiatry is concerned with 'functional' disorder of the mind, self or psychic apparatus, brought about mainly by intra- and interpersonal forces of a psychological and social kind. Here the use of the word 'functional' is not

physiological but psychological. The psychoses illustrate the dilemma, with the organic psychoses rooted in nervous system pathology and physiology, and the 'functional' psychoses conceived of in psychic formulations.

In recent years the conceptual dilemma for the psychiatrist has been made more acute by developments in the neurosciences, especially in psychopharmacology, neurochemistry and brain-imaging techniques. More and more attention is being paid by psychiatrists to these developments, which have often revealed unsuspected structural or functional (in the neurological sense) disorders in their patients. For neurologists I would also argue that a wholly organic approach, which ignores or overlooks the impact of psychological and social factors in neurological disorders, is incomplete and, from the patient's point of view in particular, inadequate. The present widely held concept of neurology as organic and psychiatry as 'functional', with neuropsychiatry sitting uneasily between, is unsatisfactory.

These contrasting views of structure and function by neurologists and psychiatrists have not come about by chance, but have been shaped by forces which have led to the separation of neurology and psychiatry as distinct disciplines with ill-defined borders. If we are to understand the present situation and to see our way foward to a more satisfactory and less confusing conceptual framework it is important to understand what these forces and developments were.

Historical background

In the beginning there were no neurologists or psychiatrists, but there were 'nervous diseases'. According to Lopez-Piñero (1983), the concept of 'nervous diseases' emerged in Britain with Willis (1622–75) and Sydenham (1624–89). For example, both viewed hysteria and hypochondria as nervous diseases and not, as in the Galenic tradition, vapours emanating from the uterus or the spleen, liver and stomach. According to Willis (1682), hysteria "the so-called uterine disease is primarily a convulsive disease caused by an alteration of the nerves and the brain". The concept of nervous diseases was consolidated in the 18th century, when they also became fashionable, due to the influence of, among others: Cheyne (1733), whose treatise on the "English malady" suggested that "these nervous diseases being computed to make almost one-third of the complaints of the people of condition in England"; and of Whytt (1765), who expressed the opinion that "all diseases may, in some sense, be called affections of the nervous system, because in almost every disease, the nerves are more or less hurt;

and in consequence of this, various sensations, motions and changes are produced in the body".

It is to Cullen (1710–90) that we owe the term 'neurosis'. William Cullen succeeded Robert Whytt to the Chair of the Practice of Physic at Edinburgh. For Cullen the word 'neuroses' was no more than a neologism for Whytt's 'nervous diseases'. Cullen recognised four classes of disease: three were general (I pyrexiae, II neuroses and III caquexiae), the fourth local (IV locales). The class 'neuroses' was defined as "affections of sense and motion without fever or evidence of local disease", that is, they were general and functional affections of the nervous system and the presence of any local lesion would exclude them from the class. In his subclassification (below) of the neuroses, we see some disorders which belong to modern neurology (convulsions, paralysis, etc.) and some to modern psychiatry (hysteria, melancholia, etc.):

Comata (e.g. apoplexy, paralysis)
Adynamiae (e.g. syncope, hypochondriasis)
Spasmi (e.g. convulsions, chorea, hysteria, tetany)
Vesaniae (e.g. melancholia, mania, impaired judgement)

The concept of neuroses was taken up in France by Pinel (1725–1826), who translated Cullen's textbook. He, too, described neuroses as alterations of sensitivity and motility which are not accompanied by fever, inflammation or structural lesion (Pinel, 1798). His classification of the neuroses (below), like Cullen's nosology, contains a mixture of modern neurology and psychiatry, as well as some general medical disorders undoubtedly influenced by the nervous system:

Neuroses of the senses (e.g. amaurosis, diplopia, deafness, tinnitus)
Neuroses of cerebral function (e.g. coma, hypochondria, amentia, catalepsy, melancholia, mania, hydrophobia)
Neuroses of Locomotion (e.g. convulsions, chorea, palsy, tetanus, aphonia)
Neuroses of nutrition (e.g. dyspepsia, asthma, palpitations, colic, anorexia)
Neuroses of sexual function (e.g. priapism, hysteria)

The clinico-anatomical method set limits to what could be included under the class neuroses. As the discovery of any structural lesion by definition excluded a disorder from this category, the stage was now set for the systematic contraction of the neuroses. More and more disorders were eliminated by the progressive triumphs of French and other European neuropathologists and cerebral localisers throughout the 19th century, culminating in the great achievements of Charcot (1825–93) at the Salpêtrière. At the same time rearrangements of the classification

of the neuroses on anatomical principles were introduced, such as that of Jaccoud (1872):

Brain neuroses (e.g. mental diseases)

Cerebrospinal neuroses (e.g. epilepsy, hysteria, catalepsy)

Brain-stem neuroses (e.g. chorea, tetanus, paralysis agitans)

Peripheral neuroses (e.g. anaesthesias, neuralgias, hyperkinesias)

The point remained, however, that these were all functional disorders of the nervous system for which there was no known structural pathology. If structural pathology was discovered in a neurosis it was either reclassified or sometimes a certain ambiguity crept in with the use of such phrases as 'symptomatic neurosis', for example idiopathic and 'symptomatic' epilepsy.

The same forces in the 19th century which were leading to the contraction of the neuroses were also leading to the growth of neurology as an independent scientifically based discipline. Thus the first textbook of neurology from Germany by Romberg (1840–46) was based on physiological or functional principles. Nervous diseases were classified into two main divisions: neuroses of sensitivity and neuroses of motility. However, by the end of the century neurological textbooks were firmly rooted in the new anatomy and pathology and to a much smaller extent on physiological principles, that is, on structure more than function. Furthermore the new neurophysiology was based on the principle of functional localisation following the pioneering studies of, for example, Broca (1865) and Wernicke (1874) with respect to speech and Ferrier (1878) with respect to motor and sensory functions. This new functional approach was however of a rather static kind, with lesions interrupting activities or pathways with fixed functions. Gowers' *Manual of Diseases of the Nervous System* published in 1886 illustrates the many new neurological diseases that had been discovered and classified on the basis of the new principles of neuropathology and localisation of function. Neurological textbooks, such as Gowers', still included functional disorders (i.e. neuroses), but exemplified the great reduction that had taken place in the number of neuroses of sensation and motility since Cullen, Pinel and Romberg.

Before turning to parallel developments in 19th-century psychiatry, it is appropriate to refer to the views of Hughlings Jackson (1835–1911). He accepted that some disorders of the nervous system were functional (i.e. were neuroses), including some insanities, which he linked to current evolutionary theories, proposing the concept of dissolution of nervous system function. However, Jackson recognised two kinds of abnormal function. As the normal function of nerve tissue was to "store up and expend force", so abnormal function could be either (a) loss of function (i.e. reduced or absent storage and expenditure), or (b) overfunction (i.e. increased storage and expenditure), the latter also contributing to *instability* of function. The former could lead to palsies and anaesthesias, the latter to epilepsies, chorea and tetanus. He believed that both had a pathological basis. However, although the "destroying lesions" responsible for the former were usually readily enough apparent to the pathologist, this was often not the case for his "discharging lesions", for which he had to invoke "morbid nutrition", for example in idiopathic epilepsy. Jackson emphasised that he was not using the word functional in the conventional 19th-century way of "absence of or undetected brain pathology" (Jackson, 1873).

Just as the number of neurological neuroses (functional disorders of the nervous system) was diminishing towards the end of the 19th century, a wholly new concept of the neuroses arose in the evolving discipline of psychiatry. Psychiatry has a longer history than neurology, as Hill (1964), among others, has described. Especially prominent throughout the 19th century was the German and Austrian school of neuropsychiatry, illustrated by Griesinger (1817–68), a contemporary of Romberg in Berlin, and Meynert (1833–92) in Vienna. For them, mental diseases were brain diseases. Meynert (1884) subtitled his psychiatric text book *Diseases of the Forebrain*. Neurosyphilis and general paralysis of the insane were the model. The French clinico-anatomical method was applied as vigorously to mental diseases as it was being applied to neurological diseases, although with less satisfactory results. Kraepelin (1856–25) belonged to this tradition, and so did Freud (1856–1939). Freud was well grounded in the new neuroanatomy, neuropathology and neurology, but he found these an incomplete explanation of the clinical phenomena he was observing, as his studies on aphasia made clear (Freud, 1891). As a young man he spent several months of 1885–86 at the Saltpêtrière in Paris, where he was greatly influenced by Charcot, who was now studying hysteria and hypnosis, which led him to suspect the presence of subconscious and psychological mechanisms. On his return to Vienna, Freud became more interested, not so much in how his patients spoke, but in what they said! Instead of brain disease, disorder of the psychic apparatus was to be understood and explained in relation to the new disciplines of psychoanalysis, psychology and sociology. Thus was born 20th-century dynamic

psychiatry, which for the most part has tended to dominate 20th-century neuropsychiatry. This is illustrated by what has happened to the neuroses. With Freud and the dynamic psychiatrists appeared a whole new range of disorder and meaning – psychoneuroses (i.e. anxiety neurosis, obsessional neurosis, depressive neurosis, etc.). No longer disorders of sensation and motility to be understood on the basis of disturbance in nervous system physiology, but disorders of the psychic apparatus to be interpreted in terms of unconscious motivation or maladaption to psychological or social pressures or conflicts. Thus the words 'neurosis' and 'functional' were taken over by the dynamic psychiatrists with a new meaning. The growing numbers of neurologists and diminishing numbers of neuropsychiatrists were left with the word 'organic'.

In retrospect it is surprising that neurologists allowed psychiatrists to hijack the words 'neurosis' and 'functional' and invest them with new meaning without a protest. Kinnier Wilson (1878–1937) is distinguished, among other reasons, for the discovery of the disease which bears his name and for his textbook of neurology which was published in two volumes in 1940 after his death. He was the last British neurologist to include a section on 'the neuroses' in a textbook of neurology, and his classification can be summarised as:

Motor neuroses (e.g. tics, rhythmias, myospasms, myotonia, torticollis, occupational)

Sensory neuroses (e.g. neuralgias (e.g. trigeminal), causalgia, acroparaesthesias)

Reflex neuroses (e.g. eneuresis, retention)

Psychoneuroses (e.g. obsessional, anxiety)

In keeping with 19th-century neurological tradition, he recognised motor, sensory, reflex and psychoneuroses. Although he does not discuss psychoneuroses, as these belong to psychiatry, he does protest that to equate 'psychoneurosis' and 'neurosis' is to take a part for the whole. He goes on to maintain that "no radical distinction can exist between a 'neurosis' and any other type of nervous syndrome. In theory and by etymology it should denote disturbance of the intrinsic function of nerve tissue".

Kinnier Wilson understood that current neurological opinion took the word 'neurosis' to signify a disorder of nervous function for which, as yet, no underlying structural basis had been found. However, he pointed out that "molecular change must accompany all reactions whether those of a neurosis or of structural disease and, if on the one hand it induces lesions that can be seen and in the other not, no fundamental separation between them is thereby

effected". He argues persuasively for the retention of the words neurosis and functional in the neurological camp. For him neurological symptoms, whether in the presence of structural disease or not, exhibit a dynamic quality which can only be explained by a dynamic neurophysiology, a functional disturbance in the nervous system which owes something to Jackson's views, as well as newer concepts of excitation and inhibition. Psychiatrists can have their psychoneuroses and explain them as they wish, but if they take over the words 'neurosis' and 'functional' completely, then presumably new words would have to be invented to describe the disturbances in nervous system function observed and treated by neurologists. He would have been disappointed to learn that the antithesis between 'organic' and 'functional', which he regarded as false, is even more deeply rooted today, as Trimble (1982) has also deplored. Other recent authors who have discussed changes in meaning which have occurred to the words 'organic' and 'functional' since the 19th century include Jeannerod (1985), Harrington (1987), and Clarke & Jacyna (1987).

The present scene

I have described how two processes in particular led to the progressive evolution of neurology and psychiatry as independent disciplines: on the one hand, the triumphs of neuropathology and the clinico-anatomical method culminated in the progressive replacement of the earlier functional neurology (i.e. disorders of sensation and motion) by a structurally based discipline associated with a rather fixed functional localisation; on the other hand, the evolution of dynamic psychiatry took with it the concepts of functional disorder and neuroses (nervous diseases) and gave them a new meaning within the conceptual framework of a psychic apparatus either separated from or only obscurely linked to the nervous system. Two consequences of these developments have been that: (a) psychiatry has tended to split into two camps with its neuropsychiatric wing having common roots and links with neurology; and (b) neurologists have tended either to overlook those complex disorders of function in the nervous system, which did not seem to fit into their more simplified views of functional localisation, or even to pass them off as in some way 'psychiatric'.

Two modern trends highlight the difficulties posed by a predominantly organic, structurally based and functionally localised neurology and a predominantly 'functionally' based psychiatry: (a) in neurology there is growing evidence that the disorders of function in the nervous system associated with

structural disease, or even unassociated with structural disease, are much more complex and dynamic than hitherto understood; and (b) in psychiatry the discovery of structural lesions by modern imaging techniques are proving very difficult to integrate into 'functional' disorders.

Disorder of function in neurology

Excitability of the cerebral cortex

Function within the nervous system is achieved by "transient electrical potentials travelling the fibres of the nervous system" (Sherrington, 1941). Some insight into the functioning of the human cerebral cortex in health and disease was gained by Penfield's studies of cortical stimulation in patients with epilepsy undergoing evaluation for surgery (Penfield & Jasper, 1954; Penfield, 1958). He showed that functional activity in the cortex was not simple, repeatable and fixed, but complex, variable and dynamic. As in animals, functional localisation does not exist in 'centres' or 'points' but in areas and patterns that extend into various regions of the brain. Although the order of cortical representation of function across, for example, the motor or sensory cortex may be consistent from patient to patient, the site and size of representation may not only vary between patients but even within patients at successive explorations. As also noted by Grunbaum & Sherrington (1901, 1903) in anthropoids there is considerable variation in the degree to which an individual's cortex can be stimulated. Some variation is due to either facilitation or extinction, depending on the time between successive stimulations. However, the character and intensity of a response are also influenced by stimulation of adjacent points, implying that response will vary with the internal or external environment. Instability of response is a characteristic of the human cortex (Penfield & Welch, 1949). A motor or sensory response can be displaced into a previously unresponsive territory by advancing stimulations. Sometimes motor responses can be elicited from the sensory cortex or sensory responses from the motor cortex.

Seizure discharges often sensitise the cortex ('epileptic sensitisation') so that evidence of the functional activity of a particular area may be elicited by electrical stimulation, where usually no response would be found. For example, the temporal cortex, which ordinarily gives no psychical response to stimulation may, in the case of an epileptic patient, produce hallucinations or illusions, but only when that part of the cortex has been the seat of epileptic discharges. This activation does not necessarily apply only to patterns of response which appear in the patient's seizures, but can involve neighbouring elements of the cortex and other patterns of response. On other occasions after a seizure the cortex may be in a refractory state and this may be associated with displacement of responses to other areas of cortex. Depression of sensitivity to stimulation of one area may be associated with hypersensitivity of another area.

Disorder of function in epilepsy

The study of epileptic patients provides other evidence of dynamic disorder of function in neurological disease (Trimble & Reynolds, 1986). Even in the presence of an obvious cerebral lesion it has to be asked why seizures occur in some patients but not in others, and why seizures occur in an individual patient at particular times and not at others. It is often apparent that provocative factors, especially of a sensory or emotional kind, play a triggering role. Sometimes it is the summation of several factors that triggers an individual attack: anything that may increase the instability around Jackson's 'discharging lesion' (e.g. change in level of alertness or sleep, physical or emotional stress or fluctuation in hormonal pattern associated with menstruation) may precipitate a seizure.

Other considerations relating to the effects of individual seizures on brain function may also be important. It is apparent that most epileptic patients are well controlled on treatment or go into spontaneous remission (Reynolds et al, 1983). About a quarter, however, go on to develop chronic epilepsy apparently resistant to medication. How does this come about? Certain factors increase the risk of chronic epilepsy, such as brain damage, neurological, psychological and social handicaps. In addition, the longer seizures continue after the start of treatment the less likely they are to remit (Elwes et al, 1984). This is in keeping with Gowers' (1881) hypothesis that each seizure increases the predisposition to the next one. The natural history of untreated epilepsy is largely unknown, but in a retrospective study of new referrals with between two and five untreated tonic–clonic seizures it was remarkable that, in most patients, the time interval between successive seizures was shortening, suggesting an escalation of epilepsy (Elwes et al, 1988). All this suggests that early effective treatment may be important to prevent the evolution of chronic epilepsy (Reynolds, 1987, 1988). Epilepsy should perhaps be viewed not as a random succession of seizures but as a process – a process in which important events occur in the brain between seizures and in which the early course of the disease

influences the later prognosis (Reynolds *et al*, 1983; Reynolds, 1989). It should be clearly understood that there are processes in the brain which lead to *remission* of epilepsy as well as escalation of the disorder.

Kindling

An experimental model which is to some extent relevant to Gowers' view of seizures begetting seizures and Penfield's observations on 'epileptic sensitisation' of the cortex is that of kindling (Goddard, 1967; Wada, 1976, 1981; Reynolds, 1989). In this model repeated subthreshold electrical or chemical stimuli progressively increase convulsive response, eventually culminating in a seizure. The subsequent application of a single subthreshold stimulus will again evoke a seizure. Eventually chronic seizures can be produced *without evidence of tissue damage*. There are variations of the model depending on the species, the nature of the stimulus, and the area of the brain to which it is applied, but a central feature is that every one of the stimuli are necessary to kindle the seizure, provided they are applied at sufficient intervals. In other words each stimulus leaves its mark on the brain, but the nature of this mark has so far eluded detection. If a subthreshold stimulus can change brain function, why not a seizure itself? Indeed, it is certain that some functional change takes place, as evidenced by the clinical effect of convulsive therapy in depression.

The mirror focus

Another model which remarkably illustrates the remote functional effects of a structural lesion in the brain is the mirror focus (Morrell, 1969). The mirror focus is a new epileptogenic focus in the same area of brain but contralateral to the original focus. The secondary focus is induced by and can become completely independent of the original epileptogenic focus. Again, the time scale of the phenomenon varies in different species and is longest in man. Morrell (1985) has marshalled the evidence, derived from studies of patients evaluated and treated surgically for unilateral temporal lobe lesions, that the phenomenon occurs in humans. Successful temporal lobectomy may be undertaken in patients with a unilateral structural lesion despite bitemporal epileptogenic discharges if the contralateral discharges have not yet become independent.

The influence of environment and social factors on cerebral activity and structure

Aggression can be studied in animals by means of electrical stimulation of the brain. Offensive-defensive reactions have been related to many subcortical structures, extending almost continuously from forebrain to brain-stem and involving ventral septum, pre-optic area, amygdala, stria terminalis, anterior and posterior hypothalamus, posteroventral nucleus of the thalamus, tectal area, central grey, reticular substance and spinothalamic tract (Delgado, 1967). There is, however, much that is uncertain in the anatomical and functional relationships of these various areas. Furthermore, many of the studies have been in restrained (i.e. caged) lower animals and without regard to social situations. Delgado (1967) and Delgado & Mir (1969) have overcome many of these limitations by studying monkeys equipped with intracerebral electrodes in whom stimulation was achieved by means of radio stimulators. The animals formed part of an established colony with three or four other monkeys, so that individual and group behaviour could be studied in various free ranging and social situations. The full pattern of well organised, purposefully orientated aggression, adapted to changes in the environment and related to the animals' past experience, was evoked by stimulation of the nucleus ventralis posterolateralis of the thalamus and the pedunculus cerebellaris medius. Of particular interest is that this full effect was only evident when the social rank of the stimulated monkey was high and disappeared when the animal was in a subordinate position. Thus, when a monkey's social status was low, brain stimulation induced only increased motor activity and occasional threats, which provoked attacks against it. As social rank improved stimulated attacks against other animals increased. The effect of stimulation of the same cerebral point therefore differed in degree and had opposite social consequences, depending on hierarchical position. Like the studies of epilepsy previously described, these findings indicate that functional representation in the brain should not be expressed in absolute terms, but cerebral activity is in a dynamic state modified by environmental and social inputs.

Environmental factors not only modify the function of the brain but may also alter its *structure*. The infant or immature brain is especially vulnerable to such modification. Experimental studies have shown that early loss of visual stimulation in one eye, or disruption of the usual binocular stimulation, will lead to permanent change in the architecture of the occipital cortex (Wiesel & Hubel, 1965; Blakemore & Cooper, 1970). The clinical counterpart is the child with uncorrected strabismus. To avoid diplopia, visual impulses from the weak eye are suppressed and permanent blindness develops. This does not happen in the adult or mature nervous system. Similar effects of sensory deprivation have been described in other

areas of the brain, and conversely an enriched and stimulating environment enhances the branching of cortical dendrites and the development of dendritic spines (Bennett *et al*, 1964; Volkmar & Greenough, 1972). These observations are probably relevant to the effects of early emotional and social deprivation on later mental health and behaviour, as illustrated in the early infant deprivation studies in monkeys (Harlow *et al*, 1971) and the behavioural imprinting investigations of ethologists (Lorenz, 1970).

The neurological examples described above illustrate that whether or not structural disease is present, disorder of function in the nervous system is much more complex and dynamic than is usually envisaged by such phrases as 'functional localisation'.

Structural disease in psychiatry

Computerised tomography in schizophrenia

There is no doubt that in the last decade there has been a remarkable rekindling of interest in structural brain disease in psychiatric disorders, stimulated by the development of non-invasive, increasingly sophisticated imaging techniques. Most attention has focused on schizophrenia, especially the chronic disease. Since the report by Johnstone *et al* (1976), many studies using computerised tomography (CT) have confirmed significant lateral ventricle enlargement and increased ventricular:brain ratio (VBR) in chronic schizophrenia compared with various control groups (Reveley, 1985; Owens *et al*, 1985), so much so that Farmer *et al* (1987) felt able to say that this finding "may now be regarded as probably the most replicable biological feature which investigations of the condition have yet revealed". Even so, not all studies have confirmed the finding. Smith & Iacono (1986) have compared the data in 14 positive studies and seven negative studies. The VBR was significantly lower in the control groups from the positive studies than in the controls from the negative studies. They concluded that the differences between the studies had more to do with the choice of controls than schizophrenic patients. Owen & Lewis (1986) have also analysed the choice of controls and suggest that some differences between control values can be accounted for by the fact that sometimes patients with conditions known to be associated with ventricular enlargement have been used, whereas in others there has been a selection bias against controls with large ventricles. Even if it is accepted that the association of ventricular enlargement with schizophrenia is a reliable finding it is certain that it is not specific for the disorder as similar observations have been reported in manic–depressive illness (Pearlson & Veroff, 1981; Standish-Barry *et al*, 1982).

The significance of ventricular enlargement in schizophrenia is an even more contentious issue. At first it was suggested that it might be related to cognitive impairment ("the dementia of dementia praecox"; Johnstone *et al*, 1978) or the 'negative' clinical features of a 'type 2' syndrome (Crow, 1980) but subsequent studies have not supported this hypothesis (Owens *et al*, 1985; Kalakowska *et al*, 1985; Farmer *et al*, 1987). Others have suggested a relationship to different clinical subtypes, for example paranoid schizophrenia (Nasrallah *et al*, 1982), but again this has not been confirmed (Farmer *et al*, 1987). The latter authors reported an association with Schneider's first-rank symptoms and a complex relationship with Feighner diagnostic categories. Several studies have examined the relationship between enlarged ventricles and the genetic background of schizophrenia. Reveley *et al* (1982, 1984) reported that, in monozygotic twins discordant for schizophrenia, the schizophrenic probands had significantly larger ventricles than the unaffected control twins. Furthermore, large ventricles were associated with the absence of a family history of 'psychiatric disorder'. The authors therefore suggest that schizophrenia can be categorised into a familial form with normal ventricles and a presumed genetic aetiology, and a non-genetic form associated with enlarged ventricles due to environmental insults to the brain. However, several non-twin studies have cast doubt on the proposed inverse relationship between enlarged ventricles and a positive family history of schizophrenia (Nasrallah *et al*, 1982; Owens *et al*, 1985; DeLisi *et al*, 1986; Farmer *et al*, 1987).

Other uncertainties remain. Do the reported CT abnormalities antedate or postdate the onset of schizophrenia? Are they static or do they evolve in parallel with the clinical picture? Do they predispose to schizophrenia? Are they an intrinsic aspect of the disorder or are they the result of schizophrenia and its treatment? Such questions can only be clarified in the light of longitudinal imaging studies over many years, which have not yet been adequately undertaken (Nasrallah *et al*, 1986; Scottish Schizophrenia Research Group, 1989). Do patients with CT abnormalities represent a subgroup with so-called organic as opposed to 'functional' schizophrenia? Kalakowska *et al* (1985) looked specifically at indices of 'organic dysfunction' in schizophrenia and found no correlation even between the indices themselves (i.e. enlarged ventricles, cognitive impairment and 'soft' neurological signs). Neurological signs were related to a history of developmental abnormalities,

cognitive impairment to higher doses of current medication, and large ventricles to neither of these variables. This suggested that the three signs may be determined by different sets of factors. Furthermore there were no clinical differences between those with and without organic signs, but only evidence of a more unfavourable prognosis in the former (Williams *et al*, 1985).

Where in the brain is schizophrenia?

In addition to the more general and widespread abnormalities suggested by the CT findings, many other studies of a structural (CT, MRI, neuropathology) or functional (cerebral blood flow, psychometry, evoked potentials, PET and SPECT) kind have focused interest on specific brain regions as the site of the lesion or dysfunction in schizophrenia, for example the frontal lobes, the temporal lobes and limbic system, the left hemisphere, the basal ganglia, the corpus callosum, the hypothalamus, diencephalon and even the cerebellum (Andreasen, 1986). Indeed, we are in the midst of an explosion of interest in studies of this type. It seems that many authors regard the seat of the lesion or dysfunction in this disorder as one of the several sites described above on which they have focused their attention and investigations. By way of illustration, Weinberger *et al* (1986) and Berman *et al* (1986) have summarised their own and other evidence implicating the frontal lobes in schizophrenia and suggest a physiological dysfunction of the dorsolateral pre-frontal cortex to account for both the 'negative' and 'positive' features of the disease. A study using magnetic resonance imaging is said to be in keeping with the 'hypofrontality hypothesis' (Andreasen *et al*, 1986). Others have emphasised the importance of the temporal lobes in schizophrenia (Trimble, 1987).

The number and variety of attempts to localise schizophrenia in this or that region of the brain emphasises their implausibility, which stretches the credulity of a neurologist, who is used to seeing many patients without schizophrenia with lesions in the incriminated regions of the brain. These attempts to localise schizophrenia are in part based on what some psychiatrists view as a rediscovery of the writings and wisdom of 19th-century neurologists, with their emphasis on functional localisation. This renewal of interest in localised function in psychiatric disorders is sometimes referred to, especially in the USA, as behavioural neurology (Pincus & Tucker, 1985). However, disorder of function in the nervous system is now seen to be complex and dynamic. Is it conceivable that the complex disorders of neurological/psychological

function which occur in schizophrenia can be understood in terms of only one system such as the dorsolateral pre-frontal cortex?

Conclusions

Two modern developments suggest the possibility of reconciling the logically confusing, if practically convenient, diverging trends in neurology and psychiatry. (a) The current widely held view that neurology is wholly 'organic' and somehow synonymous with structural disease of the nervous system is fallacious. Neurological patients have complex dynamic disorders of function in the nervous system, whether or not they have structural disease. These disorders of function cannot be understood wholly in terms of oversimplified notions of functional localisation. A single structural lesion may have remote functional effects far from the pathological site. Cerebral function is profoundly influenced by psychological and social factors. (b) In psychiatry the renewed interest in and discoveries of cerebral pathology with modern imaging techniques are proving difficult to integrate because they are being inappropriately linked to functional localisation. It need not be expected, for example, as seems to be a common view, that such hypothetical lesions or dysfunctions will be found in all cases of schizophrenia. Like epilepsy, schizophrenia may or may not be associated with cerebral pathology which may sometimes influence the course and prognosis. This need not lead to separate categories of organic and functional in the psychological sense. Both, however, remain functional disorders of the nervous system (neuroses) in the older, neurophysiological sense of the word, whether or not detectable pathology is present. Both are influenced by psychological and social factors. Why should one (epilepsy) be viewed as organic and the other (schizophrenia) as functional? Nor is the answer to reclassify schizophrenia as organic, as some demand. Psychiatrists might profitably spend less time taking sides in inappropriate conflicts between false dichotomies, and neurologists might usefully spend more time studying the influence of psychological and social factors on brain function and on their patients' functional disabilities.

In the 18th and 19th centuries, neurology was conceived in terms of disorders of 'sensation and motion', as a functional discipline. The difficulty at that time, for many historical reasons, was to know where to place disorders of the 'mind' in this scheme of things. In the event they were split into 'neuropsychiatry' and 'psychodynamic psychiatry' (Hill, 1964). It is not difficult today to envisage the

mind with its varied activities (attention, memory, mood, etc.) as a function of the brain, like sensation and motion. This in no way undermines the importance of psychological, social or psychodynamic factors in either psychiatric or neurological disorders, but it does profoundly alter our conception of both types of disorder and the relationship of the two disciplines.

References

ANDREASEN, N. C. (ed.) (1986) *Can Schizophrenia be Localized in the Brain?* Washington, DC: American Psychiatric Press.
——, NASRALLAH, H. A., DUNN, V., *et al* (1986) Structural abnormalities in the frontal system in schizophrenia: a magnetic resonance imaging study. *Archives of General Psychiatry*, **43**, 136–144.
BENNETT, E., DIAMOND, M. C., KRECH, D., *et al* (1964) Chemical and anatomic plasticity of the brain. *Science*, **146**, 610.
BERMAN, K. F., ZEC, R. F. & WEINBERGER, D. R. (1986) Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. II. Role of neuroleptic treatment, attention, and mental effort. *Archives of General Psychiatry*, **43**, 126–135.
BLAKEMORE, C. & COOPER, G. F. (1970) Development of the brain depends on the visual environment. *Nature*, **228**, 477–478.
BROCA, P. (1865) Sur la faculte du langage articule. *Paris Bulletin Societie Anthropologie*, **6**, 337–393.
CHEYNE, G. (1733) *The English Malady: or, A Treatise of Nervous Diseases of all Kinds, as Spleen, Vapours, Lowness of Spirits, Hypochondriacal and Hysterical Distempers.* London: Strahan & Leake.
CLARKE, E. & JACYNA, L. S. (1987) *19th Century Origins of Neuroscientific Concepts.* Berkeley: University of California Press.
CROW, T. J. (1980) Molecular pathology of schizophrenia: more than one disease process. *British Medical Journal*, **280**, 66–68.
CULLEN, W. (1769) *Apparatus ad Nosologiam Methodicam, seu Synopsis Nosologiae Methodicae in Usum Studiosorum.* Edinburgh: Creech.
—— (1777) *First Lines of the Practice of Phsyic.* Edinburgh: Creech.
DELGADO, J. M. R. (1967) Aggression and defense under cerebral radio control. In *Aggression and Defense, Neural Mechanisms and Social Patterns* (eds C. D. Clemente & D. Lindsley). UCLA Forum in Medical Science, no. 7, vol. V., pp. 171–193. Berkeley: University of California Press.
—— & MIR, D. (1969) Fragmental organization of emotional behaviour in the monkey brain. *Annals of the New York Academy of Science*, **159**, 731–751.
DELISI, L. E., GOLDIN, L. R. HAMOVIT, J. R., *et al* (1986) A family study of the association of increased ventricular size with schizophrenia. *Archives of General Psychiatry*, **43**, 148–153.
ELWES, R. D. C., JOHNSON, A. L., SHORVON, S. D., *et al* (1984) The prognosis for seizure control in newly diagnosed epilepsy. *New England Journal of Medicine*, **311**, 944–947.
——, —— & REYNOLDS, E. H. (1988) The course of untreated epilepsy. *British Medical Journal*, **297**, 948–950.
FARMER, A., JACKSON, R., McGUFFIN, P., *et al* (1987) Cerebral ventricular enlargement in chronic schizophrenia: consistencies and contradictions. *British Journal of Psychiatry*, **150**, 324–330.
FERRIER, D. (1878) *The Localisation of Cerebral Disease.* London: Smith, Elder & Co.
FREUD, S. (1891) *Zur Auffassung der Aphasien.* Wien. (Authorised translation with an introduction by E. Stengel (1953) London: Imago Publishing Company.)
GODDARD, G. V. (1967) Development of epileptic seizures through brain stimulation at low intensity. *Nature*, **214**, 1020–1021.

GOWERS, W. R. (1881) *Epilepsy and Other Chronic Convulsive Disorders: Their Causes, Symptoms and Treatment.* London: Churchill.
—— (1886) *Manual of Disorders of the Nervous System.* London: Churchill.
GRUNBAUM, A. S. F. & SHERRINGTON, C. S. (1901) Observations on physiology of the cerebral cortex of some of the higher apes. *Proceedings of the Royal Society, London*, **69**, 206.
—— & —— (1903) Observations on physiology of the cerebral cortex of anthropoid apes. *Proceedings of the Royal Society, London*, **72**, 152.
HARLOW, H. F., HARLOW, M. K. & SUOMI, S. J. (1971) From thought to therapy; lessons from a primate laboratory. How investigation of the learning capability of rhesus monkeys has led to the study of their behavioural abnormalities and rehabilitation. *American Science*, **59**, 538–549.
HARRINGTON, A. (1987) *Medicine, Mind and the Double Brain.* Princeton: Princeton University Press.
HILL, D. (1964) The bridge between neurology and psychiatry. *Lancet*, **i**, 509–514.
JACCOUD, S. (1872) *Traite de Pathologie Interne* (2nd edn). Paris: Delahaye.
JACKSON, H. J. (1873) On the anatomical, physiological and pathological investigation of epilepsies. *Reports of the West Riding Lunatic Asylum*, **3**, 315–339.
JEANNEROD, N. (1985) *The Brain Machine.* Cambridge, Massachusetts: Harvard University Press.
JOHNSTONE, E. C., CROW, T. J., FRITH, C. D., *et al* (1976) Cerebral ventricular size and cognitive impairment in chronic schizophrenia. *Lancet*, **ii**, 924–926.
——, ——, ——, *et al* (1978) The dementia of dementia praecox. *Acta Psychiatrica Scandinavica*, **57**, 305–324.
KALAKOWSKA, T., WILLIAMS, A. O. ARDERN, M., *et al* (1985) Schizophrenia with good and poor outcome. 1: Early clinical features, response to neuroleptics and signs of organic dysfunction. *British Journal of Psychiatry*, **146**, 229–246.
KINNIER WILSON, S. A. (1940) *Neurology.* London: Arnold.
LISHMAN, A. W. (1978) *Organic Psychiatry: The Psychological Consequences of Cerebral Disorder.* Oxford: Blackwell Scientific.
LOPEZ-PIÑERO, J. M. (1983) *Historical Origins of the Concept of Neurosis* (trans. D. Berrios). Cambridge: Cambridge University Press.
LORENZ, K. (1970) *Studies in Animal and Human Behaviour*, vol. 1 (trans. R. Martin). London: Methuen.
MEYNERT, T. (1884) *Psychiatrie: Klinic der Erkrankungen def Vorderhirns.* Vienna: W. Braumuller.
MORRELL, F. (1969) Physiology and histochemistry of the mirror focus. In *Basic Mechanisms of the Epilepsies* (eds H. H. Jasper, A. A. Ward & A. Pope), pp. 357–370. Boston: Little Brown.
—— (1985) Secondary epileptogenesis in man. *Archives of Neurology*, **42**, 318–335.
NASRALLAH, H. A., JACOBY, C. G., McCALLEY-WHITTERS, M., *et al* (1982) Cerebral ventricular enlargement in subtypes of chronic schizophrenia. *Archives of General Psychiatry*, **39**, 774–777.
——, OLSON, S. C., McCALLEY-WHITTERS, M., *et al* (1986) Cerebral ventricular enlargement in schizophrenia. *Archives of General Psychiatry*, **43**, 157–159.
OWEN, M. J., LEWIS, S. W. (1986) Lateral ventricular size in schizophrenia. *Lancet*, **ii**, 223–224.
OWENS, D. C. C., JOHNSTONE, E. C., CROW, T. J., *et al* (1985) Lateral ventricular size in schizophrenia; relationship to the disease process and its clinical manifestations. *Psychological Medicine*, **15**, 27–41.
PEARLSON, G. D. & VEROFF, A. E. (1981) Computerised tomographic scan changes in manic depressive illness. *Lancet*, **ii**, 470.
PENFIELD, W. (1958) *The excitable cortex in conscious man.* The Sherrington Lectures. Liverpool: Liverpool University Press.
—— & WELCH, K. (1949) Instability of response to stimulation of the sensorimotor cortex of man. *Journal of Physiology*, **109**, 358–365.

—— & Jasper, H. (1954) *Epilepsy and the Functional Anatomy of the Human Brain*. London: Churchill.

Pincus, J. H. & Tucker, G. J. (1985) *Behavioural Neurology*. Oxford: Oxford University Press.

Pinel, P. (1798) *Nosographie Philosophique, ou la Methode de L'Analyse appliquee a la Medicine*. Paris: Brosson.

Reveley, A. M., Reveley, M. A., Clifford, C. A., et al (1982) Cerebral ventricular size in twins discordant for schizophrenia. *Lancet, i*, 540–541.

——, —— & Murray, R. M. (1984) Cerebral ventricular enlargement in nongenetic schizophrenia; a controlled twin study. *British Journal of Psychiatry*, **144**, 89–93.

Reveley, M. A. (1985) Ventricular enlargement in schizophrenia: the validity of computerised tomographic findings. *British Journal of Psychiatry*, **147**, 233–240.

Reynolds, E. H. (1987) Early treatment and prognosis of epilepsy. *Epilepsia*, **28**, 97–106.

—— (1988) Prevention of chronic epilepsy. *Epilepsia*, **29** (suppl. 1), S25–S28.

—— (1989) The process of epilepsy. In *The Clinical Relevance of Kindling* (eds T. Bolwig & M. R. Trimble), pp. 149–160. Chichester: Wiley.

——, Elwes, R. D. C. & Shorvon, S. D. (1983) Why does epilepsy become intractable? Prevention of chronic epilepsy. *Lancet, ii*, 952–954.

Romberg, M. H. (1840–46) *Lehrbuch der Nervenkrankheiten des Menschen*. Berlin: Duncker.

Scottish Schizophrenia Research Group, MacDonald, H. L. & Best, J. J. K. (1989) The Scottish first episode schizophrenia study. VI. Computerised tomography brain scans in patients and controls. *British Journal of Psychiatry*, **154**, 492–498.

Sherrington, C. S. (1941) Man on his nature. *The Gifford Lectures, Edinburgh 1937–8*. Cambridge: Cambridge University Press.

Smith, G. N. & Iacono, W. G. (1986) Lateral ventricular size in schizophrenia and choice of control group. *Lancet, ii*, 145.

Standish-Barry, H. M. A. S., Bouras, N., Bridges, P. K., et al (1982) Pneumoencephalographic and computerised axial tomography scan changes in affective disorder. *British Journal of Psychiatry*, **141**, 614–617.

Trimble, M. R. (1981) *Neuropsychiatry*. Chichester: Wiley.

—— (1982) Functional diseases. *British Medical Journal*, **285**, 1768–1770.

—— (1987) The neurology of schizophrenia. In *Recurrent and Chronic Psychoses* (ed. T. J. Crow). Edinburgh: Churchill Livingstone.

—— & Reynolds, E. H. (eds) (1986) *What is Epilepsy?* Edinburgh: Churchill Livingstone.

Volkmar, F. R. & Greenough, W. J. (1972) Rearing complexity affects branching of dendrites in visual cortex of rats. *Science*, **176**, 1445–1447.

Wada, J. A. (ed.) (1976) *Kindling*. New York: Raven Press.

—— (ed.) (1981) *Kindling 2*. New York: Raven Press.

Weinberger, D. R., Berman, K. F. & Zec, R. F. (1986) Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. I. Regional cerebral blood flow evidence. *Archives of General Psychiatry*, **43**, 114–124.

Wernicke, K. (1874) *Der Aphasische Symptomkomplex*. Breslau: Kohn & Neigart.

Whytt, R. (1765) *Observations on the Nature, Causes and Cure of Those Disorders Which Are Commonly Called Nervous, Hypochondriac or Hysteric*. Edinburgh: Beckett & Du Hondt.

Wiesel, T. V. & Hubel, D. H. (1965) Extent of recovery from the effects of visual deprivation in kittens. *Journal of Neurophysiology*, **28**, 1029–1040.

Williams, A. O., Reveley, M. A., Kolakowska, T., et al (1985) Schizophrenia with good and poor outcome. II. Cerebral ventricular size and its clinical significance. *British Journal of Psychiatry*, **146**, 239–246.

Willis, T. (1682) *Opera Omnia*. Amstelodami: Wetstenius.

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