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New concepts concerning mechanisms involved in the production of epileptic seizures and their significance for the classification of the epilepsies

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NEW CONCEPTS CONCERNING MECHANISMS INVOLVED IN THE PRODUCTION OF EPILEPTIC SEIZURES AND THEIR SIGNIFICANCE FOR THE CLASSIFICATION OF THE EPILEPSIES

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I. Introduction

The group of clinical disorders known as epilepsy has been recognized by the medical profession since the time of Hippocrates. Loss of consciousness as an essential feature of epilepsy was recognized by the early Greek writers. Among his other contributions to the study of epilepsy, Hippocrates differentiated between idiopathic or true epilepsy and symptomatic seizures following trauma to the head or spasms without loss of consciousness. This differentiation was generally accepted until the time of Hughlings Jackson. For example, Reynolds in his book "Epilepsy" (38) published in 1861 stated that the term epilepsy could be properly applied only to idiopathic seizures and that convulsive seizures where consciousness was not lost could not be considered epilepsy. In the latter group he included the "epilepsies" which were manifestations of definite brain lesions. Idiopathic epileptic seizures were diagnosed on the basis of absence of localizing features in the onset and absence of any signs of systemic or brain disease. The pathologic process was thought to be a state of hyperexcitability in the "center of reflection".

Hughlings Jackson (12) proposed that all "epilepsies" were in reality one, i.e., that all convulsions were manifestations of the same underlying process, which was an occasionally discharging lesion, the various external manifestations of which were dependent upon varying strengths of discharge and upon the cere-

bral localization of their onset.

Jackson also predicted that three levels of functional differentiation would one day be demonstrated in the central nervous system. The lowest level was to be found in the spinal cord, medulla and pons where the different parts of the body have representation as units. The middle level he considered to be in the cerebral cortex where the representation was of functions, i.e., movements and differentiation of sensation. The highest level, a final motor and sensory integrative center which might form the neural substratum of consciousness was thought by him to be in the frontal region. Although more recent studies have necessitated correction of some aspects of this hypothesis, Jackson's concept of functional levels in the nervous system is still very useful.

During the twentieth century, it has been the custom to consider those epilepsies produced by a demonstrable brain disease as symptomatic; those in which there was no pathologically demonstrable lesion were regarded as idiopathic epilepsy. Generally regarded as symptomatic or focal seizures were focal motor or Jacksonian seizures and auras which prior to the time of Jackson were regarded as merely premonitory signs of a seizure and not as actual seizures in themselves. According to Jackson these epigastric, visual, auditory, olfactory and psychic sensations immediately preceding a seizure were the first evidence of an abnormal

nervous discharge and constituted the "local signature" of an attack (12). Usually regarded as idiopathic were petit mal attacks and various minor seizures such as episodes of giddiness, a feeling of strangeness, sudden sensory phenomena related to the visual, auditory or gustatory spheres which were not followed by a generalized motor convulsion. Also regarded as idiopathic were episodes of a dreamy sensation and periodic, temporary derangements of mentality called epileptic equivalents. The term grand mal was used to disignate a type of seizure, i.e., a generalized or major motor convulsive seizure regardless of etiology or type of onset (7).

The purpose of this paper is to relate how recent research in basic neurophysiology and epileptology and the experience gained from almost twenty years of experience in clinical electroencephalography have led to (1) a theory of a "centrencephalic" mechanism for the genesis of idiopathic seizures and (2) a broadening of the category of symptomatic epilepsy to include some seizures previously considered as seizures, for example, various psychic phenomena now known to be associated with electrical discharge in the temporal lobe.

II. The Theory of a "Centrencephalic" Origin of Idiopathic Seizures.

A. Basic Research: The Diffuse Projection System of the Brain Stem.

In 1942 Dempsey and Morison (2,3,4) reported the discovery of a thalamic system, low frequency electrical stimulation of which evoked widely distributed, high-voltage, cortical waves, which increased in amplitude with successive stimuli. These responses were observed whenever stimulating electrodes were placed in the medial thalamic nuclei near the internal medullary lamina. Single electrical impulses administered to the medial intralaminar nuclei likewise produced bursts of rhythmic activity in widespread areas of the cortex. Dempsey and Morison showed that the production of these diffuse cortical responses, which they called recruiting responses, was independent of the specific thalamic relay systems, and that their widespread distributation through the cortex was not dependent upon long cortico-cortical connections.

The investigations of Dempsey and Morison have been extended, principally in the laboratories of Jasper (1, 8,9,10,13,14,16) and Magoun (39,42,43,44). The thalamic structures involved in the production of the recruiting response have been determined to be the intralaminar nuclei, including the centre median, the nucleus ventralis anterior and the rostral portion of the reticular nucleus (9,13,39,42). Interconnections between these nuclei and other parts of the brain are profuse. They project to widespread areas of the cortex without relaying through the specific projection nuclei of the thalamus (40), but they are apparently

interconnected with those nuclei (9,42), and receive fibers as well from the lower brain stem reticular formation (44). Jasper has called these nuclei and their projections the "diffuse thalamic projection system" (14).

The lower brain stem reticular formation has also been found to project to the cerebral cortex directly, as well as via thalamic relays (15,27,28,40), and has a profound influence upon the activity of the forebrain. Moruzzi and Magoun (29) showed that electrical stimulation of the brain stem reticular formation abolishes existing electrocortical synchrony in the forebrain, which is replaced by desynchronized activity thus reproducing the EEG change seen in wakefulness or in the arousal reaction to natural stimuli. In the "encephale isole" preparation acute lesions interrupting this reticular activating system were found to abolish the EEG pattern of wakefulness and to result in recurring slow waves and spindle bursts like those of sleep (20). Lindsley, Schreiner, Knowles and Magoun (21) showed that similar lesions in chronic preparations were followed by chronic somnolence and EEG synchrony. Magoun (24) in a paper discussing this activation function of the reticular formation stated that the essential elements mediating this function were a series of ascending relays coursing forward through the mesencephalic tegmentum, subthalamus, hypothalamus, and ventromedial thalamus into the internal capsule.

The brain stem reticular formation receives collateral fibers from the sensory-afferent tracts, and impulses delivered over these collaterals, like direct stimulation of the reticular formation, results in the desynchronization of cortical electrical activity and behavioral arousal (42). If the ascending reticular relays are interrupted however, these responses are minimized or abolished entirely (21,21).

Corticofugal connections to these diffusely projecting brain stem systems (the diffuse thalamic projection system and the lower brain stem reticular formation) have repeatedly been demonstrated (17,35).

B. The "Centrencephalic" Theory.

In their recent book, Epilepsy and the Functional Anatomy of the Human Brain (35), Penfield and Jasper present the following theory, portions of which had appeared in earlier papers (13,14, 30,31,32). There exists in the brain stem a neuronal system with to-and-fro connections with all parts of the cerebral cortex. They call this system the "centrencephalic system", and define it precisely as "that system of the higher brain stem which has been in the past, or may be subsequently shown to have equal functional relationship to the two cerebral hemispheres". They hold that the thalamic reeticular system and the brain stem reticular formation are parts of this centrencephalic system. The centrencephalic system is conceived of as responsible for the maintenance of

consciousness and for integrating the activity of the various thalamo-cortical segments of the forebrain, for which its location and anatomical connections make it ideally suited. This theory is supported by the evidence presented in the last section, at least insofar as the existence of the postulated structures and the function of the maintenance of consciousness are concerned. The validity of the postulated integrative function is more tenuous, being based largely upon certain observations of the results of electrical stimulation of the human brain during surgery (35,37).

Another non-adaptive function for which the centrencephalic system is likewise ideally suited is the production of generalized seizures (classical grand mal and petit mal) and the mediation of the development of certain focal seizures, originating elsewhere in the brain, into generalized convulsions. The following evidence supports the proposition that generalized seizures without focal features (idiopathic seizures) can originate in the centrencephalic system.

The ordinary petit mal attack results in complete unconsciousness and either arrest of movement, akinesis or myoclonic jerking. These seizures are associated with a most specific form of electroencephalographic tracing, the three per second bilaterally synchronous wave-and-spike pattern, an important feature of which is the sudden onset of the bilaterally synchronous discharges from

homologous areas of the two cerebral hemispheres. Hursch (11) showed that the bilateral discharges remain synchronized after section of the corpus callosum; hence comissural pathways are not necessary for the maintenance of bilateral synchrony. These observations point to the existence of a centrally located neuronal system with projections to both cortices as the site of the original petit mal discharge.

The complete electroencephalographic pattern of the petit mal attack has never been reproduced by electrical stimulation of any portion of cerebral cortex, but Jasper and Droogleever-Fortuyn (18) demonstrated that bilaterally synchronous three per second wave-and-spike patterns could be obtained from widespread cortical regions while stimulating a local area in the antero-mesial thalamus of the cat. Hunter and Jasper (10) showed that electrical stimulation within the intralaminar nuclei of the thalamus especially rostrally and bordering upon the dorso-medial and antero-medial nuclei produced a sudden arrest of responsiveness which they termed the "arrest reaction". During arrest the animal remained immobile with no loss of tone, and failed to respond to usually effective stimuli. The "arrest reaction" persisted beyond the period of thalamic stimulation, accompanied by an after-discharge resembling very closely those of the petit mal seizure in man, and including the slight twitching movements about the eyes and face so commonly seen in these attacks, and then ceased

abruptly.

More intense and more rapid stimulation of the same regions producing the "arrest reaction" would produce first a petit-mal-like attack and then a generalized convulsion of the grand mal type. During both the period of thalamic stimulation and the ensuing petit-mal-like phase a bilaterally synchronous three per second wave-and-spike discharge was recorded from the cortex and was associated with a similar type of wave form in the thalamus. During the grand mal-like phase the electrocorticogram and electrothalamogran showed rapid, high-voltage activity simulating closely the form of the EEG at the onset of such attacks in man.

These experimental results support Penfield and Jasper's hypothesis that idiopathic petit mal and grand mal seizures originate in a centrally located brain stem system.

The pathogenesis of centrencephalic seizures is still obscure. Various hypotheses have been proposed, such as differential sensitivity to metabolites, vascular instability, metabolic defects, developmental abnormalities in the brain stem and birth trauma (7,19). None have been proved, but at any rate the theory of centrencephalic origin of idiopathic seizures renders postulation of generalized brain disease unnecessary.

C. Definition of Idiopathic Epilepsy

In the light of the foregoing theory and data, idiopathic seizures may be defined as those seizures due to the abnormal

discharge of electrical activity in the centrencephalic system of the brain stem, which start with loss of consciousness, or rarely obnubilation, with or without bilateral primitive muscular activity (tomic spasms and/or clonic jerks), but without focal indications of any kind (including auras or electrical foci in the EEG), and without demonstrable disease of the brain. All other types of seizures are considered symptomatic (6,35).

III. Symptomatic Epilepsy.

A. Definition of Symptomatic Epilepsy.

Symptomatic seizures may be defined as those seizures due to an abnormal electrical discharge secondary to demonstrable disease process or structural damage within the brain.

B. Types and Causes of Symptomatic Seizures.

Symptomatic seizures may be either generalized or focal. Generalized symptomatic seizures are caused by generalized brain disease, such as encephalitis, meningitis or neurosyphilis. Such seizures are often indistinguishable from idiopathic grand mal seizures.

Focalsymptomatic seizures may be defined as any seizure beginning with a neuronal discharge in the vicinity of a demonstrably abnormal focus within the central nervous system (35). The more common causes of such seizures are cerebral cicatrix, resulting from trauma or infection, expanding lesions as neoplasm or ischemia, local microgyria due to infantile compression or ischemia,

brain cysts, cerebral vascular disease, and congenital lesions (35).

Focal symptomatic seizures may be of numerous different clinical types. It is convenient to divide them into five major groups on the basis of external manifestations and the site of onset of the discharge as follows:

1. Somatic motor seizures
2. Sensory seizures
3. Autonomic seizures
4. Psychic seizures
5. Automatisms

A brief sumary of the outstanding clinical features and the probable site of the original discharge causing each type follows.

1. Somatic motor seizures

The best known type of somatic motor seizure is the Jacksonian or Rolandic motor seizure which is a focal motor seizure due to abnormal electrical discharge in the precentral gyrus. The Jacksonian march, a progression of the convulsive activity to neighboring external members corresponding to the spread of discharge to contiguoug cortical areas on the precentral gyrus is likewise well known. Other types of somatic motor seizures are masticatory seizures which consist of movements of jaw, tongue, lips and throat as in swallowing without loss of consciousness, produced by abnormal discharge in the Rolandic representation of of these elements, and versive seizures characterized by turning

of the head, and sometimes the entire body, with conjugate deviation of the eyes. These seizures usually arise in the cortex of the contralateral frontal lobe, but may originate in the occipital lobes, and rarely in the brain stem (35). Less well known types are tonic mesencephalic seizures, opisthotonic seizures which arise in the vicinity of the midbrain outside the centrencephalic system, and postural seizures caused by abnormal discharge in the supplementary motor areas of one hemisphere (35).

2. Sensory seizures

Focal sensory seizures are caused by abnormal electrical discharge in an area of primary sensory representation. Any sensory modality may be involved. Sensory seizures consisting of numbness, tingling, sense of movemnt,etc. usually arise in the postcentral gyrus, and visual seizures, consisting of flashing lights, dimming of vision, etc., arise in the occipital lobe. Other types of focal sensory seizures are auditory, vertiginous, and olfactory or uncinate fits, arising in the temporal lobe (35).

3. Autonomic seizures

Visceral phenomena are quite aften associated with somatic motor or sensory seizures. However seizures also occur which are confined to the autonomic nervous system. These may be viscerosensory or visceromotor. Among other types of visceral phenomena which have been observed are the epigastric aura and the sense of nausea, probably associated with disturbances in the temporal

region, and pupillary change, vasomotor, respiratory and secretory phenomena, the central nervous system representation of which is thought by Penfield and Jasper to be at least partially located in the diencephalon (35).

4. Psychic seizures

A local epileptic discharge in certain areas of the cerebral cortex may produce psychic phenomena. These phenomena include (1) illusions, (2) emotional states, (3) hallucinations, and (4) forced thinking. Generally speaking the first three seem to be the result of an epileptogenic discharge in the parts of the temporal and parietal cortices concerned with memory recording while the location of the causative discharge for forced thinking has as yet not been determined (35).

5. Automatism

Automatisms are the ictal or postictal actions of a patient, who has not lost motor control but has lost to some degree his understanding and his ability to make memory records. He acts like an automaton, carrying on simple or habitual activities. Such behavior may occur either during exhaustion following a generalized convulsive seizure or as the result of a focal cortical discharge usually arising in the circum-insular cortex and occasionally in the frontal cortex.

To conclude this brief summary of the various types of focal symptomatic seizures it should be stated that all of

these types may or may not progress to a generalized major convulsion. This will be discussed more fully later.

C. Epileptogenic lesions

In the discussion of focal symptomatic seizures, the question of epileptogenic lesions is of importance. What makes a lesion in the central nervous system capable of originating epileptic discharge? According to Penfield (35) cicatrization of nervous tissue results in relatively insufficient blood supply to the area immediately surrounding the scar. He believes this is true regardless of whether the scar is a meningocerebral cicatrix or a simple atrophic lesion of the gray matter with no involvement of the meninges. The histologic picture of both types is basically similar. It consists of central aganglionic scar tissue with an almost complete absence of capillaries. Outside this lies an intermediate zone of altered gray matter in which are seen microscopic evidences of nervous tissue necrosis. There are numerous blood vessel trunks in this area which is presumably supplied by anastomotic trunks between the intracerebral and extracerebral vascular systems in the meningocerebral cicatrix and between the vessels of supply of the aganglionic core and and the normal gray matter in the simple atrophic lesions. However this intermediate zone is almost as deficient in capillaries as the central core. Penfield and Humphries (34)

showed that perivascular nerves were less numerous on arteries of the normal cortex than upon arteries of the same size in a cerebral cicatrix. Whether the arteries in the scar are therefore more responsive to autonomic control, i.e., constriction, awaits further investigation. Penfield (35) on the basis of the foregoing observations postulates that the necessary condition for focal epileptic discharge is a local ischemia at the periphery of the lesion whether caused by lack of sufficient capillary bed, increased vasomotor response or periodically increased metabolic demand of the gray matter relative to the existing blood supply.

Penfield, Erickson and Tarlov (33) have reported a series of 703 cases of intracranial tumor in which they included neoplasms, brain abscesses, tuberculomas, and extra- and intracerebral hematomata. They reported that epileptic seizures are associated with 37% of supratentorial tumors. They believe that the chronicity of the lesion and its location are the two most important factors in determining whether or not it will give rise to epileptic seizures. They found that the more chronic types of tumor are more apt to produce seizures than those whose course is acute and that the closer a lesion is to the sensorimotor cortex the higher is the incidence of seizures. Individual predisposition and hereditary tendency are thought by them to play little if any part in the

production of such focal seizures. They theorize that the site of seizure production is the frontier of the tumor mass in the adjacent nervous tissue, not yet destroyed, but which has its blood supply somewhat compromised by the process of thrombosis in the adjoining lesion.

D. Methods of spread of epileptogenic discharge

Another question involving focal seizures is the manner of spread of the discharge. Two methods of spread have been demonstrated (26, 31, 35). One is spread through the feltwork of the cortex, which is composed of fibers running and crossing in all directions along which electrical impulses travel. The discharge may thus move from one cortical field into a functionally unrelated field. The second method of spread is by neuronal projection. The discharging focus can, by sending impulses to a distant area to which it is related by projection tracts, activate the recipient area, and thus set up a secondary focus or foci. This spread is mediated according to McCulloch (26) by the white matter. These projections may be either to other cortical areas or to subcortical structures.

Thus it may be seen that a focal seizure may develop into a generalized convulsion either by spreading through the feltwork of the cortex or by activating the centrencephalic system, which in turn projects seizure discharge along its diffuse corticipetal projections to all areas of the cortex.

A Jacksonian or somatic motor seizure which begins for example in the hand and progressively involves the arm, face, etc., is an example of the first type of spread, i.e., to adjacent areas of cortex by means of the cortical feltwork. It may also spread to involve the entire cortex via cortico-cortical projections immediately subjacent to the cortex and thus end in a generalized convulsion, but this should not be termed a grand mal seizure according to Penfield (35), since the centrencephalic system is not involved. Only if a generalized seizure is produced through the mediation of the centrencephalic system, either by primary discharge there or by activation of this system by focal discharge elsewhere may it be called a grand mal seizure according to his conception. Penfield also believes that the loss of comprehension and memory recording seen in automatism accompanying focal discharge in the temporal lobe is due to the firing of that focus into the part of the centrencephalic system concerned with memory recording and understanding. In this type of seizure the centrencephalic system obviously does not activate the entire cortex to produce a generalized convulsion, the mechanism involved being one of inhibition by interference with the function of a part of the brain stem and perhaps of its corticipetal connections.
It will be noted that a number of types of seizures, including autonomic seizures, psychical seizures and automatism have been

shown in the past twenty years to be of the focal symptomatic type rather than idiopathic as they were previously regarded, and it may be expected that as diagnostic techniques are improved, more types of seizures will become regarded as symptomatic. With the postulation of a centrencephalic system, all epilepsies in a sense become focal, at least in their origin. What causes one seizure originating in the centrencephalic system to result in only transient loss of consciousness (petit mal), while another produces by its spread to the cortex a grand mal seizure is one question still to be answered. What lesion, anatomical, biochemical or otherwise produces the original discharge in seizures now regarded as idiopathic is another unsolved problem. However it seems pertinent to again call attention to the firm belief of Hughlings Jackson stated many years ago that all epilepsies are focal in origin.

IV. Summary

1. A brief historical review of the most important concepts regarding the pathogenesis of epilepsy is given.
2. Experimental data indicating the existence of a "centrencephalic" integrating system in the ascending reticular system of the brain stem are presented and the role of that system in the maintenance of consciousness is discussed.
3. The role of the centrencephalic system as the center of

discharge for petit mal and grand mal seizures is discussed and evidence for this is presented. Idiopathic seizures are defined in the light of this theory.

4. Symptomatic seizures are defined and a summary of the various clinical types of seizures regarded at the present time as symptomatic is given.
5. A discussion of the characteristics of epileptogenic lesions and of the various methods by which a focal discharge may spread through the central nervous system is presented.
6. The implications of the centrencephalic theory and other advances in epileptology in recent years for the classification of the epilepsies are noted.

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