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Neurocutaneous melanosis and epilepsy surgery

To the Editor: Dr Jean Latrelle, an eminent Parisian neurologist at the time of a meeting in Harriman, N.Y., started his discussion by saying, "Everything has been written, but not everything has been read".

I found the description of a patient with neurocutaneous melanosis by Oliveira de Andrade *et al*. (*Epileptic Disord*, 2004; 6: 145-52) interesting. For the past 30 years we have been following a similar patient. She was an intelligent, 29 year old, right-handed female. Birth, development, and family history were normal, and she had no illness that might lead to cerebral seizures. She had a vest type giant nevus from birth, which extended from her back to the extremities. Minor seizures started at the age of 3 years, with a feeling of fear and a painful grabbing sensation in her stomach followed by trembling of the body for 10 to 30 sec. She would call or run to her mother. Minor seizures continued over the years. When she was in her 20s, the attacks started with a sudden uncomfortable feeling in the head described as "high voltage". She felt cold or hot, shivered, and had "goose pimples". There was a variable degree of impairment of consciousness, but she was usually not fully unconscious. The episodes lasted a few seconds, and most were purely subjective. Only rarely did she fall in her minor attacks. At times they occurred singly or in brief clusters, but usually they recurred every 2 to 3 min for up to 12 or 15 hours. These prolonged bouts occurred once or twice a month. At such times, her mood changed; she became quiet and irritable. She had a frequent desire to void and was unable to carry on with her work. When these episodes occurred at night, she was unable to sleep since the brief feelings awakened her. She found these prolonged episodes to be uncomfortable, interfering with her work and social life. She had five major tonic clonic attacks in her early 20s.

After suitable localization studies she had a right temporal resection. There was no meningeal melanosis. The amygdala was replaced by a dark, brownish yellow, rather discrete mass measuring 7-8 mm in diameter. It was adherent to the tip of the pes hippocampus which was markedly increased in consistency. She had no further seizures with impairment of awareness but has continued to have some auras, presumably coming from the same hemisphere. This patient, with amygdaloid melanosis was described in 1980 (Andermann *et al.* 1980). She has been fully functional as a hospital social worker since. This lady illustrates very well, like the patient presented by Oliviera de Andrade, that seizures in patients with extensive nevi do not necessarily present with melanoma, nor is there necessarily malignant deterioration. It is unlikely that surgical treatment would lead to development of malignancy and her retardation is also not a reason not to consider surgical treatment. It is much better to be slow without seizures than slow and have seizures as well. As we stated in our 1980 report, melanosis of the amygdala occurring as part of neurocutaneous melanosis may of itself cause symptoms and should be added to the list of small lesions in the temporal lobe leading to complex partial seizures. □

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A critical review of the different conceptual hypotheses framing human focal epilepsy

To the Editor: Nair, Mohamed, Burgess and Lüders published a theoretical paper (*Epileptic Disord* 2004; 6: 77-83) analyzing the validity of the "epileptogenic zone" concept of Penfield and Jasper versus the slightly extended model of Talairach and Bancaud, involving not only the strict seizure onset but also the "early seizure spread" zone, and the "large network" hypothesis of Spencer. They unsheathed their sword to defend the concept accordingly, in which only the ictal onset zone is relevant for determining the "epileptogenic zone", a concept attributed by them to Penfield and Jasper.

Although the title of the paper (*A critical review of the conceptual hypotheses framing human focal epilepsy*) promises a conceptual approach to the existing models of focal epilepsies, they address almost entirely the question of how epilepsy surgery proves or disproves the strict focal or more extended network models.

The topic they address is of great importance as regards the grounds for surgical activity. Surgical treatment is, on one hand a very successful procedure but on the other hand it raises serious theoretical questions that we are inclined to sweep under the carpet. We would like to emphasize some of the questions that surround the conceptual hypotheses of focal epilepsies.

Historical aspects

Penfield and Jasper were operating on epilepsy patients on the basis of the clinical semiology of seizures, interictal EEG (frequently taken from the cortical surface explored during surgery), brain lesions detected by the methods available at that time (pneumoencephalography, angiography, skull x-ray and by visual inspection of the exposed cortex), and seizure symptoms elicited by electrical stimulation of the cortex. They tried to reproduce the "initial phenomenon of the patient's attacks" by electrical stimulation of the exposed cortex, working under local anaesthesia, but they were rarely able to establish the "initial ictal-onset zone", and they were not thinking in terms of ictal EEG at all. When, after a local excision guided by a visible cortical abnormality and/or electrical stimulation eliciting seizure phenomena, interictal spiking was still present, they recommended further extension of the excision (Penfield 1954 and 1956, Gloor 1986). So it seems to be rather questionable to attribute the idea of the value of the ictal onset-zone (based on the localization of spontaneous seizure onset) to them.

Can surgical results verify any epilepsy model?

Firstly, it is questionable whether the validity of any concept of pathophysiology of focal epilepsies can be verified or disproved by the results of surgical resections.

If we explore the interictal and ictal manifestations of a "focal" epileptic disorder by different methods, including functional neuroimaging data, it cannot be restricted to a circumscribed cortical area, although the resection of a small cortical area could provide a seizure-free state.

If it were possible to entirely remove the epileptogenic zone during surgery, the patients would remain seizure-free without antiepileptic drug treatment. In reality, some of them remain seizure-free after tapering of the drugs, but some of them never become seizure-free without drugs. In addition, the phenomena of "running down" and "building up": stepwise decreases and the re-occurrence of seizures long periods after surgery, are also not understandable within the framework of the "pacemaker resection" concept.

Our increasing knowledge about the organization of cortical functions and in particular the higher cognitive functions argues against the homunculus-like and solitary functional representations in the majority of the cortical areas, including temporal, frontal and parietal cortices, apart from the sensori-motor strip. We should think in terms of networks of multiple, flexible, parallel functional representations rather than the classical theory involving cortical representations. If it is true, the epileptic malfunction should also be considered as a network disorder, possibly with multiple parallel dysfunctioning of cortical areas, in contrast to the classical doctrines of cortical functional localization the sensory-motor areas suggested by Penfield (Penfield already faced this problem when he stimulated the temporal cortices as was shown in the classical paper of Gloor).

Different concepts for focal, versus system-related epilepsies?

The Penfield and Jasper concept fails to explain the thalamo-cortical pathophysiology of generalized, idiopathic epilepsies explored by a variety of researchers from Gloor to Steriade and co-workers in the recent past. In addition, we should consider that the generalized epilepsy category seems to be more and more untenable. Instead of "generalized" we should consider a bilateral partial epilepsy involving the thalamocortical structures and conse-

quently widespread cortical associative areas. Therefore, the theories of idiopathic, generalized epilepsies approach more and more the concepts of focal epilepsies. If we believe that epilepsies have some common physiopathogenetic features, a theory explaining the pathophysiology of a focal epileptic disorder should be applicable to the generalized epilepsies as well.
However, because of the dichotomous way of thinking we can exclude generalized epilepsies saying that focal and generalized epilepsy represent quite different categories. However, what of the case of mesial temporal lobe epilepsy, which is thought to belong to the focal epilepsies, although there are much data concerning the involvement of both temporal lobes and the whole limbic system. The success of different kinds of temporal lobectomies can hardly be explained by the Penfield-Jasper doctrine since the "pacemaker area" of temporal lobe seizures is either in the hippocampus-amygdala complex or in parahippocampal structures, however the resection necessary for the seizure-free state involves, in the majority of cases, a more extended area of the temporal lobe.

Disorder or symptom-(seizure) oriented approach

A further aspect to be discussed is the relationship between epileptogenesis and seizure genesis related to the epileptogenic zone.
There is a certain kind of tautological thinking if we say that the epileptogenic area is an area the excision of which results in seizure-freedom. Although epilepsy is a disorder producing seizures, seizures are not synonymous with epilepsy.
The absurdity of identification with or reduction of the epileptic process to ictogenesis is apparent if we take into consideration the years without any seizures after identification of the original epileptogenic lesion and before the first of later, recurring seizures. We do not know how many structures, and which spatial network are involved in the development of an established "pacemaker" area. Furthermore, in certain epilepsies, the seizures are far less characteristic features of the epileptic disorder, and the interictal epileptiform activity is the main cause of all the severe cognitive symptoms that the patients suffer from. It is so in LKS and ESES, although these are surely partial epilepsies or at least they have partial features with secondary generalization. Even the surgical solution in these epilepsies is based upon the so-called "interictal" and not on ictal symptoms. Seizures cannot be identified with epilepsy, seizures are just the visible symptoms of epilepsy. If we want to understand the physiopathogenesis of epilepsies, or even purely focal epilepsies, we should look beyond the seizures.

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Reply from the Authors: We read with interest the comments of Drs Halász, Holló and Rásonyi and welcome an opportunity to try to answer some of the questions they raised. It is interesting to notice that a good number of the discrepancies pointed out by Halász *et al.* arise from differences in the definition of the terms.

In our article, we have defined the epileptogenic zone as "the area of cortex from which seizures originate and whose surgical resection leads to seizure-freedom". Dr Halász and collaborators are correct when they point out that this approach is addressing primarily the question of the approach that should guide the surgeon when he is trying to render a patient seizure-free by resection of cortical tissue. Indeed, the objective of the manuscript was very practical and no attempt was made to discuss the complex pathophysiology of focal seizures. We also agree with Dr Halász that the title of our manuscript "A critical review of the different conceptual hypothesis framing human focal epilepsy") was probably slightly misleading considering that we did not discuss the pathophysiology of focal epilepsy but only the concept of "epileptogenic zone" as defined above.

On the other hand, it is clear that Penfield and Jasper endorsed the *concept* of relatively limited epileptogenic zones, even if they usually did not directly measure the "seizure-onset zone". The main purpose of our article was to compare the concept of epileptic zone (as defined above) and its actual influence on epileptic seizures, between different epilepsy surgery schools. In this regard, it is interesting to note that the concepts of epileptic networks as an integral part of the epileptogenic zone can only arise from the actual recording of ictal EEG discharges. Therefore, it is not surprising at all that Penfield and Jasper actually conceived the epileptogenic zone as a limited cortical area from which seizures arise, without even addressing the possibility that areas of "early" spread could be part of it.

In their letter, Dr Halász *et al.* argue that the functional alterations produced by focal epilepsy are not restricted to a very limited cortical zone, but produce widespread alterations. There is no doubt that cortical areas are extensively interconnected and therefore, it is not surprising that any alteration of function in a given cortical area will affect, to varying degrees, most of the entire brain. The assumption that epileptic seizures originate from a limited cortical area certainly does not contradict this concept! We also feel that it is a gross misrepresentation to assume that Penfield and Jasper conceived the cortical areas included in their homunculi as functioning in isolation. However, the description of the homunculus is certainly extremely valuable since it guides us as regards the eloquent cortical areas the resection of which may produce specific neurological deficits and whose activation by epileptic discharges produces typical ictal symptoms. This value is independent of the fact, certainly recognized by

any neurophysiologists, that normally, none of these areas will function in isolation.

Dr Halász *et al.* argue that it is "absurd to reduce the epileptic process to epileptogenesis". Again it is a matter of definition. We feel that we can only use the term epilepsy if a certain condition produces epileptic seizures or an equivalent. For example, let us consider two patients with exactly the same type and degree of mesial temporal sclerosis, one with seizures and the other patient just having symptoms related to the pathological damage (for example, memory difficulties). It would certainly be difficult to argue that the second patient has epilepsy just because he has a lesion that frequently produces epileptic seizures. In other words, there is no such thing as an epileptic process without seizures. There are only pathological processes that cause epileptic seizures. The situation of LKS and ESES is different. In this case, it is assumed that the symptomatology (cognitive symptoms) is the consequence of interictal discharges. Interictal discharges are actually "small seizures" that tend to synchronize only a limited number of neurons and, therefore, do not produce clinical symptoms or, in the case of LKS or ESES, only produce cognitive deficits mainly as "ictal" or "postictal manifestations".

Dr Halász *et al.* also argue that the concept of a "limited" epileptogenic zone is contradicted by the "running down" or "building up" phenomenon, as well as by the observation that some patients after surgery only become seizure-free on medications, or that some patients require more extensive cortical resections for seizure-freedom. It is difficult to understand why these observations should contradict the Penfield/Jasper model of the epileptogenic zone. The "running down" and "building up" phenomena only imply that the extension of the epileptogenic zone (area from which seizures may arise) can change over time. The fact that a patient is only seizure-free if he takes medicine indicates that surgery did not remove the whole of the epileptogenic zone and that the remaining epileptogenic zone is less active and can now be controlled with antiepileptic medication. Finally, those cases in which selective amygdalo-hippocampectomy was ineffective, point to the fact that the epileptogenic zone was slightly more extensive and, therefore, required a more extensive surgery.

Summarizing, we agree with Dr Halász *et al.* that the article does not discuss the pathogenesis of focal seizures as possibly implied in this title. The objective of the article was to discuss the concept of the epileptogenic zone as clearly defined in the introduction. None of the arguments presented by Dr Halász *et al.* contradicts the fact that Penfield and Jasper conceived the epileptogenic zone as a very limited cortical area that did not include cortical regions to which the seizure discharge would spread after its initiation (Talairach and Bancaud, and Spencer). □

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