Section of Neurology

President—HUGH GARLAND, T.D., M.D., F.R.C.P.

Meeting
March 5, 1959

HUGHLINGS JACKSON LECTURE

Excitation and Inhibition in Epilepsy

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ADMIRABLE in Hughlings Jackson's papers is his pithy way of telling a clinical story with running commentary of interjection and footnote. In his Lumleian Lectures (Jackson, 1931) he presents a case of local epilepsy in what he calls a drama of four acts. In the opening scene "A man, B., was seemingly quite well when he arrived at my house after a walk of about a mile." In the second act a fit begins in the toes of the left foot. Of the first act Jackson remarks: "The patient was not really well when he arrived at my house. He had a persistent discharging lesion, presumably in a few cells of his leg centre; so to say, he always carried it about with him, or, to speak more precisely, it was a persistent, quasi-parasitical, hyperfunctionable part of himself." This was indeed what he meant. Elsewhere he says: "The discharging lesion is a local, persisting, hyperphysiological state of nerve cells induced by some pathological change", and again, "These discharges are to be looked upon as gross exaggerations of healthy nervous discharges". As to the form this exaggeration might take he remarks in a later paper "I do not mean that 'nerve impulses' after discharges which produce convulsion travel faster than those after discharges of health, but that in the former case more numerous 'nerve impulses' are emitted in a given time, or else that more nerve cells are simultaneously discharging". Translated into terms of electrically recorded potentials these hypotheses are now seen to be correct, which is an indication both of Hughlings Jackson's imaginative genius and of his influence upon the form of neurophysiology as we know it to-day.

There are many questions about epilepsy to which there is still no satisfactory answer. What is the basis of the persistent discharging lesion such as Jackson's patient carried about with him? I do not, of course, mean to ask whether the patient had a tumour or a scar, but how such a tumour or scar causes a liability to seizures. Again, what is it that determines the onset of a seizure in a person carrying this liability? And once the seizure has begun what determines its cessation? To all these questions Jackson, and many others who have followed him, have devoted a great deal of thought yet they are perhaps worth reconsideration at the present time in the light of recent physiological and biochemical research. Setting aside the first question for the moment, let us consider what clinical observation may have to tell us about the excitation or inhibition of seizures.

CLINICAL OBSERVATION

The observation that in some cases an epileptic seizure might be provoked by physiological or psychical stimuli is an old one. Evoked seizures —a better term than reflex epilepsy—were recognized by Jackson (1925) and fully described by Gowers (1901). An excellent account of the subject is given by Allen (1945). I have found them described in 65 out of 1,000 consecutive patients presenting in my consulting-room with the complaint of epileptic seizures, but am convinced from retrospective analysis that other examples might have been discovered by proper enquiry. Precipitation by a particular stimulus in certain cases may be observed only in a small proportion of the seizures and may be omitted from the story, and in some instances the nature of the stimulus is such that it may easily escape notice. This until a few years ago was true for flickering light, now recognized as a common precipitant of *petit mal*. The element of flicker is, however, not essential and abrupt transition from darkness to light may evoke a seizure. The converse may also obtain. Two of my patients had attacks with a sudden change from light to darkness, as when entering a cinema. One of these almost always had a minor seizure within a second or two of closing her eyes when going to sleep, and her clothes had to be made especially loose to prevent exposure to darkness when dressing or undressing. It is evident, therefore, that the "off" as well as the "on" signal from the retina may be effective. This

may also be true for hearing. In one of my cases there was a particular liability for seizures to occur at moments of sudden transition from noise to unexpected silence.

It is well known that the visual or auditory stimulation required to excite a seizure may be of a complex kind. The act of reading provides a striking example and was clearly described by two of my patients, though it is only in the past three years that "reading epilepsy" has become widely recognized (Bickford *et al.*, 1956; Chavany *et al.*, 1956; Bingel, 1957; Stevens, 1957). In one of my patients writing was said to cause attacks, and I was able to witness a seizure thus precipitated. A comparable case was recorded by Gordon (1928). On the auditory side musicogenic epilepsy has long been known (Critchley, 1937), and there are other complex variants.

There are also cases in which a particular movement may evoke seizures, especially, as Gowers noted, movement after rest—getting out of a chair quickly or turning over in bed.

Precipitation of attacks by visceral stimuli is, I suspect, more common than has generally been supposed. When the association is constant it is easily recognized. For example, a man who had occasional major attacks in his sleep was also liable to minor seizures in the day, taking the form of sudden confusion and a sense of familiarity lasting two or three minutes. These never occurred except when he was eating and only towards the end of a heavy meal. The bigger the meal and the more quickly it was eaten the more likely he was to have an attack. Having become aware of this, he took care to avoid gastric distension and was thus able to avoid attacks, but on a recent occasion was obliged to eat a rushed meal, got a feeling of gastric distension and was unable to bring up wind (a procedure which had been previously effective in preventing an attack). He then had the usual aura, this time followed by a major seizure. Another patient also had his minor attacks only when eating and only after he had eaten a good deal. "If", he said, "I eat slowly and read they never happen." A comparable case is recorded by Allen (1945). Working backwards from these cases in which the association was invariable I have noted others in which attacks have occurred more often during meals than appeared likely from coincidence. Such observations illustrate the complex nature of the effective stimulus in certain cases and the consequent need for close interrogation before it is decided that there is no precipitating cause for epileptic seizures.

I shall refer only in passing to other and well-known stimuli that may evoke seizures—startle, sudden noise, painful or tactile stimulation, or a burst of anger, for example. It is also recognized that the evocation of seizures may be conditioned as in the case of a patient who learned to produce attacks in himself by looking at a safety-pin (Mitchell *et al.*, 1954).

In some cases of evoked epilepsy the activity or stimulation is effective only if prolonged for some time. Reading epilepsy is one example. The seizure does not occur when reading is begun but only after several minutes and sometimes only after two or three hours. Auditory stimulation also may need to be repeated or prolonged to evoke seizures. Critchley (1937) records a case in which attacks would develop if the patient heard a noise of a continued or monotonous order, such as machinery in a workshop or a kettle on the boil, and in one of my own patients reiterative noise such as a frog croaking or a cat mewing would precipitate seizures. In both instances the auditory stimulus had to continue for some time before the fit developed. The prolonged exercise of a particular mental activity may also be responsible. Playing chess in one of my patients and adding figures in another were very likely to end in an attack. In a case reported by Bingel (1957) seizures occurred after playing cards for any time longer than two hours.

That a chronic state of peripheral excitation may cause an increased liability to seizures appeared true in a patient who proved to have a right parasagittal meningioma. Twenty-three years before the onset of his seizures his left leg had been amputated below the knee. The attacks at first took the form of clonic twitching limited to the muscles of the stump, lasting a minute or two, and continued thus at the rate of one every two or three days for a year. The seizures then gradually altered in that the twitching would extend at first to the thigh, then to the abdomen and finally to the arm, and eventually he had an attack in which he lost his senses. During the two years in which he had been subject to the minor attacks he had accepted the opinion that his symptoms were due to irritation in the stump, though he himself had not been aware of any new or abnormal sensation in it. He had therefore removed his artificial limb whenever convenient during the day as well as at night, and had never experienced a seizure when it was off. I have assumed in this case that afferent impulses, which were always present but of which he was unaware, and which on arrival at his cortex had no effect under normal conditions, were a contributory cause of epileptic seizures when the tumour was present. If we assume that of all the afferent stimuli reaching the brain only a comparatively small fraction are perceived, the number of cases in which seizures

may be observed by the subject to be evoked by stimulation may be significant.

The arrest of a seizure after it has begun by means of some mental or bodily activity or a particular stimulus must be assigned to an inhibitory process. It has been many times described and in its simplest form is not uncommon. I have found it recorded in 53 out of the 1,000 cases already mentioned. In 25 instances it was stated that the attack could at times be cut short by some kind of mental effort. Most of these patients could not describe the occurrence better than to say that by pulling themselves together or by an effort of concentration they were able to snap out of it. But in 8 cases a description was volunteered of a deliberate switch of mental attention. For example, one patient with an aura of noise said "I may at this stage be able to jump my thoughts about and stop it". Another, whose attacks began with a sudden faraway feeling, a nice sort of feeling, said "If I don't think about it it's all right, but if I say 'Oh, Oh, look out, be careful' my mind automatically goes that way and I'm out". A patient who was himself a doctor and recognized his minor seizures, which consisted of a sudden feeling at the back of the nose going on to a disturbance of thought, stated "By an effort of concentration I can always fight it off, but on one occasion I thought 'How will it develop?' and at once lost my senses". On this occasion he had a major seizure.

The arrest of focal seizures by local stimulation of some kind was described by 12 of my patients and is so well known that the symptoms need not be described in detail.

The inhibitory process involved in arrest of seizures may be subject to the establishment of conditioned reflexes as in the remarkable case described by Efron (1956, 1957).

Physiology

Although it is now more than twenty years old the observation of self-sustained after-discharge of electric potentials in the cortex following electrical stimulation deserves first consideration, for the pattern and sequence of events correspond closely with those observed in a convulsive seizure, whether excited electrically or occurring as the result of disease. Cortical after-discharge following electrical stimulation, therefore, may be regarded as the counterpart of a subclinical seizure. Of especial interest is the manner in which the after-discharge ceases. Having continued for a time at a regular frequency of about 10 to 14 per second, the spikes then grow larger, and appear in groups with pauses in between. These pauses become gradually longer, up to half a second or more, until the after-discharge ceases. Following this, if the potentials of the after-discharge have been very large, the whole area may be left inexcitable as well as inactive for 10 to 20 seconds. These observations are quoted from the classic paper of Adrian (1936), suggesting in his words "a conflict between a process by which each wave makes the system more unstable and an opposing process which causes a slower and slower recovery and ultimately stops all activity for many seconds". This process, he remarked, might be an inhibition, an accumulation of waste products or an exhaustion of active material, "though if it is an exhaustion it must be one which affects every neurone—even those which have only come into action at the height of the after-discharge". This objection to the hypothesis of exhaustion has never been answered. No evidence has been brought forward to sustain the hypothesis of waste products. The possibility of an inhibitory process remains and has received some support from the observations of Rosenblueth and Cannon (1942). If the state of inexcitability and inactivity immediately following the cessation of discharge represents inhibition it is inhibition of a degree which is not found under normal conditions, and we may deduce that an abnormal state of excitation has in its turn evoked an abnormal state of inhibition.

We must next consider the observations of Eccles (1957) and his collaborators, derived from recording with the micro-electrode the potentials within single motoneurones. They have demonstrated two different types of potential, the excitatory post-synaptic potential (E.P.S.P.) and the inhibitory post-synaptic potential (I.P.S.P.), each obtained by an appropriate mode of peripheral stimulation. These potentials result from the flux of ions across the cell membrane, the flow being governed by changes in the permeability of the membrane, which again are determined by the effect upon the membrane of excitatory and inhibitory transmitter substances. The change of potential, therefore, whether a depolarization (E.P.S.P.) or a hyperpolarization (I.P.S.P.) records in electrical terms the culmination of a series of chemical events. Arising from these and related studies there are several observations of especial interest to the student of epilepsy. The first is the discovery that within the spinal cord the motoneurone gives off a collateral branch forming a synapse with a Renshaw cell, which in turn makes synaptic connexions with motoneurones. It has been demonstrated that the function of the Renshaw neuron is strictly inhibitory. Thus each time the motoneurone develops an axon potential it excites an inhibitory impulse to motoneurones. Excitation evokes inhibition.

Phillips (1956) has applied the micro-electrode method to Betz cells in the cat and has discovered waves of hyperpolarization occurring not only as a sequel of excitatory activity in the cell but as independent happenings. He has further shown (Phillips, 1959) that inhibitory as well as excitatory effects can be produced in a Betz cell by antidromic stimulation of pyramidal fibres in the medulla other than the axon of the cell under observation by the micro-electrode. He has referred in this connexion to the long-established anatomical observation that the Betz cells give rise to axon collaterals ending on short interneurones which form synapses with Betz cells, an arrangement so like that of the axon collateral of the motoneurone to the Renshaw cell that it seems possible that, as in the spinal cord so in the cortex, the motor cell each time it discharges an axon potential excites an inhibitory interneurone to discharge a volley of impulses aimed at itself and its neighbours—a feedback system, which, as Phillips remarks, would be important in tending to prevent convulsive activity.

If we assume that there are inhibitory neurones in the cortex the recent observations of Eccles (1957) and his collaborators on the action of strychnine upon the motoneurone become important in relation to the effect of this substance in producing focal epileptic activity when applied to the cortex. These workers have shown that strychnine has no direct effect upon the excitatory post-synaptic potential of the motoneurone in reflex excitation, but causes a great diminution of the expected inhibitory post-synaptic potential provoked by an appropriate stimulus. Eccles suggests that strychnine acts by competing with the inhibitory transmitter substance for the appropriate receptor patches on the sub-synaptic membrane, and speaks of it as the curare of the inhibitory synapse. If this should be true for cortical cells we should have the answers to a number of questions, but at the same time further questions to be answered. If the epileptic activity produced by strychnine is caused by a defect of inhibition whence comes the excitation? It may arise from afferent stimuli which would under normal conditions be inhibited and then have no electrical or clinical effect. It was long ago observed that if strychnine was applied to the motor cortex in a weak enough solution and for a short enough time convulsive activity was absent, but could be evoked by a sensory stimulus aimed at the appropriate area of cortex. Another answer to the same question might be that the resting activity of cortical cells may amount to convulsive activity when the inhibitory brakes are out of action. The effect of strychnine, on this hypothesis, would be satisfying for the clinician in that it offers the possibility of a persistent discharging lesion in the Jacksonian sense, which may be clinically subliminal except when some combination of stimuli, in space and time, evokes local excitation, stimuli of a kind and degree that would have caused no perceptible effect had it not been for the absence of inhibitory tone.

Relevant to the excitation of seizures by sensory stimuli are observations arising from the question raised by Adrian (1954) whether the afferent messages which can evoke sensation are allowed at all times to reach the cerebral cortex or are sometimes blocked at a lower level. There is now evidence recently reviewed by Dawson (1958) suggesting the existence of tonic activity descending from the cortex, and probably from the brain-stem and cerebellum, having an inhibitory effect at synapses on the afferent pathways. If it is accepted that the afferent inflow to the cortex is thus subject to continuous inhibitory control what might happen if this control were withdrawn? Dawson (1947) had previously observed, in certain patients subject to myoclonic seizures which could be provoked by sensory stimulation, that a sensory stimulus applied to the periphery led to an electrical response recorded from the scalp over the sensory area which was many times larger than that found in healthy people. These observations raise the possibility that depression of inhibitory control resulting from cerebral disease might cause a pathological increase in the size of an afferent volley, which in its turn could be a factor in the excitation of epileptic discharge. Further studies on the unanæsthetized cat by means of implanted electrodes (Hernandez-Peón *et al.*, 1957) suggest that inhibition of afferent inflow may be selective, and its direction governed by attention, so that, for example, impulses set up in the visual pathways by photic stimulation are depressed when the animal is at the same time exposed to an auditory or olfactory stimulus. If a change in the direction of attention can thus selectively inhibit afferent inflow, and if, as has been suggested, the evocation of epileptic discharge may sometimes depend upon a particular stimulus pattern, the effect of a deliberate switch of attention in arresting certain seizures might thus be explained.

Biochemistry

The biochemical factors in epilepsy must be of primary importance. The abnormalities of electric potential associated with seizures are as much an effect of ionic flux across the cell membrane as is convulsive movement, and neither can give us any direct knowledge of the essential nature of the discharging lesion. It is natural that the identification of excitatory and inhibitory

transmitter substances within the central nervous system should have been the centre of attention. So far the only one that is known is acetylcholine, which acts at the synapse of the axon collateral of the motoneurone with the Renshaw cell, and the question whether acetylcholine operates as a transmitter in the brain has been actively pursued. There is experimental evidence suggesting that acetylcholine plays a part in some epileptic seizures (Feldberg, 1956).

Another interesting line of enquiry began with the discovery by Florey (1954) that an extract of mammalian brain or spinal cord had an inhibitory effect upon the stretch receptor of the crayfish. This organ when subjected to moderate continuous stretch sends impulses up the afferent nerve at a frequency varying with the strength of the exciting stimulus. When the preparation is immersed in a solution containing small amounts of Florey's inhibitory, or I, factor these impulses cease and return as soon as the solution has been washed off. The I factor has since been identified as γ-amino-butyric acid (GABA) (Bazemore *et al.*, 1957). The effects of topical application of GABA to the cortex have now been studied in some detail (Purpura *et al.*, 1957; Iwama and Jasper, 1957), and it is agreed that it abolishes the surface negative response to direct cortical stimulation with the appearance in its stead of a surface positive wave. Its effect upon potentials evoked in the cortex by stimulation of the sensory nucleus of the thalamus is to abolish the surface negative element of the normal diphasic response with an apparent small increase in the surface positive component. Whether the surface negative component has its origin in the apical dendrites, or in independent superficial neurones, is uncertain, but in either case it is assumed to be the effect of synaptic excitation. GABA therefore appears to block excitation in the superficial layer of the cortex, and unmask inhibition, and its action thus resembles, but is opposite to, that of strychnine. It is therefore not surprising that it has been found that oral premedication with GABA will protect animals against convulsions artificially induced by chemical means (Hawkins and Sarett, 1957).

GABA is present in considerable quantity in the brain, being formed *in situ* from glutamic acid by the catalytic effect of an enzyme which requires as co-enzyme pyridoxal phosphate. This is of interest as it has long been known that one of the symptoms resulting from pyridoxine deficiency in animals is epilepsy. Of further interest have been clinical observations reported from the U.S.A. The first of these concerned the case of an infant in whom constant and intractable convulsions began three hours after birth (Hunt *et al.*, 1954). The child was admitted to hospital at the age of 2 weeks and the history contained the observation that there had been two brief periods of freedom following an injection of a proprietary vitamin compound. This was confirmed, and by analysis and the process of elimination it was proved that the anti-convulsant factor in the compound was pyridoxine. It was then found that a daily dose of 2 mg. of pyridoxine orally controlled the seizures absolutely so that there was no recurrence except when the dose was omitted. In this case, therefore, there appears to have been an inborn error of metabolism, possibly familial, as a sibling had begun to have convulsions four hours after birth and died at the age of 30 hours. Comparable cases have since been reported (Bessey *et al.*, 1957). Another observation was that of a widespread epidemic throughout the U.S.A. of generalized seizures in infants, beginning between the ages of 2 to 4 months and usually occurring several times a day. It eventually transpired that all these infants had been artificially fed and that the food they had been given was a particular brand of liquid milk substitute. When they were fed with another brand of milk substitute the seizures ceased. Analysis of the responsible milk substitute showed a gross deficiency of pyridoxine content as compared with similar preparations, this being due to a new method of sterilization which involved excessive heating. The preparation was withdrawn from the market and the epidemic ceased (Moloney and Parmelee, 1954; Coursin, 1954, 1956).

These observations suggest that GABA may be a natural anti-convulsant, present and formed in the brain, and that, when its production from glutamic acid is obstructed by pyridoxine deficiency, epilepsy is one of the results, at any rate in infants. From the evidence at present available it would appear that GABA is not an inhibitory transmitter substance, but that it blocks excitation, and that this effect is not confined to the sub-synaptic inhibitory areas but extends to the whole soma-dendritic membrane (Kuffler and Edwards, 1958). Elliott (1958) suggests that GABA exists in the interstitial fluids and exerts continuous effects on neuronal activity.

Reverting to the stretch receptor organ of the crayfish, we find another observation that may be relevant to an old-standing problem. Elliott and Florey (1956) have found that picrotoxin and Metrazol do not obviously affect the activity of the stretch receptor neurone, but that both substances prevent the inhibitory effect on the preparation of relatively high concentrations of factor I or GABA. Strychnine does not show this effect. Picrotoxin and Metrazol in high

dosage are convulsants in the crayfish, while strychnine is not. In fact the potencies of picrotoxin and Metrazol as convulsants in the crayfish are roughly inversely proportional to the concentrations of these drugs required to prevent the action of factor I. It has further been observed in mice that seizures induced by Metrazol can be prevented by oral premedication with GABA (Hawkins and Sarett, 1957). We may here have a clue to the convulsant action of Metrazol in man for which there has never been any satisfactory explanation.

Other recent observations that may be relevant to epilepsy are those upon the nature and functions of the blood-brain barrier (Bakay, 1956). Most substances when injected into a vein or into the peritoneum in animals penetrate the brain slowly and are thus found later and in smaller quantity than in other organs. Moreover, having gained entry to the brain, they are equally slow to pass the barrier in the other direction. The blood-brain barrier, as Tower (1958) has remarked, "functions as a homeostatic mechanism to stabilize the neuronal environment and confers upon the central nervous system a considerable degree of biochemical autonomy". The recent work of Millen and Hess (1958) has suggested that the barrier lies in the ground substance between the capillaries and the neuroglial feltwork and that the ground substance is a muco-polysaccharide. Local injury to the surface of the brain, as by a hot needle, ruptures the capillaries and injures the perivascular ground substance, thus allowing vital dyes and other substances to gain access to the intercellular spaces of the brain. Penetration of these substances beyond the area of injury is prevented by the undamaged ground substance in the surrounding uninjured areas. These observations introduce the possibility of a local accumulation in excess of substances having an excitatory or inhibitory effect as the result of an inward leakage from plasma to brain. The opposite possibility must also be allowed for—leakage from brain to plasma.

Recent experiments by Purpura *et al.* (1958) are of interest in this connexion. They first observed that the intravenous injection of γ-amino-butyric acid produces neither any alteration of surface potentials nor any detectable increase in the brain concentration of GABA, thus confirming other evidence showing that GABA does not effectively penetrate the blood-brain barrier. They then proceeded to effect local damage to the cortex and found that under these conditions GABA given systemically caused changes of electrical potential confined to the region of the local barrier breakdown, comparable with those produced by topical application. Of further interest was the observation confirming previous work, that in the neighbourhood of a lesion produced by freezing with ethyl chloride spontaneous paroxysmal activity would develop—in fact a spike focus. Under these conditions the injection intravenously of GABA caused disappearance of the negative spike, the appearance of high-voltage positive sharp waves, and at the end of about 12 seconds a normal record. The injection of GABA in large amounts, 30 mg./kg., would abolish paroxysmal activity for several hours. The authors note that the inhibitory effect thus produced is greater and much more prolonged than that following the topical application of GABA in the region of a spike focus.

Clinical Problems

From this brief review it would appear that there is physiological and biochemical support for the existence of inhibitory systems in the brain which have among their functions that of an anticonvulsant, and that a failure in one or other of these systems may suffice to cause epileptic seizures. This hypothesis does not exclude the possibility of primary excitation, such as might result from an excess of excitatory transmitter substance, having the same effect. There is indeed experimental evidence which supports this.

I shall conclude by presenting some facts of clinical observation which in the absence of scientific interpretation invite speculation. The first is the occurrence of seizures resulting from the presence of an extracerebral tumour, for example a meningioma lying upon the motor cortex. To begin with some assumptions, let us suppose that the persistent discharging lesion, in Jackson's sense, is caused by a local disorder of function involving a block of inhibition or enhancement of excitation. This is generally supposed to be the effect of local circulatory disorder. The next assumption often made is that the seizures are an effect of anoxia. This, however, receives little support from experiment or clinical enquiry. The local ischæmic episodes which we commonly observe as the result of arterial narrowing usually take the form not of an epileptic seizure but transient loss of function. Another possibility would be the local accumulation of waste products as the result of venous obstruction. This has been investigated, so far with negative results (Pope *et al.*, 1946). A further possibility worth consideration is whether, either as the result of vascular congestion or deformation of the brain, there may be a local breach in the blood-brain barrier, with local accumulation of a substance which enhances excitation or blocks inhibition; or on the other

hand leakage from the brain of an inhibitory substance. This, however, is mere speculation, and it has to be admitted that the question of how a meningioma causes seizures is unsolved. Even if it were answered there remain others. Why are the seizures only occasional and by what are they occasioned? This is, of course, a question that applies to epileptic seizures in general, and to which the answer may be in part that seizures may be evoked by specific stimulus patterns. If, as has already been suggested, there is under normal conditions a variable and fluctuating control of afferent inflow, the coincidence in time of two factors, specific stimulus and weak inhibition, might be necessary. It seems essential, however, to invoke another factor of a more general kind, if only to explain why of two patients having apparently identical tumours one has frequent seizures and the other few or none. Into this field of enquiry I shall not venture.

We sometimes observe cases in which after a "spontaneous" seizure the patient is confident, with good reason, that he will have a period of complete freedom, and a refractory period may also occasionally be observed after evoked seizures. Through the kindness of Mr. Falconer I have had the opportunity of examining a patient under his care in whom the refractory state was of exceptional interest (Falconer and James, 1959). The case is to be published, but I have permission to refer in advance to those observations which are relevant to the problems under consideration.

The patient, a very intelligent male aged 18, was subject to spontaneous seizures, which at the time of his admission to hospital would occur three or four times daily. The attacks were brief and not necessarily attended by loss of consciousness but often caused him to fall, and were therefore a cause not only of inconvenience but danger. He had been aware for some time that after a seizure he would be immune for several hours. He had also learned that he could elicit an attack by rubbing the right side of his face with the back of his right hand. This rubbing, if repeated at a certain rate, would, if the attempt were successful, evoke a sensation described as like something caressing the right cheek and temple. This sensation would then continue spontaneously in a rhythmic or pulsating fashion and end in a seizure. He could usually thus precipitate a seizure if he had had no attack in the preceding two hours, but the shorter the time he had been without a seizure the greater was the duration of the rubbing required to provoke one. Observation by Dr. James revealed a remarkably constant inverse relationship between the amount of stimulation required and the length of time since the last attack. The patient, who was leading an active life, had made practical use of his knowledge, and would retire to a convenient place and provoke a seizure in order to prevent such an occurrence in awkward situations. He proved at operation to have an angiomatous malformation at an appropriate site in the left post-central gyrus.

There appear to be at least two possible modes of interpreting these observations. According to the first, the local accumulation of an excitatory substance led eventually to an excessive discharge. The excitatory substance, being presumed to be a precursor of the excitatory transmitter substance, was exhausted in the course of the discharge and the refractory period corresponded with that required for re-accumulation. The hypothetical excitatory substance might conceivably be a constituent of normal plasma accumulating locally in excess owing to a leak in the blood-brain barrier. An alternative hypothesis would be that the effect of the local lesion was depression of the tonic inhibitory control of afferent impulses. Either chance stimulation of the appropriate area, or self-stimulation, initiated a seizure. The excitation then evoked local augmentation of inhibition, which, having caused cessation of the discharge, continued as a tonic inhibitory state with a gradual decay up to the point at which first a large, and then a smaller, volley of afferent impulses would break through, and finally, if no attack were artificially evoked, the normal afferent inflow would provoke an apparently spontaneous attack. If this latter interpretation should be correct we still have to enquire what are the chemical processes underlying this sequence of events, but it would at least be possible to imagine the local lesion to be causing a defect of function, that is to say, a defect of inhibitory function, which would bring it into line with what has been suggested in myoclonic seizures, and is generally a more satisfactory kind of explanation for the clinician and pathologist than that implied by the concept of local irritation.

Conclusion

It has been possible in this lecture to discuss only a few of the recent advances in neurophysiology and biochemistry. It is in the latter field that further discoveries are to be hoped for which will throw a light into the many dark corners which are now open only to speculation. When the transmitter substances in the brain are known, together with their backgrounds of enzyme and substrate, and when the chemical environment of the nerve cell and its susceptibility to changes in the constituents of the plasma are better understood, the neurologist may feel less bewildered by the problem of epilepsy than he is to-day. Meanwhile the work of Hughlings Jackson stands as an example for all students of epilepsy not only to record their

observations in the greatest detail but to be constantly asking questions about all that has been observed.

I am greatly indebted to Dr. C. G. Phillips and Professor R. H. S. Thompson for their advice and encouragement in the preparation of this lecture.

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