

COMMENTS FOR THE COMMISSION ON CLASSIFICATION - RE: AETIOLOGY OF EPILEPSY

1. It is my opinion that the proposed classification scheme should feature aetiology more strongly. A schema which we are using in our book is presented in the table below
2. In preparing this scheme for our book, we noted five particular points:
 - a. Definitions - terms must be clearly defined. The usage of the terms *idiopathic* and *symptomatic* for instance has widely differed in the past 150 years. However, they are widely used my own view is that they should be retained.
 - b. Multifactorial cause of epilepsy - as Lennox and many before him frequently reiterated, epilepsy is in the great majority of cases multifactorial. This means that in any individual, the epilepsy is often the result of both genetic and acquired influences and also influenced by provoking factors. Assignment in such cases to any single aetiology is therefore to an extent arbitrary. Although, causation is divided into specific aetiological categories in table 1, it is recognized that epileptogenesis in individual cases will often involve multiple categories, often to a highly significant degree.
 - c. Aetiology .v. mechanism - it is also worth recording here that even the meaning of "aetiology" has indeed changed over the years. In Jackson's times, for instance, aetiology referred largely to the mechanisms of epileptogenesis, the final common pathway in Jackson's view, rather than the causative lesions (this is further discussed in the historical introduction). In the future a mechanistic classification would be ideal. However at present this is unrealistic. Broadly speaking though, the mechanisms underpinning idiopathic, symptomatic and provoked epilepsy are quite distinct and this is another reason for dividing the epilepsy into these three categories.
 - d. Focal .v. generalized epilepsy - it should be emphasized that an aetiological categorization often does not divide the epilepsies into clear-cut focal or generalized subdivisions, and the distinction (problematic as it is) does not map across the idiopathic .v. symptomatic categorization. This, some symptomatic epilepsies are generalized and some idiopathic epilepsies are focal. Furthermore, both generalized and focal seizures may be 'provoked', and provoked seizures can be either genetic or acquired.
 - e. Flexibility - it is important to recognise that classification may change over time as knowledge of aetiology accrues. No classification should be considered to be set in stone. Furthermore, in all classifications there are cases in which the inclusion into any particular category is difficult. In the epilepsies, this particularly applies to some childhood syndromes.
3. In our book, the aetiology of the epilepsies is divided into 4 main categories. We note that the Commission has not included a 'Provoked Epilepsy' category - we feel this is an omission.

The definitions we have used in the current draft of our book are:

i. Idiopathic epilepsy - *an epilepsy of predominately genetic origin and in which there is no gross neuro-anatomical or neuropathological abnormality*. The advances in genetics have been particularly fruitful in the area of epilepsy aetiology, and in the past 10 years a number of new mendelian idiopathic epilepsy syndromes have been delineated. However, the epilepsies with presumed multigenic or complex inheritance have proved more difficult to elucidate, and their genetic basis has largely eluded explanation, but this is an area in which development is predicted in the next 5-10 years. We have included in this category the conditions which have a presumed multigenic basis, even where this has not been yet identified - and it could be reasonably argued that they would be better moved to a cryptogenic category. However, their general clinical features and age specificity point strongly to a presumed genetic aetiology and it is for this reason that these conditions are included here.

ii. Symptomatic epilepsy - *an epilepsy with an acquired or genetic cause that has resulted in causative gross neuro-anatomical or neuropathological abnormality*. We include in this category developmental and congenital disorders where these are associated with cerebral pathological changes, whether genetic or acquired (or indeed cryptogenic) in origin. MRI imaging has been of great importance in clarifying the cortical developmental disorders, which are now often classified on imaging grounds, and modern molecular biology and genetics have uncovered the mechanism or genetic causes of many of these conditions. The acquired causes are dealt with in the book within 8 subdivisions

iii. Provoked epilepsy - *an epilepsy in which a specific systemic or environmental factor is the predominant cause of the seizures and in which there are no gross causative neuro-anatomical or neuropathological changes*. Some 'provoked epilepsies' will have a genetic basis and some an acquired basis. The reflex epilepsies are included in this category (which are usually genetic) as well as the epilepsies with a marked seizure precipitant.

iv. Cryptogenic epilepsy - an epilepsy of presumed symptomatic nature in which the cause has not been identified. The number of such cases is diminishing, but currently this is still an important category, accounting for at least 40% of adult-onset cases of epilepsy.

5. There are obviously cases where categorisation is difficult. These revolve particularly around: (a) the differentiation of 'presumed genetic' and 'cryptogenic', for instance in relation to the benign focal epilepsies or even the idiopathic generalised epilepsies; (b) the categorisation of some of the childhood syndromes, some of which are included under the 'idiopathic grouping' but evidence of a genetic basis is not very strong - for instance, the Panayiotopoulos syndrome - and others are included in the symptomatic epilepsy, in spite of the fact that there is a presumption of a genetic cause in at least a proportion of cases - for instance in the West or Lennox-Gastaut syndromes. In the future, as further knowledge accrues, it is quite possible that some of these epilepsies will be reclassified.

TABLE: An aetiological categorisation of epilepsy

Main category	Subcategory	Subcategory	Examples ¹
IDIOPATHIC EPILEPSY	Pure epilepsies due to single gene disorders		Benign familial neonatal convulsions; Autosomal dominant Nocturnal Frontal Lobe Epilepsy; Generalised epilepsy with febrile seizures plus; Severe myoclonic epilepsy of childhood
	Pure epilepsies with complex inheritance		Idiopathic generalised epilepsy (and its subtypes); benign partial epilepsies of childhood
SYMPTOMATIC EPILEPSY	Predominately genetic or developmental causation	Severe childhood epilepsy syndromes	West syndrome; Lennox Gastaut Syndrome
		Progressive myoclonic epilepsies	Umverricht-Lundborg disease; Dentato-rubro-pallido-luysian atrophy; Lafora body disease; mitochondrial cytopathy; neuronal ceroid lipofuscinosis; myoclonus renal failure syndrome
		Neurocutaneous syndromes	Tuberose sclerosis, neurofibromatosis, Sturge-Weber syndrome
		Other neurological single gene disorders	Angelman syndrome; lysosomal disorders; neuroacanthocytosis; organic acidurias; Prphyria; pyridoxine-dependnet epilepsy; Rett syndrome; Urea cycle disorders; Wilson's disease
		Disorders of chromosome function	Down syndrome; Fragile X syndrome; 4p-syndrome; ring chromosoame 20
		Developmental anomalies of cerebral structure	Hemimengencephaly; Focal cortical dysplasia; Agyria-pachygyria-band spectrum; Agenesis of corpus callosum; Polymicrogyria[

			schizencephaly; Periventricular nodular heterotopia; microcephaly
	Predominately acquired causation	Hippocampal sclerosis	
		Perinatal and infantile causes	Neonatal seizures (various causes); cerebral palsy; post-vaccination
		Cerebral trauma	Open head injury; closed head injury; neurosurgery; non-accidental head injury in infants
		Cerebral tumour	Glioma; ganglioglioma and hamatoma; DNET ; hypothalamic hamartoma; meningioma; secondary tumours
		Cerebral infection	Viral meningitis and encephalitis; bacterial meningitis and abscess; malaria; neurocysticercosis, tuberculosis; HIV
		Cerebrovascular disorders	Cerebral haemorrhage; cerebral infarction; arteriovenous malformation; cavernous haemangioma
		Cerebral immunological disorders	Rasmussens encephalitis; SLE and collagen vascular disorders; inflammatory disorders
		Degenerative and other neurological conditions	Alzheimer disease and other dementing disorders; multiple sclerosis and demyelinating disorders; hydrocephalus; arachnoid cyst and porencephaly
PROVOKED EPILEPSY		Provoking factors	Fever; menstrual cycle and catamenial epilepsy sleep-wake cycle; metabolic and endocrine-induced seizures; drug-induced seizures; alcohol and toxin-induced seizures
		Reflex epilepsies	Photosensitive epilepsies; startle-induced epilepsies; reading epilepsy; auditory-

			induced epilepsy; eating epilepsy; hot-water epilepsy
CRYPTOGENIC EPILEPSIES ²			

¹ These examples are not comprehensive, and in every category there are other causes (usually lumped together in a final section chapter).

² By definition, the causes of the cryptogenic epilepsies are 'unknown'. However, these are an important category, accounting for at least 40% of epilepsies encountered in adult practice.

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