*Epidemic Encephalitis.** By IVY MACKENZIE, M.D., F.R.F.P.S. Glasg., Visiting Physician, Victoria Infirmary and Eastern District Hospital, Glasgow.

HAPPILY it is not expected that in opening a discussion the speaker should make a systematic survey of the subject under review. He may assume that those who may take part are already familiar with the main facts and features of the subject, and it is his business to make appropriate and, if possible, provoking remarks, thus focusing attention on some of the problems suggested by his own experience.

In seven successive years, from 1918 till 1924, the attention of the profession in Glasgow was directed to a " new disease," accounts of which had come during the same period from various parts of the world, and a description of which had already been given a year earlier by von Economo in Austria. That it was new admits now of no question, for there is nothing in the literature of medicine to compare with the phantasmagoria of disorder manifested in the course of this strange malady. There is scarcely a sign or symptom of nervous derangement which did not at one time or another make its appearance during the epidemics. Into the maze of contradictory phenomena it seemed almost impossible to read anything like a rationalized order of events which might be termed a disease entity. Profound and prolonged torpor, protracted and resistive sleeplessness, paralysis, violent jactitation, chorea, athetosis, and convulsions, pains referable to the head, limbs, and internal organs, every conceivable anomaly of movement of the external and intrinsic muscles of the eye, giddiness and rotatory displacement of the body, abnormal reactions of alimentation, circulation, and respiration, delirium, maniacal excitement and fever, comprise some of the outstanding features of this picture of chaos.

The original attempts to interpret the phenomena in the light of nosological principles took various directions. An anatomical basis was soon established in the non-purulent form of encephalitis which was discovered in every case which came to *post-mortem* examination. One result of this discovery, however, was to transfer the confusion to another field of discussion. Non-purulent encephalitis had been described in a variety of diseases. It was present in the cephalic form of poliomyelitis, in the cerebral paralysis of children,

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in Wernicke's syndrome, and as a sequel of a number of acute infections, chief among these being influenza.

The prevalence of influenza at the time of the outbreak lent colour to the view that the new disease was associated with that infection. There were others who, inspired either by aversion to "new diseases" or by doubt as to the existence of anything which might be termed a "disease entity," sought refuge in the proposal to regard the phenomena as a form of polio-encephalitis. Objection, moreover, was taken to the term "lethargic encephalitis," because, on the one hand, lethargy was not invariably present, and, on the other hand, the morbid reaction was not always confined to the encephalon.

Classification of symptoms, pathological anatomy and logical disputation failed individually and collectively to unravel the tangle which the initial stages of the epidemic presented. The efforts of the laboratory were no more successful, for examination of the cerebro-spinal fluid and bacteriological investigation afforded no data of importance, and experimental research gave no results. It is a striking commentary on the nature of morbid processes, and on the part which the clinician plays in their interpretation, that the disease had to reveal its own identity in the course of time before it could be even partially understood. It soon became apparent that, however obscure the microbic origin, however bizarre and baffling the preliminary disturbances, the tendency of the human organism to preserve its identity found expression in the long run in sequelæ which constituted a fairly reliable standard of reference. It is just this issue of encephalitis in peculiar and characteristic sequelæ which justifies its recognition, not only as a disease entity, but as a new disease.

For what is it that constitutes a "disease entity" or a "new disease"? The physician is concerned, not, like the naturalist, with a wide range of different organisms theoretically adapted in an average way to an average environment, but with a single organism, the human subject, striving to preserve its identity in adverse circumstances. In this struggle all those tendencies and activities which are stabilized in the processes of normal life assert themselves. The conflict is not confined to the part first affected. The unity of the organism provides for the participation of a variety of immediate and distant reactions in the attempt to maintain or restore order. If the initial assault be severe, as in an acute infection or a cerebral hæmorrhage, confusion and disorder are likely to prevail. If this stage be survived, the course of events will be determined by the extent of the damage, and by the efforts of the organism, successful or otherwise, to restore a state of equilibrium.

It is the organic substratum to the chaos of disease that has a deciding influence on the course of the morbid process; it determines the tendency of disease to manifest itself only in a limited number of ways, and it also determines the more or less constant features of each manifestation. These tendencies are exhibited to advantage in disorders of the great integrating systems of the organism, and especially in the nervous system; it is just these tendencies that render possible the classification of disease.

There enter into the concept of a disease other considerations which have reference to its incidence, as well as to its course. In the case under review we attribute its origin to an infective agent; we interpret the initial symptoms as due to the irritation and destruction of nervous elements for which the poisons of the infective agent have a special affinity; we explain the late and permanent symptoms as expressions of partially successful or unsuccessful efforts of rehabilitation.

In claiming for lethargic encephalitis the status of a new disease entity it is contended:

1. That while nothing is known of the toxic agent except that it produces encephalitis, it is not the toxic agent of influenza or of poliomyelitis or of herpes.

2. That the sites of toxic reaction in the central nervous system are peculiar to lethargic encephalitis, and are distinct from the sites involved in other forms of encephalitis, such as cerebral influenza, polio-encephalitis, Wernicke's disease, and the cerebral palsies of children.

3. That the sequelæ of encephalitis, while they are the hall-mark of the disease, are not phases of progressive infection, but phases of attempted adaptation.

4. That the history of the successive epidemics in Glasgow indicates a change of type which is not recognized in any other infection of the central nervous system.

These contentions are based on an experience of the disease extending over nine years. During this period about six hundred cases have been examined, and two hundred of these have passed through my own wards in the Eastern District Hospital and Victoria Infirmary. The brain and spinal cord of 40 cases which came to *post-mortem* examination have been examined. Through the courtesy of Dr. Chalmers and of Dr. MacGregor I have been in constant touch with the Health Department, where a very thorough and extensive investigation of the problem has been carried on from 1918 till the present time. I have also had the advantage of regular collaboration with my colleague Dr. Marshall.

### 1. *The Toxic Agent.*

I cannot pretend to be conversant with the literature on this aspect of the problem, but there does not seem to be any reason to believe that the site of infection or the character of the organism have been recognized.

### 2. *Pathological Anatomy.*

The usual feature of the *post-mortem* evidence was the absence of change visible to the naked eye. This was all the more striking in view of the pronounced character of the clinical disturbance. Apart from general congestion, nothing abnormal was noted beyond isolated greyish specks in the basal nuclei and mid-brain of six patients who died in the acute stage, and a relative poverty in pigment in some of the cases which came to necropsy after prolonged Parkinsonian illness. In the spinal cord of 5 cases minute areas of infiltration in the posterior cornua could be seen on naked-eye examination.

This is in marked contrast with what we have observed in other cases of non-purulent encephalitis. In 4 cases of influenza, areas of infiltration, some of them as large as a shilling, were visible on the cerebral cortex. (One of these showing naked-eye changes in each island of Reil is exhibited in the Pathological Museum.) In 2 cases of encephalitis due to the toxæmia of pregnancy, extensive hæmorrhagic exudates could be seen with the naked eye in the basal nuclei and mid-brain. (One of these is exhibited in the Pathological Museum.) In a case of Wernicke's disease extensive hæmorrhagic softening was seen in the mid-brain, and in lesser degree in the basal nuclei and cerebral cortex. Two cases of polio-encephalitis were observed in which translucent reddish areas of softening were visible in the cerebrum and mid-brain, as well as in the anterior cornua of the cord. There are on record cases of non-purulent encephalitis in which there were no naked-eye signs of disease in the brain on *post-mortem* examination, but these are generally admitted to be rare. It is thus permissible to draw the general conclusion that the encephalitis known as lethargic encephalitis differs from other forms of encephalitis in that there is, on the whole, an absence of naked-eye signs of disease in the central nervous system. No account need here be taken of the encephalitis due to syphilis, tubercle, malaria, or trypanosome infection, for these obviously belong to a quite different category.

With regard to microscopic lesions, a distinction can be drawn between the cases which died in the early stage of the disease and those which came to *post-mortem* examination after a prolonged Parkinsonian illness. In the former the lesions are diffuse, are of a

moderately acute inflammatory character, and, as pointed out by Turnbull and McIntosh and Douglas McAlpine and others, tend to be more pronounced in the basal nuclei of the cerebrum and in the mid-brain, and especially in the mid-brain and in the substantia nigra of that region. Occasional foci of reaction may be noted in the cerebral cortex, pons, upper reaches of the medulla, and in the posterior cornua of the cord. The anterior cornual nuclei are not involved. The inflammatory reaction is represented in perivascular infiltration, occasional hæmorrhage, deposits of salts in the vessel-walls and surrounding tissues, degeneration of neurones, and occasional neuronophagia and proliferation of glial cells. The reaction is not so intense as in poliomyelitis and in influenza, and is quite different from that in Wernicke's disease or in the encephalitis of pregnancy, which is essentially hæmorrhagic and not of the nature of a true inflammation.

In the Parkinsonian syndrome there is a consensus of opinion that the most pronounced lesions are in the substantia nigra. Our own findings in this respect accord fully with those of Jacob, Douglas McAlpine, and others who have gone carefully into the problem. It is questionable, however, whether the depigmentation, degeneration of neurons, demyelination, gliosis and slight vascular change in this region are accurately interpreted as inflammation, or, in other words, as a process in which the infective agent is still active. I am not convinced that the histological appearances resemble those observed in such chronic affections of the central nervous system as syphilis, tubercle, malaria or trypanosomiasis. On the other hand, I am in agreement with Hoffmann that in some cases there are changes, though of a minor degree, in the basal nuclei of the cerebrum. The possibility must be taken into account that the degeneration of the substantia nigra is not an isolated lesion accountable for the clinical phenomena in the sense in which anterior cornual degeneration accounts for the disabilities of poliomyelitis, or destruction of the motor cortex accounts for hemiplegia of the upper neuron variety. It is more likely that the Parkinsonian sequelæ are the expression of a disordered function of the whole compendium of reflexes related to the basal nuclei of the cerebrum, the mid-brain and the vestibular apparatus, and concerned with the regulation of those phases of automatic posture which render voluntary movement possible. Histological evidence in those cases that died in the acute stages of the disease indicates the implication of the whole series of nodal centres of correlation between the caudate nuclei and the vestibular nuclei. Such wide-spread involvement is presumably the basis of an original derangement of function of this extensively consolidated mechanism,

and the exhaustion and degeneration of the substantia nigra may quite well be a by-product, as well as a contributing factor to the subversive process. Very little is known of the functional anatomy of the substantia nigra. Douglas McAlpine makes a very significant remark as to the difficulty of determining the condition of the nerve-fibres which course to and from it. A solution of this problem would certainly throw much light, not only on the Parkinsonian syndrome, but on the physiology of the basal nuclei and of automatic movement.

The results of pathological investigation warrant a general statement on the nature of the disease. The toxins of encephalitis show a predilection for the great correlating centres of the nervous system—that is, for the grey matter on the afferent side of the proprioceptive system, for certain nuclei in the base of the brain, and for the posterior cornua of the cord. It is significant that there is practically no evidence of disease in the cerebral cortex, in the red nuclei, or in the anterior cornua of the cord. In sharp contrast with this is the affinity of the toxins of influenza for the cortex and of the toxins of poliomyelitis for the anterior cornua.

### 3. *The Sequelæ of Lethargic Encephalitis.*

The initial signs are varied. Sudden or insidious in its onset, it may be mistaken for acute mania, hæmorrhage, influenza, acute abdominal disease, lumbago, disseminated sclerosis, chorea, epilepsy, and other conditions. The prevalence of an epidemic was often the most reliable clue to a diagnosis. Frequently it was only when the acute stage had passed and the characteristic sequelæ appeared that it was possible to recognize the real nature of the disease. But these sequelæ are characteristic and peculiarly distinct in the manner in which they appear in children, on the one hand, and in adults on the other.

In the case of children the main disorder consists of profound emotional instability with perversion of conduct. Ebullitions of excitement with uncontrollable impulse, often expressed in outrageous and criminal conduct, afford the evidence of a serious dissolution of nervous integration in the early stages of the disease. There is no clouding of perception as in epilepsy, for when the spasm has subsided there is clear recognition of what has happened, and often an expression—even a precocious expression—of regret. The presumption is that the peculiar character of the sequelæ in children is determined by the fact that the disease has supervened during the early developmental period, and that neural dissolution has occurred in the basal structures before the association centres of the cerebrum have become consolidated with each other, and with the lower

automatic centres over which they are destined to exercise control. When, at a later stage in children, a Parkinsonian phase develops, the psychomotor excitement abates. I know of only one case out of fifty in which recovery may have occurred.

The Parkinsonian syndrome, the common sequel in adults, may emerge immediately from the acute stage or may not supervene for months or years. It comprises in its general uniformity of expression a great variety of somatic and visceral disorders, including inhibition of movement, tremor, excessive salivation, greasiness of the skin, outbreaks of sweating, abnormality in sugar metabolism, attacks of hyperpnœa, and occasionally excessive increase in weight. Combined in varying degree in the single characteristic sequela are the features of two distinct diseases—paralysis agitans and katatonia. It is a paralysis agitans with vegetative disorder, and it is katatonia without the stupor. It is inconceivable that such a varied disorder should be due to a lesion confined to the substantia nigra, in the sense in which infantile paralysis is due to destruction of the anterior cornua, or hemiplegia to ablation of the motor cortex.

I have pointed out elsewhere that the initial involvement of the ocular and vestibular apparatus is consistent with the presence of acute changes in the basal nuclei and brain-stem. The parts of the central nervous system originally affected are essentially those whose integration is concerned in the postural and automatic movement necessary for voluntary control by cortical activity. This great compendium of reflexes has its nodes of integration in the basal nuclei of the cerebrum, in the mid-brain, in the vestibular nuclei, and in the posterior cornua of the cord. It is known to physiologists as the proprioceptive system, and it is suggested that the Parkinsonian sequela is due to a functional derangement of this system incident to destruction of some of its vital parts in the early stages of encephalitis. This conception is consistent with the anatominal findings on which a comparison was made with poliomyelitis and influenzal encephalitis. The lesion in poliomyelitis is in the anterior cornua, in influenza in the cerebral cortex, and in lethargic encephalitis in the correlating centres in the basal nuclei and posterior cornua.

The manner in which a great neuro-muscular compendium may be functionally deranged is seen to advantage in the case of the respiratory mechanism, in which normal health may be impeded by the pathological reactions of coughing, sneezing, hiccup, or the closely allied phenomenon of vomiting. Pathological physiology has to do, not merely with absence, diminution, or increase of normal function; it deals with the aberrant irradiation of stimuli and with

subversive reactions which are absolutely inconsistent with normal function, but which may be kept within limits by stabilized organic tendencies. The pathological physiology of the Parkinsonian syndrome is the study of an organized chaos—a chaos induced in the first instance by destruction of important integrations, and reorganized on an unstable basis in the process of rehabilitation. A suggestive analogy may be found in cardiac disease, in which the circulatory failure, which is often long delayed, bears some resemblance to the Parkinsonian syndrome. The adaptive process is not confined to the heart itself. It extends to the peripheral circulation, in which altered tonus plays a part. When the subversive element in the adaptation gains the ascendancy the failure due to œdema and waterlogging occurs in the peripheral circulation. It is not unlikely that the progressive disability in the Parkinsonian syndrome is due, not to the continued activity of the original toxin, but to aberrant irradiation and subversive tendencies in a poorly adapted proprioceptive system. This conclusion is supported by the remedial effect in some cases of intensive treatment with belladonna and hyoscine.

The outlook in this sequel is no more favourable than that in the special disorder in children, although great improvement may occur and progress may be stayed in many cases by the treatment mentioned.

Of those who survive the acute stage few make a recovery. Not more than sixty out of three hundred were free from all signs and symptoms two years after the infection. It is a remarkable fact that in a disease involving vital centres of the brain and producing such pronounced aberrations of conduct and impediments to behaviour, there should be practically nothing in the nature of dementia in the sense in which that term is understood by the alienist.

### 4. *History of the Disease in Glasgow.*

Looking back on the history of the disease in Glasgow several points of interest arise. Profound lethargy marked the earliest cases in 1918. The first 6 cases I saw never came out of the state. In 1919 the initial symptoms were often those of acute excitement. In 1920 (and to a lesser degree in 1924), a large proportion of those affected were children, and the majority of these showed choreiform agitation. In 1921 and 1922 the majority affected were adolescents and adults, and the initial symptoms were again severe, although in some cases they were insidious and took the form of transient giddiness or diplopia. In a few cases the disease began with epileptic seizures. In 1923 and 1924 the onset was, as a rule,

more gradual; and we now know from the sequelæ which have developed in the interval that the infection may occur without producing any inconvenience that could reasonably be ascribed at the time to encephalitis. In 1924 some cases were so misleading as to determine a definite diagnosis of disseminated sclerosis. In one instance Dr. Marshall and I demonstrated on several occasions, as a typical example of disseminated sclerosis (ankle clonus, positive Babinski, absence of abdominal reflexes, nystagmus), a case which afterwards became lethargic, and which, on *post-mortem* examination, revealed the definite evidence of encephalitis in the basal nuclei and in the posterior cornua. There was no histological evidence of disseminated sclerosis. I have four *post-mortem* records of similar cases. It is important to note that the optic nerves were normal in each case. There has been no epidemic since 1924, and in the interval I have not seen a single acute case in which the diagnosis of lethargic encephalitis was unequivocal.

(For discussion, *vide* p. 776.)

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## *The Pathology of Epidemic Encephalitis.** By J. Godwin Greenfield, M.D., F.R.C.P.

### 1. *Ætiology: The Virus of the Disease.*

Epidemic encephalitis resembles many of the common infectious diseases in being caused by a virus which no one has seen, or has been able to grow in an artificial medium. Whether it has been possible even to transmit the disease to animals is still a matter of dispute, although the most recent work tends to confirm rather than to discredit the assertions of those who claim to have done so. This work is of the greatest interest, and it is of special importance in that it clarifies some of the difficult clinical problems which the disease presents. In particular, it seems to shed light on the question why the more acute forms of the disease are less often followed by progressive sequelæ than those in which it begins more insidiously.

Those who have claimed to infect animals with the disease must be divided into two groups. The protagonists of the first group are Loewy and Strauss of New York, and Kling and his associates in Sweden. Some of those who obtained the earliest positive results in this country must also be included in this group. These

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