5 Organisation of basic science in epilepsy with special reference to the International League Against Epilepsy

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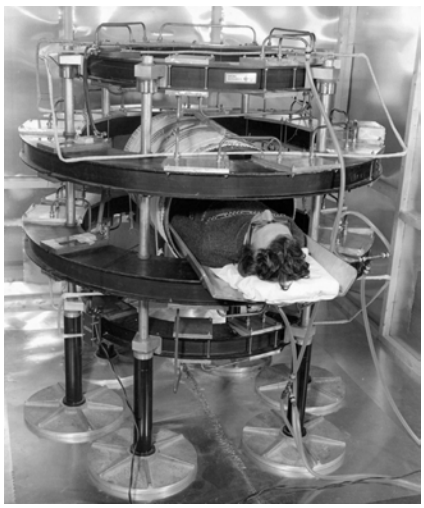
For the purposes of this review, basic research is defined as investigations into fundamental neuronal mechanisms of seizures and epilepsy. Most, but not all, basic research is carried out with experimental animal models of seizures and epilepsy, but much information was gained about fundamental neuronal mechanisms by observing patients with epilepsy in the early years of neuroscience. In recent years it has become increasingly possible to carry out basic research directly with patients as a result of the growth of epilepsy surgery programmes and the development of non-invasive functional neuroimaging technology. Conversely, not all research that uses experimental animal models of seizures and epilepsy has, as its main objective, to elucidate fundamental neuronal mechanisms of these conditions. For instance, animal models of seizures, and occasionally of epilepsy, are commonly used to screen potential antiepileptic compounds, and these studies are not considered basic research in this chapter. Animal models of seizures, and occasionally epilepsy, are also used as a means of perturbating the system in order to investigate basic mechanisms of normal brain function. This important area of neuroscience is also not considered here, although occasionally it has unexpectedly resulted in major insights into epileptic mechanisms, as was the case with the recognition of the phenomenon of kindling (Goddard *et al.* 1969).



An early magnetic resonance scanner. (From John R. Mallard, 'Magnetic resonance imaging – the Aberdeen perspective on developments in the early years', *Physics in Medicine and Biology* 15, R45–R60, 2006. Reprinted with permission from IOP Publishing Ltd)

The state of basic research in 1909

Although the International League Against Epilepsy (ILAE) was founded as a clinical society, by 1909 a considerable amount of research on the brain had already resulted in some general concepts about the neuronal basis of epilepsy. Almost half a century earlier, in England, John Hughlings Jackson made seminal contributions to our understanding of focal seizures by correlating ictal semiology with the location of lesions of the neocortex and hippocampus, identified at autopsy (Taylor 1958). At the time, epilepsy was believed to consist of generalised tonic–clonic seizures of mesencephalic origin. Although clinicians such as Todd (1856) in England, Bravais (1827) in France and Griesinger (1867) in Germany had already described focal ictal and postictal phenomena, the concept of localisation of function in the brain had fallen into disrepute among neuroscientists since the turn of the 19th century as a result of the unfounded theories of the Austrian phrenologist Franz Joseph Gall (1800).

However, by the mid-19th century early neuroscientists were beginning to resurrect this area of investigation with more legitimate scientific observations. Broca (1861) in France localised the site of motor language function based on clinical pathological correlation, and Fritsch and Hitzig (1870), in Germany, mapped cortical motor function in the dog with faradic stimulation. In the United States, Robert Bartholow (1874) provided an interesting, if controversial, footnote to history by being the first physician to stimulate the human motor cortex, through a cancerous skull defect in his house servant, and describing its behavioural effects. Ferrier (1874) reproduced Jackson's clinical pathological observations by stimulating monkey cortex. This confirmation of the cortical location of various ictal behaviours ultimately led to surgical resection of otherwise 'invisible' lesions responsible for epilepsy, localised preoperatively on the basis of ictal semiology (Macewen 1881; Horsley 1886). For many years after this, intraoperative cortical stimulation was an important localising technique for epilepsy surgery (see Engel 2005). Openchowski (1883) was perhaps the first to describe an experimental animal model of recurrent seizures when he created an epileptic focus by localised cortical freezing.

Basic research 1909–1940

It is of interest that the rather long mission statement issued by the League after its founding in 1909 included the following: 'The League will devote itself to special projects on behalf of epileptics, and to finding a cure and means of prevention, as well as providing aid and social rehabilitation. Nor will the League neglect experimental research and comparative physiopathology, or laboratory work, which is essential for elucidating a series of problems as complex as those raised by the origin, evolution and nature of seizure disorders, with their attendant range of somatic and psychic complications' (see Chapter 1). These intentions notwithstanding, there seems to have been very little League interest in basic research during the early years. Although the preliminary programme for the 1912 congress in Zurich listed a paper by Krainsky titled 'Pathogenesis of Genuine Epilepsy', Krainsky apparently never appeared to present this work.

From 1909 to 1940 relatively few papers published in *Epilepsia* focused on the basic science of the epilepsies. This state of affairs may have two explanations: first, the League in its formative years chose to emphasise clinical and sociological issues in the journal and, second, it is possible that most of the scientific work dealing with experimental animal models of epilepsy was published in other journals. A review of the early issues of *Epilepsia* indicates that the first scientific paper was published in 1914 by Bouché (1914). This paper, in French, bears the title 'Contributions Experimentale a l'Etude des Convulsions Toniques'. Bouché, a Belgian scientist, begins by stating that the work we are going to read about is an attempt to resolve a controversy that originated in 1863 with a paper by Nothnagel. Nothnagel had excited a particular region in the fourth ventricle in non-anaesthetized rabbits and observed tonic seizures and irregular jerks. Subsequent authors used the term 'clonic seizures' when referring to these irregular jerks, a nomenclature not used by Nothnagel. Believing that clonic seizures were the result of cortical excitation, Bouché performed a series of experiments to determine the effects of activation of subcortical structures in anaesthetized young adult cats that had undergone hemispherectomies. To induce seizures, he injected absinthe intravenously. His conclusion was that the presence of cerebral hemispheres is necessary for the expression of clonic convulsions. Along the way he provided evidence that midbrain and upper brainstem structures are involved in the expression of tonic seizures. Bouché emphasised that the expression of clonic and tonic–clonic seizures in humans may be the summation of cortical and subcortical activities.

Between 1938 and 1940, William G. Lennox published three papers reviewing the available literature on epilepsy topics worldwide in 1936 and in America in 1937 and 1938. These papers appeared in *Epilepsia* in 1938 and 1940 (Lennox 1938a,b; 1940). In these three reviews, Lennox catalogued all the papers he considered significant, including clinical manifestations, pathology and basic studies. Once again, it is interesting that several of the basic studies were not actually published in *Epilepsia*.

Basic research 1941–1950

The second series of *Epilepsia* (1941–1950) contained reviews and abstracts of papers presented in other journals. There was always a section on experimental animal studies which reported on seizures induced by numerous

techniques, including agenised flour, metrazol, insulin, electrical stimulation, focal chemoconvulsants, aluminium, penicillin, fluoroacetate and partially isolated cortical slabs. Audiogenic seizures were also investigated. A common experimental approach was to produce lesions of brainstem, cortex or corpus callosum to determine how they altered seizure manifestations.

During the Second World War, German neuroscientists carried out neuropathological investigations on victims of euthanasia with brain diseases, but not epilepsy. Alexander (1948) reported in *Epilepsia* that Halavorden refused brains of 'epileptics', because 'nothing of significance would be found', and that it would 'injure the case of psychiatry'. The first international congress after the war was held in New York in conjunction with the Association for Research in Nervous and Mental Diseases. There were three basic research papers, on cerebral metabolism and metrazol convulsion in the dog by Gurdjian, Webster and Stone; changes in the oxygen tension of the cerebral cortex of the cat in experimentally induced convulsions by Davies and Remond; and histochemical and action potential studies on epileptogenic areas of the cerebral cortex in man and the monkey by Pope, Morris, Jasper, Elliott and Penfield. This was actually considered more of an American than an international meeting, however, because there apparently was only one non-American in attendance.

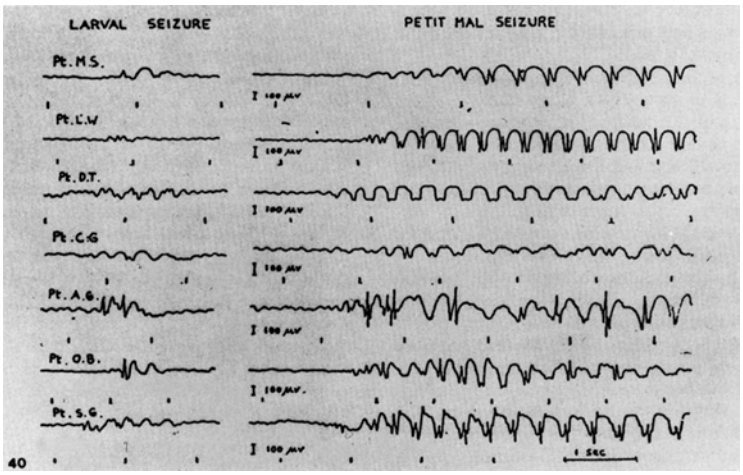
The 1949 Paris congress included a presentation, in French, on the role of the diencephalo-hypophysio-cortical system in the pathogenesis of epilepsy by Teglbjaerg; however, this congress was in conjunction with the Congress of the International Society of Electroencephalography and the International Neurological Congress, and the presentations were not designated for one society over another. Given that the EEG Society was, at the time, much more interested in basic research, it is possible that Teglbjaerg intended his paper for this organisation and not the ILAE.

Basic research 1951–2009

An important exception to the limited interest in basic research at international congresses was the 1953 congress in Lisbon, which included a major symposium on temporal lobe epilepsy organised by Henri Gastaut. By this time, Gastaut had been engaged in considerable clinical *and* basic research on temporal lobe epilepsy, and he convened this symposium to discuss his views on the topic, which were published in the third series of *Epilepsia* (Gastaut 1953). He described the creation of experimentally induced psychomotor seizures using stimulation and aluminium oxide, noted the importance of involvement of limbic structures, specifically piriform cortex, amygdala and hippocampus, and discussed contemporary neuroanatomic data of others concerning the connections of mesial temporal structures that he believed to be the anatomic substrates for temporal lobe epilepsy. The third series of *Epilepsia* also published a report of a symposium on seizure mechanisms organised by Earl Walker at the 1952 meeting of the American League against Epilepsy in Louisville, Kentucky (Walker 1952).

It was not until the fourth series of *Epilepsia*, and the editorship of Sir Francis Walshe, that the journal devoted itself to publication of serious original research, including 'informed, original and critical studies covering the fields of aetiology, pathogenesis, course, manifestations, investigations of every relevant kind, and treatment both medical and surgical'. During the 2 years of Walshe's tenure as editor, approximately 40% of the papers dealt with basic research, and the journal has subsequently continued to devote one-third to half of its pages to basic science, although this number has dipped to 20% in the past year (see Chapter 7). A crucial advance in the field of basic epileptology, which occurred at the beginning of the 1960s, was the use of intracellular recordings to demonstrate the changes in excitable properties of individual neurons belonging to an epileptogenic aggregate. Notably, one of the first papers reporting the intracellular analysis of pyramidal neurons during hippocampal seizure was published in *Epilepsia* by Kandel and Spencer (1961). Kandel subsequently was awarded the Nobel Prize in Physiology or Medicine. Another important milestone was the development of the *in vitro* hippocampal slice technique in the 1970s. The tremendous potential of this approach for investigating cellular and local circuit epileptogenic mechanisms became clear during the following years, and *Epilepsia* was on the frontline in publishing two pioneering papers (Olivier *et al.* 1977; Schwartzkroin and Pedley 1979).

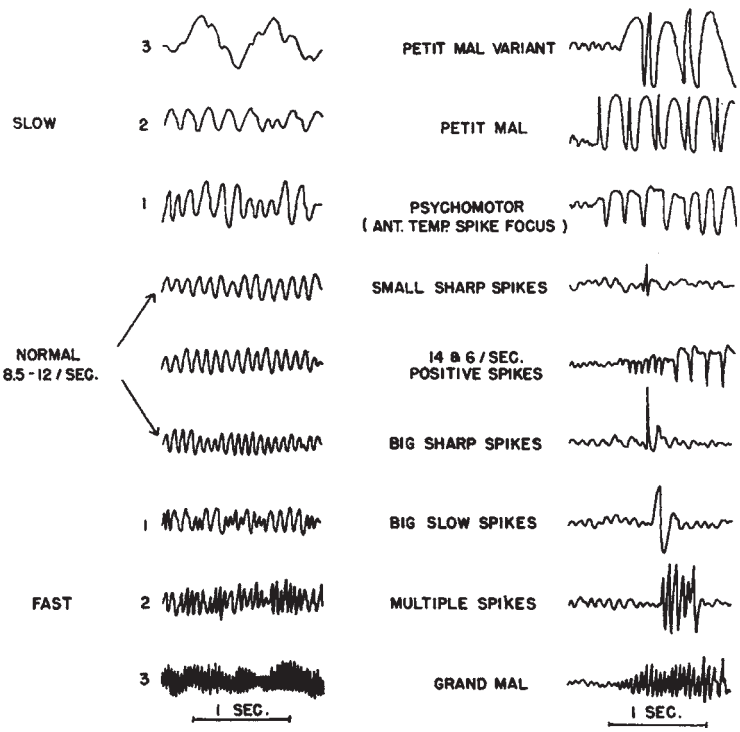
There continued to be limited interest in basic science at the international congresses over the next several decades, however, perhaps due to the appearance of a number of other national and international organisations that were more concerned with fundamental neurobiology.



An illustration by Frederic G. Gibbs, Hallowell Davis and William G. Lennox of the EEG in petit mal epilepsy.

EEG societies and the EEG journal

Major advances in the field of neuroscience developed in the mid-20th century as a result of the growth of neurophysiology, including the development of electroencephalography (EEG), the creation in 1947 of the International Federation of EEG Societies, the *EEG Journal* and the American EEG Society (Cobb 1985). Herbert Jasper, the first president of the American EEG Society and the first editor of the *EEG Journal*, was himself engaged in basic research on epilepsy, and, for many, the use of the term 'EEG' was not meant to refer to a narrow clinical discipline,



Gibbs's presentation of types of normal and abnormal EEGs. (Courtesy New York Academy of Medicine)

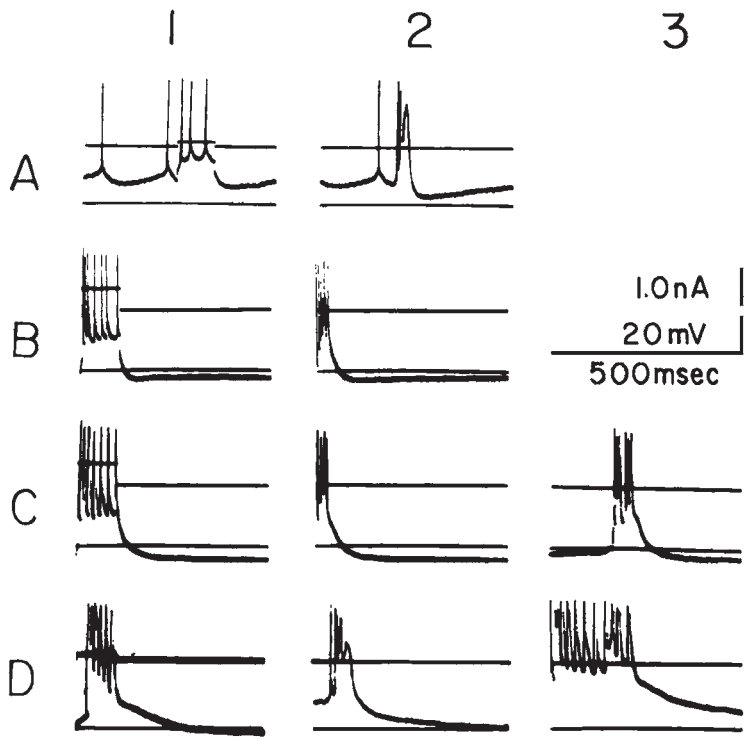
but, rather, to symbolise the entire field of basic neuroscience at the time. The annual meeting of the American EEG Society soon became the primary venue for the presentation of basic research papers on epilepsy. Similarly, much of the seminal basic research was published in the *EEG Journal*, rather than *Epilepsia*.

International Brain Research Organisation

At an International Federation meeting in Moscow in 1958, delegates voiced the need for an international society for basic neuroscience research and, in 1960, the International Brain Research Organization was founded under the aegis of the United Nations Educational, Scientific and Cultural Organization (UNESCO), and the Council for International Organizations of Medical Sciences (Jasper 1991). As this organisation met only every 4 years, the most important basic research papers were still presented at the annual meeting of the American EEG Society until the Society for Neuroscience was founded in 1970. The annual meeting of this society then became the preferred venue for presenting papers on basic neuroscience research of all types, including seizures and epilepsy.

American Epilepsy Society

The American Epilepsy Society (AES) was founded as a chapter of ILAE in 1936 and, like its parent organisation, was a clinical association (Goodkin 2007). Although a few PhDs had been presidents of the AES early on, they were not basic scientists, but clinical neurophysiologists, as EEG practitioners at that time were PhDs as well as MDs. The first basic scientists elected to the presidency of AES were David Prince in 1974 and Dominic Purpura in 1977, both of whom were MDs whose major contributions to the field were in areas of fundamental neuroscience. The AES, however, did not begin to attract significant numbers of basic scientists to its meetings until a concerted effort was made, beginning in 1983, to add basic neuroscience topics as a major part of the annual meeting. This occurred at a time when the Society for Neuroscience had grown so large that many basic



From a 1979 scientific paper by Philip Schwartzkroin and Timothy Pedley, both future editors-in-chief of *Epilepsia*.

scientists working in the field of epilepsy felt that their contributions might be more productively presented at a meeting where epilepsy was the primary interest. A large number of basic scientists were invited, by the then-vice president, Jerome (Pete) Engel, Jr., to the 1983 annual meeting of AES at the Roosevelt Hotel in New York. They were brought together to discuss whether they might be interested in joining the AES and becoming an active voice in the Society's future direction. One skeptic raised his hand and commented, 'Come on, Pete, you can't tell us that somebody like Phil Schwartzkroin could ever become president of the American Epilepsy Society.' Phil Schwartzkroin became the first PhD basic scientist president of AES in 1996.

With the broadening of the AES membership to include a large number of basic neuroscientists working in the field of epilepsy, the AES annual meeting rapidly became the premier venue for presenting and discussing advances in the understanding of the fundamental mechanisms of epilepsy, and this remains true at the time of this writing. Within several years, a major proportion of papers published in *Epilepsia* were devoted to basic research.

Commission on Neurobiology and Workshops on Neurobiology of Epilepsy

Despite the significant role that *Epilepsia* began to have in the publication of basic research on epilepsy, representation of basic scientists at the International Epilepsy Congresses of the ILAE remained quite small until the creation of the Commission on Neurobiology in 1988, and the organisation of the Workshops on Neurobiology of Epilepsy (WONOEP) as an official ILAE event.

WONOEP grew out of the Workshop on Neurotransmitters in Epilepsy (WONIEP), which was first held in Paris in 1981 under the leadership of Paolo Morselli and Kenneth Lloyd of France. This workshop was organised by Synthélabo, a French pharmaceutical firm that was developing an antiepileptic GABAergic drug called Progabide. The meeting was organised specifically to discuss the role of GABA in epilepsy. A decision was taken at the end of this meeting to broaden the theme to include other neurotransmitters, and Ruggero Fariello of the United States arranged WONIEP II in San Antonio, Texas, in 1983, which included papers on catecholamines, opioids, excitatory amino acids and neuropeptides, in addition to GABA. At WONIEP III, organised in Soverato, Italy, by Nistico of Italy, Morselli, Lloyd, Fariello and Jerome Engel of the United States, it became apparent that GABA had certain proconvulsant, as well as anticonvulsant, properties, and that simple GABAergic drugs may not be as effective in suppressing seizures clinically as drugs that work on other neurotransmitter systems. At about the same time, clinical trials of Progabide were beginning to demonstrate that this was not as useful a drug as had been hoped. As a result, Synthélabo's support for WONIEP IV was dropped; however, participants in the previous workshops strongly believed in their value and decided to seek other funding. Fariello and Giuliano Avanzini of Italy, in particular, were instrumental in obtaining sufficient financial support from several independent sources to hold WONIEP IV in Stresa, Italy, which was put together by Fariello, Avanzini, Engel and Uwe Heinemann of Germany (Avanzini *et al.* 1992). It was decided at that time to request that the ILAE create a Commission on Neurobiology, not only to continue the workshops under ILAE aegis, using the new title of Workshop on Neurobiology of Epilepsy (WONOEP), but also to organise scientific sessions and courses on basic research at the international meetings. Engel was the first chair of the Commission on Neurobiology, and the membership consisted of Avanzini, Esper Cavalheiro (Brazil), Fariello, Heinemann, Brian Meldrum (UK), Agnete Mouritzen-Dam (Denmark), R.A. Voskuyl (Netherlands), Claude Wasterlain (United States) and Wilkie Wilson (United States). Subsequent chairs and committee members are listed in Table 1.

The first WONOEP was held in 1991 in Salvador, Brazil, immediately preceding the 19th International Epilepsy Congress in Rio de Janiero, under the leadership of Engel, Cavalheiro, Wasterlain, Heinemann and Avanzini (Engel *et al.* 1992). There have now been a total of nine WONOEPs preceding international congresses, each dealing with important areas of basic research in epilepsy (Table 2), and each resulting in a published monograph (Table 3). These originally appeared as supplements to, or special issues of, *Epilepsy Research* but since 1999 have been supplements to *Epilepsia* (Berkovic *et al.* 1996; Heinemann *et al.* 1996; Schwartzkroin *et al.* 1998; Moshé *et al.* 2000; Wasterlain and Cavalheiro 2002; Bernard and Spreafico 2005). The WONOEP structure was the same as that for WONIEP, a closed 3-day meetings with 40–50 participants, each of whom gave a brief

Table 1 ILAE Commission on Neurobiology of Epilepsy.

1988–1993	
Chair:	Jerome (Pete) Engel, Jr. (United States)
Members:	Giuliano Avanzini (Italy)
	Esper Cavalheiro (Brazil)
	Ruggero Fariello (Italy)
	Uwe Heinemann (Germany)
	Brian Meldrum (United Kingdom)
	Agnete Mouritzen-Dam (Denmark)
	R.A. Voskuyl (Netherlands)
	Claude Wasterlain (United States)
	Wilkie Wilson (United States)
1993–1997	
Chair:	Giuliano Avanzini (Italy)
Members:	Yezekiel Ben-Ari (Israel)
	Esper Cavalheiro (Brazil)
	Jerome Engel, Jr. (United States)
	Ruggero Fariello (Italy)
	Uwe Heinemann (Germany)
	Christian Marescaux (France)
	Agnete Mouritzen-Dam (Denmark)
	Brian Meldrum (United Kingdom)
	Solomon (Nico) Moshé (United States)
	Mitsumoto Sato (Japan)
1997–2001	
Chair:	Philip Schwartzkroin (United States)
Members:	Esper Cavalheiro (Brazil)
	Michael Gutnick (Israel)
	Uwe Heinemann (Germany)
	John Jeffreys (United Kingdom)
	Pavel Mares (Czech Republic)
	Dan McIntyre (Canada)
	Brian Meldrum (United Kingdom)
	Solomon Moshé (United States)
	Astrid Nehlig (France)
	Asla Pitkänen (Finland)
	Luisa Rocha (Mexico)
	Jiro Suzuki (Japan)
	Annamaria Vezzani (Italy)
	Claude Wasterlain (United States)
2001–2005	
Chair:	Esper Cavalheiro (Brazil)
Co-Chair:	Asla Pitkänen (Finland)
Members:	Massimo Avoli (Italy)
	Christophe Bernard (France)
	Jerome Engel, Jr. (United States)
	Michael Gutnick (Israel)
	Uwe Heinemann (Germany)
	John Jeffreys (United Kingdom)
	Pavel Mares (Czech Republic)
	Dan McIntyre (Canada)
	Brian Meldrum (United Kingdom)
	Yoshiya Murashima (Japan)
	Solomon Moshé (United States)
	Astrid Nehlig (France)
	Luisa Rocha (Mexico)
	Phillip Schwartzkroin (United States)
	Roberto Spreafico (Italy)
	Annamaria Vezzani (Italy)
	Claude Wasterlain (United States)
2005–2009	
Chair:	Annamaria Vezzani (Italy)
Secretary:	Edward Bertram (United States)
Treasurer:	Christophe Bernard (France)
Members:	Heinz Beck (Germany)
	Marco de Curtis (Italy)
	Jerome Engel, Jr. (United States)
	Istvan Mody (United States)
	Yoshiya Murashima (Japan)
	Jeffrey Noebels (United States)
	Magda Logorhue Nunes (Brazil)
	Asla Pitkänen (Finland)
	Yoel Yaari (Israel)

presentation relevant to a central theme, with large blocs of time allocated for discussion and synthesis. Either the Commission on Neurobiology of Epilepsy or a subcommission selected participants based on competitive abstract submissions. On some occasions, there have been invited guest speakers and junior participants and, beginning in 2008, panel discussions as well as individual presentations were introduced. The purpose of these workshops has been to bring together international experts to discuss the latest advances in a particular area of research, suggest future directions and establish international collaborations.

With the creation of the Commission on Neurobiology, the International League made a commitment to ensure continued participation of basic scientists in the International Epilepsy Congress, and it was mandated

Table 2 Workshops on Neurobiology of Epilepsy (WONOEP) meetings.

Workshop	*Location*	*Organisers*	*Theme*
WONOEP 1 1991	Salvador, Brazil	Engel (US), Wasterlain (US), Cavalheiro (Brazil), Heinemann (Germany), Avanzini (Italy)	Molecular Neurobiology of Epilepsy
WONOEP II 1993	Tromso, Norway	Heinemann, Engel, Avanzini, Meldrum (UK), Mouritzen-Dam (Denmark), Wasterlain	Progressive Nature of Epileptogenesis
WONOEP III 1995	Kewarra Beach, Australia	Berkovic (Australia), Engel, Meldrum, Wasterlain	Mechanisms of Chronic Models of Epilepsy
WONOEP IV 1997	Adare, Ireland	Schwartzkroin (US), Avanzini, Cavalheiro, Engel, Heinemann, Meldrum, Moshé (US), Suzuki (Japan), Wasterlain	Parallel Studies of Epileptogenesis in Human Tissue and Animal Models
WONOEP V 1999	Cesky Krumlov, Czech Republic	Moshé, Engel, Mathern, Nehlig (France), Pitkänen (Finland), Vezzani (Italy)	Brain Plasticity and Epilepsy
WONOEP VI 2001	Iguacu Falls, Brazil	Wasterlain, Cavalheiro, Avanzini, Engel, Mares (Czech Republic), Meldrum, Moshé, Pitkänan, Schwartzkroin	Ictogenesis and Epileptogenesis
WONOEP VII 2003	Ericeira, Portugal	Bernard (France), Spreafico (Italy), Wheal (UK)	Developmental Programs in Epileptogenesis
WONOEP VIII 2005	Villiers-le-Mahieu, France	Bernard, Bertram (US)	Developmental Issues of Epilepsy
WONOEP IX 2007	Lang Kawi Island, Malaysia	De Curtis (Italy)	The Transition from the Interictal to the Ictal State

Table 3 Workshops on Neurobiology of Epilepsy (WONOEP) Publications.

Engel, J., Jr., C. Wasterlain, E. Cavalheiro, U. Heinemann, and G. Avanzini (eds.) (1992) Molecular Neurobiology of Epilepsy. *Epilepsy Research* (Suppl. 9). Elsevier: Amsterdam.

Heinemann, U., J. Engel, Jr., B.S. Meldrum, C. Wasterlain, G. Avanzini, and A. Mouritzen-Dam (eds.) (1996) *The Progressive Nature of Epilepsy. Epilepsy Research* (Suppl. 12). Elsevier: Amsterdam.

Berkovic, S., J. Engel, Jr., B.S. Meldrum, and C. Wasterlain (eds.) (1996) Third Workshop on the Neurobiology of Epilepsy (WONOEP III): Mechanisms of chronic models of epilepsy. *Epilepsy Research* 26:1–308.

Schwartzkroin, P.A., G. Avanzini, E.A. Cavalheiro, J. Engel, Jr., U. Heinemann, B.S. Meldrum, S.L. Moshé, J. Suzuki, and C.G. Wasterlain (eds.) (1998) Fourth Workshop on the Neurobiology of Epilepsy (WONOEP IV): Parallel studies of epileptogenesis in human tissue and animal models. *Epilepsy Research* 32:1–333.

Moshé, S.L., J. Engel, Jr., G.W. Mathern, A. Nehlig, A. Pitkänen and A. Vezzani (eds.) (2000) Fifth Workshop on the Neurobiology of Epilepsy (WONOEP V): Brain plasticity and epilepsy. *Epilepsia* 41:S1–S205.

Wasterlain, C.G., and E.A. Cavalheiro (eds.) (2002) Sixth Workshop on the Neurobiology of Epilepsy (WONOEP VI): Ictogenesis and epileptogenesis. *Epilepsia* 43(Suppl. 5).

Bernard, C., and R. Spreafico (eds.) (2005) Seventh Workshop on the Neurobiology of Epilepsy (WONOEP VII): Developmental programs in epileptogenesis. *Epilepsia* 46(Suppl. 5).

Bernard, C., and E.H. Bertram (eds.) (2007) Eighth Workshop on the Neurobiology of Epilepsy (WONOEP VIII): Developmental issues of epilepsy. *Epilepsia* 48 (Suppl. 5).

that either one of the official seven main themes at each congress be on basic research or that significant basic research be included among the presentations of each of the themes. Whereas basic research main themes were relatively infrequent before 1991, they have been a consistent feature of each subsequent congress (Table 4). Basic scientists are now an essential part of the International Epilepsy Congress and, in recent years, of the

Table 4 Basic research main themes at international congresses of the ILAE.

1973	13th ICE, Barcelona Neurophysiological bases of epilepsy: the epileptic neuron
1979	11th EIS, Florence Anatomo-electro-clinical correlations in human and experimental epilepsies Neurobiological basis of epilepsy
1983	15th EIS, Washington Neurotransmitters and peptides in epilepsy
1991	19th IEC, Rio de Janiero Basic mechanisms in behavioral and structural biology of the epilepsies
1993	20th IEC, Oslo Progressive nature of epilepsy: contributions of basic sciences
1995	21st IEC, Sydney Genetics and molecular biology of epilepsy
1997	22nd IEC, Dublin Structure and function of epileptogenesis
1999	23rd IEC, Prague Epilepsy and plasticity
2001	24th IEC, Buenos Aires Neurobiology of human epilepsy tissue and relevant animal models
2003	25th IEC, Lisbon Epilepsy research in the post genomic era: focus on the genetics of inhibition
2005	26th IEC, Paris Brain maturation and epileptogenesis
2007	27th IEC, Singapore Epileptogenesis in relation to genetic predisposition in abnormal brains

ICE, International Congress on Epilepsy; IEC, International Epilepsy Congress; EIS, Epilepsy International Symposium.

regional epilepsy congresses as well. Engel and Avanzini went on to become presidents of the ILAE in 1993–2001 and 2001–2005, further establishing the importance of basic research in the League's activities.

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Bartholow R. (1874) Experimental investigations into the functions of the human brain. *American Journal of Medical Science* 67:305–313.

Berkovic, S., J. Engel, Jr., B.S. Meldrum, and C. Wasterlain (eds.) (1996) Third Workshop on the Neurobiology of Epilepsy (WONOEP III). *Mechanisms of chronic models of epilepsy. Epilepsy Research (Special Issue)* 26:1–308.

Bernard, C., and R. Spreafico (eds.) (2005) Papers presented at the Seventh Workshop on the Neurobiology of Epilepsy (WONOEP VII). *Epilepsia* 46(Suppl. 5).

Bouché, G. (1914) Contribution experimentale à l'étude des convulsions toniques. *Epilepsia* 1:8–40.

Bravais, L.F. (1827) *Recherches sur les symptômes et le traitment de l'épilepsie hémiplégique.* Thése de Paris: Paris, No. 118.

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