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DISEASE OF MIND AND DISORDER OF BRAIN*

BY

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The centenary of the foundation of the National Hospital, Queen Square, is a fitting occasion for the praise of famous men, and it is opportune that the Sir William Gowers Memorial Lecture falls due to be delivered at this time. My predecessor in this task drew for us, in his brilliant and inimitable style, a picture of Gowers better than any I could present to you, and pointed the contrast between Gowers and Hughlings Jackson, the naturalist and the philosopher (Walshe, 1956). It is to the fortunate association in the early days of the Hospital of two men of genius so different in their outlook, yet alike in their aims, that we owe in large measure the tradition which has inspired their successors to this day. It is difficult to know which has had the greater influence, for their interests were complementary and combined to form a discipline of clinical neurology at a scientific level far higher than that generally obtaining in medicine at that time. Jackson's has been the greater fame. We have, perhaps, taken too much for granted what we owe to Gowers, both for his own minute and accurate descriptions of disease and the methods of observation he developed and enjoined upon others. If in this lecture I refer to Jackson as often as to Gowers it is because their contributions to my subject were of equal importance and closely linked.

The Biochemical Lesion

Gowers's greatest interest was in the patterns of nervous disorder and their classification. He sought especially for symptoms and signs that could be related to structural lesions and was convinced that in diseases such as paralysis agitans more refined methods of observation would show structural damage at the time unseen. He did not, however, believe that the microscope would necessarily reveal such lesions even in the most severe interruption of neural function if this were reversible. Thus he was impressed by the failure to discover any histological abnormality in fatal cases of acute ascending paralysis of the Landry type, and by his observation of occasional rapid recovery from the illness. The interpretation he put forward was that the paralysis was due to some toxic influence acting upon "the ramification . . . in which the pyramidal fibres must end in the grey matter and by which they are connected with the lower segment" (Gowers, 1886). He adduced, as an example of the kind of effect he had in mind, the abolition of the function of nerve-endings in muscle by curare. This is an instance of his ability, from his wide knowledge of medicine and its

physiological background, to give whatever speculation in which he might indulge a foundation in fact. He envisaged what we should to-day call a biochemical lesion.

Many other examples might be quoted of his power of deducing a principle from clinical observation and following it through to its logical conclusion. In discussing the selective, symmetrical incidence of lead palsy, after rejecting other hypotheses he says:

"It can alone be due to some slight inherent difference in the minute constitution of the nerves which enables the atoms of lead to join with the atoms and molecules of these nerves and derange the process of their nutrition, acting on these nerve fibres and not on others. . . . When we think of the fact how great is its significance. Those nerve fibres, for some reason, have not the power of resistance to a morbid chemical agent as other nerves have. They differ in their behaviour when a molecule of a metallic poison is presented to them, although they are the same in the minutest scrutiny we can give them, the same to every other test we can apply. . . . The various effects of different poisons bring before us in almost startling clearness how profound is the influence of differences far beyond our powers of scrutiny."

(Gowers, 1895.)

Evidence for a Physical Basis

Gowers was also an ardent collector of cases in which the phenomena of nervous disorder were mainly or wholly subjective but presented features sufficiently distinct to be clearly recognizable in a group of such cases. This for him was convincing evidence of a physical, as opposed to a psychogenic, basis. Nowhere is this conviction more clearly expressed than in his comment on the subjective phenomena of what he called the vaso-vagal attack. "To dismiss it," he says, "as a hysterical fancy is simply to push it out of sight with the foot. So definite a feeling must have a definite origin" (Gowers, 1907).

His insistence on the rule that symptoms should not be regarded as hysterical because they are strange led him to many valuable conclusions, some of which are still neglected. His description of what he called encephalic vertigo as an occasional occurrence in labyrinthine disease could not be clearer. "It differs from the ordinary sensation of subjective vertigo in seeming to be within the skull, not to involve the head as a whole. The brain seems to the sufferer to be turning over and over or round and round. . . . It is not only strange in character but peculiarly distressing."

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(Gowers, 1907.) He presents illustrative cases. Yet half a century later patients with this symptom are often diagnosed as hysterical simply because it is so strange.

In common with other writers of his time, Gowers observed a distinction between organic and functional nervous diseases. He was careful, however, to define what he meant by these terms. "The term organic disease," he writes in the introduction to his textbook, "as commonly used means visible disease. But visibility is partly relative: it depends upon the means of vision." He goes on to remark upon the use of the microscope and the development of staining methods which have rendered visible changes that could not before be seen, but adds: "Molecular changes in nutrition, considered as such, must be colossal to be detected. Such alterations not sufficient to be seen probably constitute the morbid process in many diseases that are commonly regarded as functional. Hence we may distinguish a class of 'nutritional disease' from those that consist in a mere derangement of function. While distinguishing these two classes we cannot entirely separate them, because nutrition and function are mutually dependent, and prolonged functional disturbances may determine nutritional change."

Gowers wrote little about mental disorder. It almost seems as if he found the subject distasteful. In discussing the mental symptoms of organic disease of the brain he writes: "With the much disputed relation of mind to brain the physician has nothing to do" (Gowers, 1886). Nevertheless, some of his observations and conclusions—the validity of subjective symptoms as evidence of a physical cause, the selective action of poisons upon a group of apparently identical neurones, and the concept of the invisible lesion—have an important bearing upon the psychological symptoms of functional nervous disorder.

Examples of Psychical Disorder

Jackson wrote much about psychological disorder and repeatedly insisted upon the distinction between psychical and physical phenomena, but applied to both his concept of dissolution as a process which as the result of a loss of function permitted the appearance of positive symptoms representing the action of the healthy parts remaining. The simplest example of this kind illustrating psychical disorder is agnosia, and it is in the most restricted forms of agnosia that there is greatest opportunity for observation. Such cases are rare, and this must be my justification for recalling one that I have previously recorded. The patient was a soldier aged 21, intelligent, quiet, and reserved. As the result of a very small penetrating gunshot wound in the occipital region he lost the perception of distance without any other disability. The evidence for this is to be found in the report to which I have alluded (Symonds, 1945).

This young man, who came under our observation a fortnight after his injury, was then ambulant and active. He made no complaint of anything wrong, but peculiarities in his behaviour attracted attention. He was disinclined to move about, and, when he did so, progressed in a slow, hesitant manner. When he walked along a corridor in which there was a corner he approached the wall facing him with his arms outstretched, turning only when he felt it. He was examined by several experienced observers, who concluded that

his behaviour was hysterical. It is to the credit of Dr. Charles Phillips that he first suggested the true explanation, but this at first was doubted because of curious discrepancies. When the patient was asked to estimate the distance of a wall opposite to him in the empty room in which he was examined he could not do so. But when he stood at one end of his ward and was asked to judge the length of it he did so, after an odd pause, with fair accuracy. The explanation, when provided by himself, was simple. He knew roughly what was the usual width of a bed and the distance between beds, and by multiplying this by the number of beds had arrived at his estimate. There were many other instances of this kind of behaviour.

I have related this case as an example of psychological disorder which at first, because it was so peculiar, was thought to be hysterical, but in fact represented the attempt of the mind to work when deprived of one of its tools. I submit that psychological disorder of much greater complexity deserves examination from this point of view.

In the case mentioned there was a demonstrable relation between local brain damage and psychical symptoms. The next group of cases to be considered is that in which there are psychical symptoms of a particular kind associated with evidence of organic disease of the brain, but with no demonstrable localization. Of the many possible examples I shall take two. The first is that of encephalitis, leaving in its wake a very distinct pattern of intellectual impairment comprising a persistent retrograde amnesia covering several years, and gross defect of recent memory with little interference with other intellectual functions. Immediate retention is unimpaired, and skills and knowledge acquired before the illness are preserved. The patient is therefore able to achieve a good score on intelligence tests, failing only on those requiring recent memory. He is able, for example, to retain eight digits, do serial subtractions and similar tasks quite well, and yet fails to remember any item of a name, address, and flower given to him five minutes previously. Recognition is affected as well as recall, and learning of new material is impossible. Comparable symptoms have been observed after bilateral temporal lobe resection.

Of equal interest is the defect of moral sense resulting in children from encephalitis lethargica. Many examples were recorded at the time of the epidemic without recognizable impairment of intellectual function, and sometimes without any of the physical sequelae commonly observed after the illness. There can be no doubt of the organic basis of the defect, which is usually irreversible, though we have no clues in this instance for localization. What is most remarkable is that this sequel did not occur in adults, suggesting that whatever structures are involved are essential for learning to distinguish between right and wrong but not necessary for the preservation of such distinction, or, to put it in another way, if learning has continued long enough the process involved has produced physical changes in such a widespread net of neurones that local damage has not the same effect as it would have at an earlier stage of the process. Whatever the interpretation may be, we seem to be dealing with a kind of moral agnosia, and observe the mind deprived of this sense proceeding to the most ruthless extremes of antisocial conduct. In this there is reasoned direction, and often great skill in escaping detection and punishment. Granted the defect, thought, feeling, and behaviour are rational.

Functional Psychoses

We now come to the much larger category of psychical disorders in which there is no direct evidence of cerebral disease, of which the most important are the functional psychoses. Before embarking on this subject I shall refer to what Jackson had to say upon it in his essay on "The Factors of Insanities" (Jackson, 1894).

"In every insanity more or less of the highest cerebral centres is out of function, temporarily or permanently, from some pathological process; for my present limited purpose it matters little what that process may be. It only matters as the pathological processes produce loss of function, that is dissolution, of more or less of the highest centres. I do not use the term function in the sense often given to it in clinical accounts of nervous maladies, as, for example, when it is said of a patient that 'his case is entirely functional.' I do not believe that there is such a thing as loss or defect of function of any nervous elements without a proportionate material alteration of their structure and nutrition. Of course the separation into structure, nutrition and function of the nervous system is artificial; it is merely a convenient device, just as the separation into the surface, weight and mass of a body is."

He then goes on to enumerate what he calls the four factors of insanities as they may be applied to the confusion and allied conditions in terms of his theory of dissolution, and continues thus:

"Although I speak of dissolution of the highest cerebral centres as if it were uniform—as if all the divisions of these centres were 'evenly' affected—it is clear enough that there are local dissolutions of those centres. That there are different *kinds* as well as different *degrees* of insanity is evident—melancholia and general paralysis for two examples. Different regions of the highest cerebral centres undergo dissolution in different *kinds* of insanity."

He ends his essay with the surmise that the causes of certain of the insanities may be found to lie not within the brain itself, but in the organs which supply its nourishment.

Although their approach is different we find little divergence between the conclusions arrived at by Gowers and by Jackson about what is meant by functional nervous disorder. Jackson, however, went much farther along the road that leads from neurology towards psychiatry. It is, I think, natural that he should have taken melancholia as one of his examples of local dissolution, for the clinical pattern of this illness in its severe forms is remarkably constant and distinct. "So definite a feeling must have a definite origin." Gowers's dictum is all the more applicable if the psychosis is regarded not only as a disorder of mood but a disorder of feeling which will account for the great variety of *dysaesthesiae* that may be observed in the illness—head discomforts, general malaise, bodily aching, and disturbance of visceral feeling, for example. In the milder degrees of the illness it is of symptoms of this kind that the patient may chiefly complain. The increasing recognition of these milder degrees and of their great frequency has led to difficulties in terminology, which have not yet been solved. Those patients who are mildly affected are obviously not insane, yet the illness is often called psychotic so that the affective disorder may be distinguished from that which is termed neurotic.

Affective and Schizophrenic Illness

Concerning the distinction between endogenous and reactive forms of depressive illness I will say nothing except that I am doubtful of its validity. It will suffice for my present argument if it is admitted that there are many cases both of the severe and of the mild degree in which the onset is without discoverable cause, physical or psychogenic. They are endogenous so far as we can see. I would like to add, however, that this is equally true of some cases in which the disorder of affect is not depression but fear; for these patients, because they are anxious instead of depressed and because anxiety is a pure form is not generally accepted as a characteristic of endogenous affective disorder, are often regarded as suffering from a neurosis.

The arguments for supporting Jackson's assumption that this disease of mind represents a regional disorder of function in the brain are many. We may first consider the evidence in favour of believing that the illness has a physical basis irrespective of localization. Some of the arguments are equally applicable to the other functional psychosis—schizophrenia, and I will take first those observations which are relevant to both diseases. The absence of psychogenic cause is notable, though it must be regarded critically owing to the possibility of emotional stress which the subject is concealing or of which he is unaware. Much has been made of unconscious emotional disorder in the aetiology of the psychoses, especially by the psychoanalytic school. Demonstrable proof of this is lacking, and it is, I think, fair to assume that the patient who complains that he feels sad although he has a satisfactory job, a good wife, and a comfortable home, and believes that he has no reason whatever for unhappiness, is usually speaking the truth. The illness is as much a foreign body as he thinks. In the schizophrenic it is harder to estimate psychogenic factors in the aetiology owing to his thought disorder; but again, when all the facts are considered, psychogenesis is conspicuously absent in most cases. The distinct clinical pattern of the illness has already been mentioned. It is again more readily observed in the affective disorder than in schizophrenia, but of either illness it may be said that the symptoms have as much validity for the experienced clinician as those of a duodenal ulcer or angina.

The strongest evidence, however, for a physical basis is the genetic factor as demonstrated especially by the study of uniovular twins. In Kallmann's (1953) series the percentage of twin partners similarly affected by manic-depressive psychosis was for uniovular twins 96% and for binovular twins 25%; in the case of schizophrenia the concordance for uniovular twins was 86% and for binovular twins 15%. Slater's figures for concordance in a similar investigation of the affective disorder, analysed by Fonseca (1959), were in uniovular twins 75%, in binovular twins 38%. These figures compare with an expected incidence for the general population of 0.4% for manic-depressive psychosis and 0.8% for schizophrenia.

Spontaneous recovery from an episode of manic-depressive illness—as much endogenous as the onset—is further evidence for a reversible physical disorder. Moreover, the response of depressive illness to electric convulsion therapy, mysterious though it be, is clearly a physical effect. On the other side, it must be observed that in neither the affective disorder nor in schizophrenia has there been any histological proof of cerebral disease,

with the possible exception in schizophrenia of the dwarf cells in the thalamus found by the Vogts. In the affective disorder one might accept without difficulty the absence of histological change; for the illness, however severe and of whatever duration, may be reversible. I have myself observed recovery from a certifiable depressive illness of ten years' duration in a woman at that time aged 60. Once improvement began recovery was complete in a few weeks. This was before the advent of E.C.T. In schizophrenia histological lesions are more to be expected. Perhaps they may yet be seen. It is not yet certain that the lesions responsible for paralysis have been identified. On the other hand, the lesion, though irreversible, may be biochemical, without visible change, as Gowers surmised might be true of many functional disorders.

We have to conclude that in neither of the functional psychoses is there proof of organic cerebral disease or even of selective biochemical disorder. The evidence for their physical basis is strong but circumstantial. It is nevertheless worth pursuing the inquiry further and asking what evidence may be found for supposing that if a physical basis does exist it is of a focal or regional kind. I use these terms not in a morphological sense, but to indicate the possibility that particular systems of neurones may be involved. Here again the distinctness of the clinical pattern may be put forward as a reason for supposing that in each of the diseases under consideration particular, and different, neurophysiological dispositions are involved. Further evidence has become available in recent years from the use of drugs.

Specific Patterns Produced by Drugs

One of the most interesting experiences for neurologists of my own generation was the appearance of Parkinsonism and other stereotyped motor phenomena after encephalitis lethargica. Here was an example, comparable with that of a lead palsy, of a remarkable selective action upon particular units of the central nervous system by a new neurotropic virus. Equally remarkable has been the experience in recent years of witnessing identical symptoms, including the oculogyric crisis, after the administration of new drugs (Heaton-Ward, Carpenter, and Jancac, 1959). We may conclude that the disease and the drug have each affected the same region, and this observation is likewise relevant to the effect of drugs in causing specific patterns of psychical disorder.

For some years it had been noted that mescaline would produce in normal subjects psychological disorder in some respects resembling that of schizophrenia. It was by chance, however, that Hofman, in 1943, in the pursuit of chemical experiments with L.S.D.25, discovered in himself remarkable effects, which he subsequently proved to be reproducible by the ingestion of minute quantities of this drug. Out of this work has evolved a considerable literature dealing with the resemblance of the psychological disorder thus produced to that of schizophrenia. The hallucinations, thought disorder, and disturbance of affect and behaviour have been regarded by many as representing a model of schizophrenic psychosis, but critical consideration of the published data makes this doubtful. The fact remains, however, that L.S.D.25 can cause psychological disorder of a very complex and fairly constant pattern. Whether the experimental psychosis exactly resembles schizophrenia or not, the experiment has shown that a psychosis of this type can be produced by the action

of a particular chemical substance, which may be presumed to act upon a particular region of the brain.

It is also worthy of remark that certain drugs, of which imipramine is the current example, can have a specific action in relieving depressive illness. On the other side, it has been learned by chance that *Rauwolfia serpentina* prescribed for arterial hypertension may sometimes cause an illness hardly distinguishable from a depressive psychosis.

Manifestations of Epilepsy

Epilepsy, as Jackson was the first to observe, provides an opportunity of studying psychological symptoms of varied and distinct patterns, and establishing some degree of correspondence of the pattern with the region of the brain involved in the epileptic discharge. Owing largely to the work of Penfield and his collaborators, a considerable body of data has been accumulated on this subject. I shall first consider those observations that are relevant to endogenous effective disorder. They have been studied in detail by Denis Williams (1956). That a paroxysmal disorder of mood may occur as a manifestation of epilepsy was recognized by Jackson and has repeatedly been observed since, and it is generally agreed that fear is the most frequent experience. This is commonly described by the sufferer as irrational and without relation to any relevant thought or memory. The patient tells us simply that he is intensely frightened of he knows not what. He recognizes the emotion as unnatural. He may even say that it seems to be coming from inside him. The subjective experience, except for its brevity, seems identical with that of the patient with an endogenous fear state, who complains of a state of fear and foreboding for which there is no cause.

Ictal depression is less often met with, but again, apart from its duration, is indistinguishable from the descriptions given by patients with affective disorder. The experience described may be simply a feeling of intense sadness or may have some reference as in the case of a boy aged 13 whose minor attacks were preceded by a feeling which he described as "like a guilty conscience as if you'd murdered someone or stolen something." At the same time he had an epigastric aura. His head then turned to the left and he lost his senses for a few seconds. As he came to himself he would sometimes wonder what he had stolen or whom he had killed.

The resemblance between forced thinking and hallucinatory experience occurring as ictal phenomena, and similar subjective symptoms in schizophrenia, has been the subject of an important paper by Karagulla and Robertson (1955), who record the various gradations from amorphous thoughts to auditory or visual hallucinations observed in temporal-lobe seizures. They have stressed the difficulty patients have in describing such experiences. My own observations include several of a schizophrenic character. Of particular interest are ideas of reference and passivity. One of my patients, if at the onset of a minor seizure she was in conversation, felt that the other person was repeating what was in her own mind. Another described "something directing me to do something I don't want to do. It may be something about the house I'm going to do. My mind somehow tells me not to do it." In another case the warning of a major seizure was of voices rapidly repeating, "Yes, you did, No, you didn't," etc., for a second or two. As Kinnier-Wilson (1927-8) observed, epilepsy cannot call into being physiological processes

that do not exist. It may be argued, therefore, that the psychical symptoms which have been described are dependent upon the isolated and therefore distorted evocation of functions regionally represented.

Of further interest in relation to schizophrenia is the occurrence of chronic mental disorder in epileptics resembling very closely the ordinary schizophrenic psychosis. Mayer-Gross, Slater, and Roth (1960) have observed feelings of passivity with ideas of reference, paranoid moods, hallucinations, and catatonic phenomena. They conclude that the close clinical similarity to schizophrenic symptomatology must be significant and is more likely to be accounted for by a like regional site than by any common factor in the pathology.

Association of Schizophrenia with Cerebral Tumour

If the symptoms of schizophrenia are the result of disordered function in a particular region of the brain it might be expected that they would occasionally result from coarse disease—for example, a tumour. Such an occurrence might be exceedingly rare, for it would be essential for the appearance of such symptoms not only that certain functions should be put out of action, but that other functions should remain in action, and in the hypothetical case it is probable that the anatomical substrata of these functions are closely related. The coarse lesion is not selective enough; it destroys too much. For the same reasons one would expect, in the case of a growth, that if such symptoms occurred they might be of transient duration, disappearing as the destruction increased. This sequence I have observed in a few cases of cerebral tumour. The occurrence is so rare that it has been dismissed as coincidence. Yet the sudden appearance at the same time of the symptoms of tumour and schizophrenia is sometimes impressive.

In one of my cases there was further evidence of a very suggestive nature. This patient was a man aged 35, a scientific worker of high intelligence, with no previous evidence of mental abnormality, who in the fortnight before his admission to hospital had had several attacks of an epileptic character. During this period he had also developed symptoms which, on admission, were indistinguishable from those of a schizophrenic psychosis. He showed the incongruity of thought and affect, thought disorder, and bizarre delusional ideas characteristic of the condition without, so far as could be judged, any clouding of consciousness. Subsequently he became drowsy, with signs suggesting a left frontal tumour, and died a fortnight after his admission to hospital after ventriculography and biopsy. At the necropsy a tumour was found involving the corpus callosum and extending forward into the left frontal lobe. Histologically this was a glioblastoma.

Two years previously this patient's sister, then aged 34, had come under the care of Dr. Hugh Garland on account of occasional epileptic seizures. She was a school-teacher with no mental abnormality. In the course of time physical signs developed, leading to the diagnosis of a left posterior frontal tumour, and five years after the first symptom an exploratory craniotomy by Mr. W. R. Henderson revealed an infiltrating glioma in this situation. Histologically this was an oligodendroglioma. After the operation she rapidly developed symptoms of mental disorder and was transferred to a mental hospital, from which, through the courtesy of Dr. R. W. Bryson, I have been able to obtain particulars. These I need not describe in detail. They were typical of a schizophrenic psychosis.

It is a remarkable coincidence that brother and sister should both have had a cerebral tumour and that in each case the same area should have been involved. The tumours were of different histological types, and, in any case, evidence of a familial incidence of cerebral gliomas, apart from those that may occur in neurofibromatosis, is, so far as I am aware, lacking. Probably, therefore, we must accept coincidence thus far. But it is difficult to accept further coincidence as the explanation of the schizophrenic psychosis in both cases. In this direction it is natural to look for a genetic factor, having regard to the observation that if one sibling has schizophrenia the chance of another being similarly affected is 14% as compared with the incidence of 0.8% for the whole population. We may then argue that the genetic factor somehow operated in determining the pattern of mental activity in what Jackson called the healthy parts remaining after the destructive lesion. If so, was the site of the destructive process, similar in the two cases, significant? We cannot be sure that it was, for account must be taken of epileptic activity in the brains of both patients, and of the possibility of diffuse interference with cerebral function by increased intracranial pressure. The question of regional significance should, however, be pursued further. A study of the incidence of schizophrenic symptoms in patients who have had gunshot wounds of the brain might possibly yield information.

Conclusions

Examples have been given of specific patterns of psychological disturbance caused by organic cerebral damage. Evidence has been presented which suggests that the two diseases of mind which we call affective and schizophrenic are the effects of functional disorder in the brain, and that each represents what Jackson called a local dissolution, the region being different in the two cases. Neurologists hitherto have not taken much part in the investigation of these conditions, partly because they have been busy with other problems, partly for lack of opportunity. The opportunity has fortunately been provided at the National Hospital by the establishment of a psychiatric unit, which, it is to be hoped, will in due course expand. Jackson saw no more incongruity in classing together progressive muscular atrophy and insanity, upon the basis for advancing scientific knowledge, than in the botanist's classification of the bamboo with common grass. If he was right, neurology has a duty to contribute its share towards the understanding of these diseases of mind which fill more hospital beds than all other nervous disorders combined.

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