



# History of epilepsy: nosological concepts and classification

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**ABSTRACT** – The purpose of this review is to provide insight into the development of the nosological views of the epilepsies, from prehistoric times to the present, and highlight how these views are reflected by terminology and classification. Even the earliest written documents reveal awareness that there are multiple forms of epilepsy, and it is surprising that they should be included under the same disease concept, perhaps because the generalised tonic-clonic seizure served as a common denominator. The Hippocratic doctrine that the seat of epilepsy is in the brain may be rooted in earlier knowledge of traumatic seizures. Galenus differentiated cases where the brain was the primary site of origin from others where epilepsy was concomitant with illness in other parts of the body. This laid the fundament for the distinction between idiopathic and symptomatic epilepsies, the definition of which changed considerably over time. The description of the multiple seizure types as they are known at present started in the late 18th century. Attempts to classify seizure types began in the late 19th century, when Jackson formulated a comprehensive pathophysiological definition of epilepsy. Electroencephalography supported a second dichotomy, between seizures with localised onset and others with immediate involvement of both hemispheres which became known as “generalised”. In recent years, advanced methods of studying brain function *in vivo*, including the generation of both spontaneous and reflex epileptic seizures, have revolutionised our understanding of focal and “generalised” human ictogenesis. Both involve complex neuronal networks which are currently being investigated.

**Key words:** epilepsy, history, nosology, classification, superstition, trephination, definition, ictogenesis, idiopathic, symptomatic

The purpose of this review is to provide insight into the development of the nosological views of the epilepsies, from prehistoric times to the present, considering the impact of the most recent research. How these views are reflected by terminology and classification will be further highlighted.

## Early history: scientific views of epilepsy versus superstition

Epileptic seizures are a possible expression of all, even rather primitive, organised nervous systems. It is therefore safe to assume that

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epilepsy has existed throughout phylogenesis including the earliest stages of humankind. Prehistoric trephined skulls have been related to epilepsy and have been found in many cultures in large quantities, many of them bearing signs of bone apposition, *i.e.* survival (*figure 1*). Some of these are related to skull fractures; a witness that prehistoric surgeons were able to treat such traumas successfully. Some of the individuals who underwent such traumas will have had traumatic seizures. In others, no evident explanation of the intervention exists, and epilepsy and severe headache have been proposed as other indications for trephination (Arnott *et al.*, 2003). There is no way of proving this, however, we know from some of the earliest medical documents, the Hippocratic texts, that the early surgeons were aware that brain wounds could cause seizures and that they should be trephined. Hippocrates' knowledge that epilepsy is a disease with an origin in the brain, may very well be based on the evidence from traumatic seizures. Aretaeus the Cappadocian in the second century recommended trephination as a treatment for epilepsy (Temkin, 1971).

This is witness to a rational, scientific approach to epilepsy very early in the history of mankind, which was in striking contrast to popular beliefs considering epilepsy as a disorder sent by gods or other supernatural forces. A Babylonian cuneiform tablet from 1067-1046 BC reveals the knowledge of different kinds of seizures and ascribes them to the influence of various demons or evil spirits (Kinnier Wilson and Reynolds, 1990). It is, however, uncertain whether natural or supernatural explanations were distinguished at the time. How different was the concept of an invisible force producing seizures in somebody from an experience of a lightning bolt coming out of the sky



**Figure 1.** Trephined skull. No signs of trauma, and bone apposition confirms that the patient survived for a considerable time. Inca, Precolumbian period.

and killing somebody, or of a wind which is invisible but real enough to drive one's boat or capsize it? We must be careful not to jump to conclusions.

For Hippocrates at around 450 BC, this distinction had become clear and he strongly opposed supernatural explanations in his famous pamphlet on "The sacred disease", taking the position that epilepsy has natural causes just like all other illnesses, and that its seat is in the brain. However, a conflict between scientific explanations of epilepsy and popular superstitions has prevailed throughout the history of epilepsy until the present day (Wolf, 2010).

## The multiplicity of epilepsy

Surprisingly, even very early texts, such as the above-mentioned Babylonian codex, reveal a knowledge that epilepsy occurs in many different forms. The extent of abstraction in subsuming many variable seizure types under one disease concept can hardly be overestimated, even considering that the generalised tonic-clonic seizure is the most pronounced manifestation of many epilepsies and is a common denominator. Whereas Hippocrates was content with explaining the various appearances by the multiplicity of natural causes (climate, winds, moon phases, dyscrasias of body fluids), this did not suffice for Galenus, the second great master of antique medicine (*figure 2*). He agreed that seizures always involved the brain, however, he believed that the primary pathology was not in the brain in all cases. He referred to cases in which he believed the primary pathology was in the brain as "idiopathic" (signifying a disease proper, with its own specific pathology). In other cases, the seizures were "sympathetic", *i.e.* concomitant with illness in another part of the body. "Sympathetic" was later replaced by "symptomatic" (another synonym of "concomitant"), but essentially Galen's distinction is valid today, even if the difference between idiopathic and symptomatic epilepsies is now defined quite differently.

## Idiopathic versus symptomatic epilepsies

If "idiopathic" was synonymous with a cause specific to the brain, epilepsy caused by primary brain lesions, such as a brain tumour, would belong to this definition which was indeed still the view in the early 19th century (Temkin, 1971). This necessitated a precision, because in these cases, epilepsy was clearly the secondary symptom to another pathology and not the disease proper. Delasiauve (1854) introduced the distinction which is still in place for idiopathic epilepsy with merely functional deviations from symptomatic epilepsy, in which a more or less appreciable cerebral lesion was found.



**Figure 2.** Complete works of Galenus, 1562 edition, Offizin Frobenius, Basel.

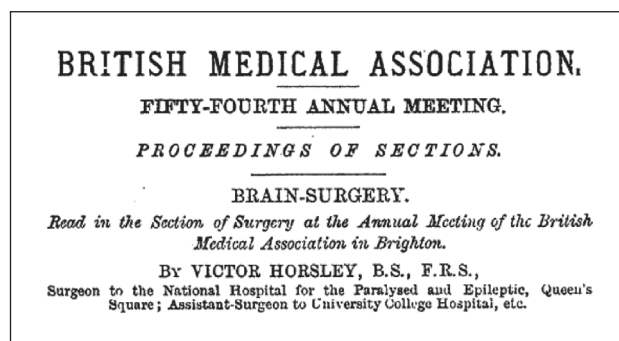
If gross brain pathology was inconsistent with the concept of idiopathic epilepsy, what then was the (functional or morphological) pathology underlying it? This question was much discussed in the period around 1900, and its clarification appeared at the time to be the major research objective for the 20th century (Wolf, 2009). Hereditary predisposition, however, was considered the primary cause (Turner, 1907; Binswanger, 1913), and this has meantime been underpinned by increasingly more detailed genetic research.

## Multiplicity of seizure types and a comprehensive definition

Until late into the 19th century, epilepsy was used synonymously with the “generalised tonic-clonic” or “grand mal” seizure. Other seizure types were termed “epileptiform”, “partial convulsions” or “epileptic equivalents”. Tissot (1770) gave a beautifully precise

description of a case of childhood absence epilepsy, and Herpin (1867) described a patient with what we now refer to as juvenile myoclonic epilepsy (JME). The identification of focal motor seizures is due to Bravais (Temkin, 1971), but it was Jackson who first fully understood the anatomical implications of these (Jackson, 1932, vol. I, p. 331ff) as temporal lobe seizures, which he proposed as “uncinate fits” (Jackson, 1932, vol. I, p. 467). The consequences of this semiological approach to seizures became immediately apparent when Jackson started to collaborate, at Queen Square in London, with the surgeon Horsley (1886; figure 3). Their second patient, whose investigations were all normal, was operated upon solely based on anatomical conclusions from the seizure semiology. At surgery, on June 22, 1886, Horsley found a tuberculoma confirming localisation, removed it together with the thumb area of the cortex which he and Jackson considered the “epileptogenous focus”, and the patient became seizure-free. This marks the birth of both epilepsy surgery and the closely related new term “focal”.

Before, minor or “incomplete” seizure types were mostly treated as unimportant and dismissed as “epileptiform”. Herpin’s monograph on incomplete seizures (Herpin, 1867) was an exception. Now Jackson understood that more could be learned about epilepsy from these than from generalised tonic-clonic seizures or “epilepsy proper”. This led him logically to an attempt to create a definition of epilepsy which was applicable to all seizure types: “a condition in which there is a sudden excessive transitory discharge of some part of the cortex” (Jackson, 1932, vol. II, p. 9). The discharge he had in mind, however, was not an electric discharge, but a “liberation of energy”



**Figure 3.** Title of Horsley’s 1886 report of the 54th Annual Meeting of the British Medical Association in Brighton regarding three operations on patients referred by Jackson who was present during the procedures. The intervention of Patient 2, on June 22 1886, was solely based upon anatomical conclusions from seizure semiology and thus represents the first instance of veritable epilepsy surgery. The concept and term “focal” arose from the collaboration between Horsley and Jackson.

(Jackson, 1932, vol. II, p. 388) which was understood chemically (Reynolds, 2007). The recent comprehensive definitions of epileptic seizures and epilepsy by the International League against Epilepsy and the International Bureau for Epilepsy (Fisher *et al.*, 2005) were an update rather than a revision of Jackson's approach.

## Early approaches to classification (table 1)

Two divergent developments were evident in the 19th century. One was unitarian in which only the idiopathic cases, with neither any recognisable brain pathology

**Table 1.** Development of classifications in epilepsy.

<b>Prolegomena: the multiplicity of epilepsy (Babylonians and Hippocrates)</b>
<b>Galenus (129-216)</b> – Seizures due to primary affection of the brain: <i>idiopathic</i> or <i>protopathic</i> (=primary) versus – Seizures due to extracerebral causes secondarily affecting the brain: <i>sympathetic</i> (= concomitant, later replaced by the synonym " <i>symptomatic</i> ")
<b>Jackson (1835-1911)</b> – Distinction of empirical vs scientific classifications for different purposes, analogous to the botanist's and gardener's classification of plants. – First anatomical conclusions based on semiology
<b>Around 1900, several similar attempts at classification in response to description of many new individual seizure types by Féré (1890), Binswanger (1899/1911) and Turner (1907).</b> According to Turner: – Minor epilepsy Aura followed or not by impairment of consciousness – Major epilepsy Incomplete or complete convulsions (may be preceded by aura) – Psychical epilepsy
<b>International League against Epilepsy (ILAE) 1964/1969: first attempt to establish an international classification of epileptic seizures, in response to chaotic development of international terminology and the new insights gained by EEG</b> – Partial – Generalised – Unilateral – Erratic in new-born – Unclassified <ul style="list-style-type: none"> <li>• Addendum: classification according to seizure frequency             <ul style="list-style-type: none"> <li>- Individual</li> <li>- Repeated                 <ul style="list-style-type: none"> <li>Fortuitous</li> <li>Cyclic</li> <li>Provoked</li> </ul> </li> <li>-Status epilepticus</li> </ul> </li> </ul>
<b>ILAE 1981: the 1964/69 classification was based upon expert opinion.</b> Problems with practical application called for a revision which became now based on expert analysis of video-recorded seizures and accepted in 1981. The revision was much more detailed. It did not affect the basic dichotomy of partial (focal, local) vs. generalised seizures.
<b>ILAE 1985/1989: Syndrome classification</b> A first rudimentary draft of an international classification of epilepsies and epilepsy syndromes was presented in 1969, together with the amended first international classification of epileptic seizures. A detailed proposal, based on critical literature review of all proposed syndromes was presented in 1985. It combined the dichotomy of focal versus generalised of the international seizure classification with the classic distinction between idiopathic and symptomatic epilepsies. In the 1989 revision, a class of cryptogenic epilepsies (=hidden cause) was added to avoid symptomatic epilepsies being wrongly classified as idiopathic when the cause could not be identified.

For developments after 1989, see text.



nor any indication of exogenous pathogenic factors, were considered as epilepsy. The other challenged any unitarian concept in that the existence of multiple seizure types was acknowledged, recognising the fact that some could be observed in both idiopathic and symptomatic cases. In 1890, for the first time, a monograph was published which addressed epilepsies in the plural (Féré, 1890). A classification appeared to be required to provide structure to the increasingly heterogeneous field.

Féré distinguished primarily partial and generalised paroxysms and subdivided the latter into:

- 1) the complete attack;
- 2) the incomplete attack;
- 3) abnormal attacks; and
- 4) isolated symptoms.

Other early attempts at classification by Turner in 1907 and by Binswanger in 1913 included, in addition, psychical “equivalents of seizures” or “psychical epilepsy” (Wolf, 2009). Whereas these and other approaches (*table 1*) now have only historical interest, Jackson contributed a distinction which is still highly relevant today, when he, under the influence of Linné, compared taxonomic classifications with classifications for practical use. Taxonomic classifications were not directly utilitarian but, rather, for “the organization of existing knowledge, and for discovering the relations of new facts”. In medicine, the latter are now called “diagnostic manuals”. Jackson’s comparison with classifications of plants by a botanist for the former, and by a gardener for the latter is still famous (Wolf, 2003).

## Epilepsy, seizures, and syndromes

Another structured approach during that period, *i.e.* the recognition of syndromes, became highly important for the understanding of the epilepsies. Great clinicians, such as Tissot (1770) or Herpin (1867), had always written case reports that described many features beyond seizures, and these reports sometimes enable us to make a retrospective syndrome diagnosis (*vide supra*). Syndromes are patterns of signs, symptoms, and, frequently, other clinical features, which beyond individual combinations, characterise groups of patients. It has been proposed that systematic syndromatic approaches started with the inclusion of biological features by Gowers (1881), when he analysed the relationship of seizures with the sleep-wake cycle (Wolf, 2009). In addition, relationships between seizures and the menstrual cycle (“catamenial epilepsy”) were discussed, and the description of syndrome-specific ages at onset, precipitating mechanisms of seizures, specific combinations of seizure types, and other features followed, most in the first half

of the 20th century. The clinical aspects then became also supplemented by typical findings of ancillary studies.

## The contribution of electroencephalography (EEG)

EEG provided the first access to direct study of the function of the living brain. This was met by great expectations to learn about pathological brain function in epilepsy. Of the highest consequence, was the discovery of the existence of bioelectrical signals characteristic of epilepsy; these were referred to as spikes or sharp waves. However, from a practical point of view, it was even more important that these could not only be observed during seizures, but also in the interictal condition. This made EEG the superior diagnostic tool in epilepsy, which remains the case.

One of the significant early findings was that two fundamentally different types of epileptiform EEG patterns could be observed. In one, the sharp waves could be localised to a limited area of one side indicating local pathology, and this fits well with the concept of focal seizures. In the other, an epileptiform discharge was seen in a more or less symmetric and synchronous distribution over both hemispheres, and it commonly occurred as a sequence of a spike or two with a subsequent high-amplitude slow wave. This spike and slow wave or brief, “spike-wave” pattern was not homogeneously expressed everywhere, but usually had an accentuation which was frontal, less frequently occipital and rarely affecting other regions. Nonetheless, it became rapidly known as a “generalised” pattern, and this term was soon transferred to the seizures and epilepsies for which this pattern was characteristic.

## Morphological investigations

Radiological investigations promised information about brain pathology *in vivo*. Somewhat disappointingly, however, these remained, for a long period, restricted to the diagnosis of a series of aetiologies of symptomatic epilepsy, even after the advent of contrasting investigations, such as pneumoencephalography and cerebral angiography. Later, with computerised tomography, many more morphological aetiologies became apparent, and investigation became more straightforward. However, the purpose still remained merely diagnostic. Only with the next generation of imaging methods that allowed functional anatomical studies of the living brain, did neuroimaging begin to seriously contribute to our nosological understanding of the epilepsies.

## The international classifications (*table 1*)

The ILAE started in 1964 to develop an international classification system because “current classifications of epileptic seizures vary considerably, and the need for a standardised and uniform system of grouping is very apparent” (Commission, 1964; *figure 4*). Not surprisingly, a “clinical and electroencephalographic classification” resulted (Gastaut, 1970) and was based upon a dichotomy of focal (or “partial”) versus generalised seizures. The classification was accepted by the General Assembly of the ILAE but did not stand the test of practical application, because some terms (such as “complex partial”) had not been defined with enough precision to avoid misunderstandings and inconsistencies of application. A revision was undertaken which used a new approach and based the definitions of seizure types on video-EEG recorded examples. The revised classification was accepted in 1981 (Commission, 1981).

The subsequently developed international classification of epilepsies and epilepsy syndromes retained the

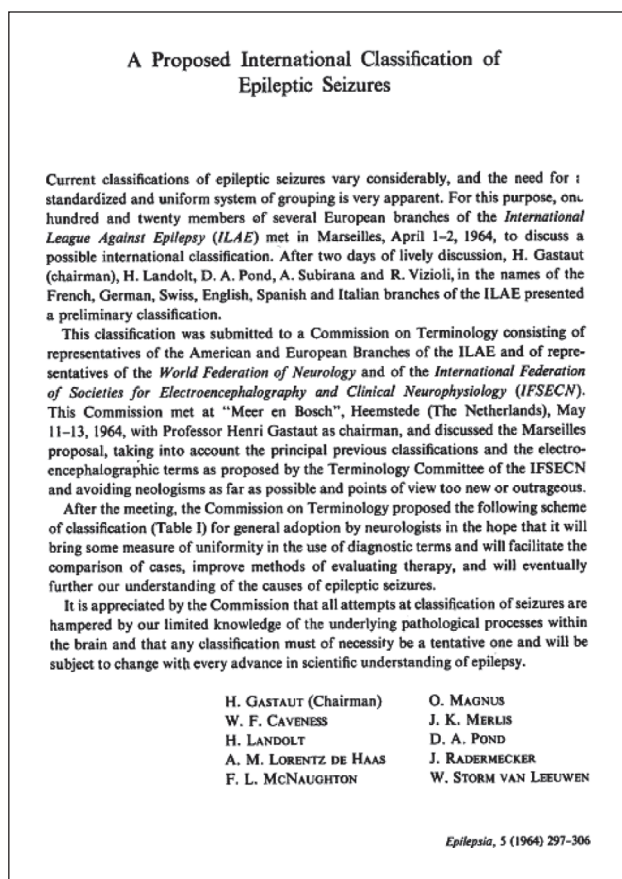
traditional distinction between idiopathic and symptomatic epilepsies. In addition, it was connected with the seizure classification by the dichotomy of focal versus generalised. A terminological problem was created by benign childhood epilepsy with centro-temporal spikes (BCECTS) and some related entities with focal seizures, with inconsistent onset and without morphological causes. They were obviously categorically different from lesional focal epilepsies but their nosological place was unclear. The solution was to create an umbrella class of “localisation-related epilepsies” (LREs) for all syndromes with focal seizures. This was meant as an interim solution until the matter would be better understood. For the international syndrome classification, all syndromes were included with critical expert review of published descriptions at an extended commission meeting in 1983 (documented in Roger *et al.* [1985]). The final classification was accepted in 1989 (Commission, 1989).

Both classifications were taxonomies, not diagnostic manuals, however, there were some compromises, such as possible classification of a patient’s epilepsy as “cryptogenic” if a symptomatic aetiology was suspected but could not be demonstrated. To make the international classification fully useful for clinicians, a diagnostic manual should and could have been developed as a supplement. This deficit created criticisms, especially from one group who proposed their own classification which focused on practical application (Lüders *et al.*, 1998).

At present, the ILAE seizure and syndrome classifications are still in use, although there is broad agreement that they are outdated. The seizure classification was built on a small video database in which a number of less common seizure types were absent and others, such as frontal lobe hypermotor seizures, had not yet been separated out. In addition, many syndromes have been discovered and described in the meantime. However, the ILAE had not installed any mechanism to currently update the classifications and integrate new knowledge. The right time to do this appears to have been missed, as in recent years our nosological understanding has undergone changes that challenge the traditional dichotomies.

## Nosological considerations: the ictogenesis of focal and “generalised” seizures

The development of focal seizures immediately appeared straightforward; a local convulsion started in the part of the body which was determined by the epileptic focus and spread from there into neighbouring areas and beyond. This progression could



**Figure 4.** Title page of the first attempt at establishing an international classification of epileptic seizures by the International League Against Epilepsy.

remain limited or increasingly involve the entire half of the body, and eventually even evolve into generalised convulsions. This observable “march of convulsion” (Jackson, 1932, vol. I, p. 333) revealed the spread of epileptic discharge through the cortex. A similar progression of subjective seizure symptoms could, with the patients’ help, also be established for non-motor seizures. The registration of focal seizures in the EEG confirmed this view.

With later findings using electrocorticography and stereo-EEG, the concept was modified and refined. The initial clinical signs and symptoms did not always indicate the seizure focus which could be in a clinically-silent area, the spread of epileptic discharge was not necessarily to adjacent areas but could take place via long-loop connections, the speed of propagation was relatively variable, and there was not only a spread of excitation but the necessary neuronal synchronisation required an interplay of excitation and inhibition.

In comparison, generalised ictogenesis was much more difficult to understand. The scalp EEG presented a primary symmetric and synchronous involvement of both hemispheres but did not provide any clues about its generation. This situation created intense controversies: were spike-waves generated cortically or subcortically? Had generalised seizures a focal onset, too, which only remained hidden in the depths of the brain? On the basis of animal studies, a “centrencephalic system”, including brain stem reticular and thalamic mechanisms, was hypothesized as the site of origin of seizures from where they spread symmetrically to both hemispheres. However, cortical mechanisms were supported by metrazol and sodium amytal studies with patients with generalised spike-waves, and Gloor (1968) formulated the concept of cortico-reticular epilepsies which became widely accepted. The mechanism of discharge could not be satisfactorily explained by either cortical or subcortical mechanisms alone, but appeared to result from an abnormal interaction of both, a kind of resonance phenomenon in a feedback circuit.

## Recent nosological developments

The new methods of functional investigation of brain activity (SPECT, PET, and fMRI) have further clarified these processes. The cortico-thalamic circuit producing absences and generalised spike-waves has been reported to include the frontal and parieto-occipital, but not the temporal, cortex, the caudate nucleus, posterior cingulate gyrus, and precuneus. Triggered from

individually different loci, this “default mode network” is considered to subserve awareness and introspective thought, appears to undergo a sequence of activation and deactivation (Moeller *et al.*, 2010; Benuzzi *et al.*, 2012). However, spike-waves in the photoparoxysmal response (PPR) appeared to be generated in an occipito-frontal cortical network without thalamic involvement (Moeller *et al.*, 2009a), whereas the thalamus did become involved when the PPR evolved into a seizure (Moeller *et al.*, 2009b).

Reflex epileptic seizures are increasingly being understood as conditions which allow the study of human ictogenesis *in vivo*. They are most common in idiopathic generalised epilepsies. Cognitive seizure precipitation is well-established in JME (Beniczky *et al.*, 2012) and appears to be related to hyperconnectivity between the motor system and fronto-parietal networks, subserving spatial working memory (Vollmar *et al.*, 2011). An fMRI investigation of reading-induced orofacial reflex myocloni (ORM), likewise, indicated that these reflex seizures are generated by excess activity in a cortico-reticular and cortico-cortical circuitry, subserving normal functions (Salek-Haddadi *et al.*, 2009). ORM are observed identically in both primary reading epilepsy (PRE, an idiopathic localisation-related epilepsy) and JME (an idiopathic generalised epilepsy). The present view of generalised ictogenesis was recently reviewed by Wolf and Beniczky (2014).

The increasing evidence that generalised ictogenesis is related to hyperactivity in physiological functional anatomical networks has led to the concept of “system epilepsies” (Avanzini *et al.*, 2012), analogous to other neurological system disorders, and in contradistinction to epilepsies due to local pathologies. This concept is presumably also applicable to idiopathic LREs, such as PRE (*vide supra*) and BCECTS (Avanzini *et al.*, 2012), and can include the interim concept of localisation-related epilepsies.

In contrast to system epilepsies, in focal lesional epilepsies, the fundamental concept of a localisable seizure onset remains, even as, more recently, we understand that focal seizure onset is not strictly local, but results from interactions, in pathogenic networks, of the epileptic focus with even relatively remote areas. These relationships at present are under investigation by many groups. It remains to be seen how these new concepts, many of which still work in progress, will eventually be reflected in future classifications. □

## Disclosures.

The author has no conflicts of interests to disclose.

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**TEST YOURSELF**

- Q1: Who introduced the term “idiopathic” epilepsy and for what conditions?
- Q2: How is the term “focal” related to epilepsy surgery?
- Q3: What is the difference between the generation of spontaneous “generalized” spike-waves and those provoked by intermittent light stimulation?

*Note: Reading the manuscript provides an answer to all questions. You can check for the correct answer by visiting the Educational Centre section of [www.epilepticdisorders.com](http://www.epilepticdisorders.com)*