CP Panayiotopoulos

A Clinical Guide to

Epileptic Syndromes and their Treatment

Revised Second Edition

Based on the ILAE classifications and practice parameter guidelines

Springer

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To my wife Thalia

because

she is a beautiful woman

my muse

the flower, the smile and the angel in my life

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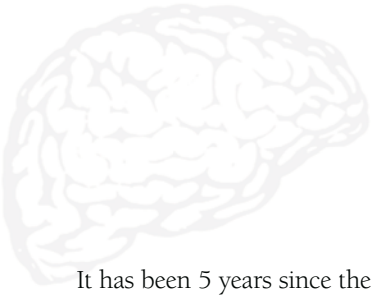

preface to the second edition

It has been 5 years since the first edition of this book was published. I have been encouraged to write a new edition by the success of the first, which sold over 10,000 copies and received excellent reviews. Even more rewarding than this has been the feedback from physicians who have been using the book in the environment for which it was written: the clinic. It is gratifying that patients and their families have also found it useful and recommend it in dedicated websites as a reliable source of information. A particularly reassuring aspect is that proposals made in the previous edition have been adopted by the ILAE Task Force in their latest report, published in 2006.

This second edition has been systematically updated to include the most recent advances in clinical epileptology. It has been written with the same principles and aims in mind as its predecessor and remains a relatively concise book, the main purpose of which is to promote proper diagnosis and appropriate management of epileptic seizures and syndromes. It is evidenced-based, achieved by integrating years of clinical experience with the best available external evidence from clinical research.

The opening chapters concentrate on the definitions and general aspects of epilepsies, describe epileptic seizures and status epilepticus, detail the imitators of epileptic seizures, provide advice on the optimal use of EEG and brain imaging in the diagnosis of epilepsies and offer insights into the principles of management. The subsequent chapters are devoted to the epileptic syndromes, which are organised according to age at onset and their main category in the ILAE classification. The presentation of each syndrome follows a common format: classification, demographic data, clinical manifestations, aetiology, diagnostic procedures, differential diagnosis, prognosis and management.

Following the advice and recommendations of reviewers and colleagues, I have included new chapters dedicated to the non-epileptic paroxysmal disorders that imitate epileptic seizures and the diseases frequently associated with epileptic seizures, in particular progressive myoclonic epilepsies. Some clinically useful sections from my previous, more specialist-orientated book, '*The Epilepsies: Seizures, Syndromes and Management*', have also been added and properly modified to suit the intended audience.

With regards to classification, particular emphasis has been given to the new ILAE report and I have provided further evidence-based proposals for consideration. The refreshing impact of Peter Wolf, President of the ILAE, Anne Berg, Chair of the ILAE Classification Committee, Phil Schwartzkroin and Simon Shorvon, Editors-in-Chief of *Epilepsia* is felt and appreciated.

The most difficult parts to prepare were the sections on anti-epileptic drugs. My recommendations are evidence-based, drawing on laborious and in-depth assessment of clinical trials, meta-analyses, formal guidelines and the best clinical evidence from eminent practising physicians. This approach has been verified because much of the advice offered in the previous edition has since been confirmed in subsequent controlled trials and in clinical practice. I am confident that my updated recommendations in this book will prove just as reliable and useful.

Realistically, I have to accept that there may be some unintentional errors and I regret any such instances. I would welcome these being brought to my attention along with any comments and suggestions for the improvement of future editions or reprints.

Finally, new practices are emerging that allow for the proper diagnosis and treatment of patients with epileptic seizures. As in all other areas of medicine, diagnostic precision is a prerequisite for meaningful management in the epilepsies, and I wish that this text will help advance and disseminate this knowledge.

C P Panayiotopoulos MD PhD FRCP

London, 28th June 2007

preface to the revised second edition

It is rewarding that the second edition of A Clinical Guide to Epileptic Syndromes and their Treatment published in 2007 appears to be fulfilling its purpose as a concise book promoting the accurate diagnosis and appropriate management of epilepsies. Like its predecessor, it has received excellent reviews and has been widely used and cited by readers, including seasoned and novice physicians, and other healthcare professionals, as well as patients and their families.

With the first print run now sold out, I felt that the time was ripe to revise rather than to reprint the second edition. This is mandated by the need to update with information on emerging therapies, important recent publications and new guidelines and ILAE proposals.

This book is mainly based on the ILAE classifications and practice parameter guidelines. A new ILAE report on classification and terminology that is currently under consultation is an important document for consideration and reflection as it contains the thoughts of the leading authorities in the epilepsies. Regarding practice parameters, the American Academy of Neurology and the American Epilepsy Society have published a three part evidence-based review focusing on pregnancy in women with epilepsy. These new proposals and guidelines are discussed extensively in this revision.

The sections concerning therapy have been expanded to include newly licensed AEDs, new indications for previously approved drugs and adverse reactions that have emerged since the first publication. Again, the recommendations made aim to be of practical use and to follow as truly as possible the principles of evidence-based medicine. New sections have been added on the principles of pharmacological management in women and the elderly, and on psychological, behavioural and cardiac adverse effects of AEDs. The recent ILAE position paper on therapeutic drug monitoring is also extensively covered.

This revision has also been updated to include significant advances, reports, reviews and debates; new citations up to a few weeks before publication have been added.

The goal of this book, as with all previous editions, is to encourage the accurate syndromic diagnosis of the epilepsies. To some extent this has now been achieved, as all current formal recommendations and guidelines make clear that a syndromic diagnosis is a prerequisite for appropriate management and good clinical practice. However, there are still uncertainties over the precise features and boundaries for each epileptic syndrome and a lack of terminological precision, which this revised edition addresses. Overall, this book remains a guide for practising physicians on how best to diagnose the epileptic syndromes and achieve optimal management.

C P Panayiotopoulos MD PhD FRCP

London, 2nd December 2009

abbreviations

AAN-AES	American Academy of Neurology–American Epilepsy Society
ACTH	adrenocorticotrophic hormone
ADCME	autosomal dominant cortical tremor, myoclonus and epilepsy
ADNFLE	autosomal dominant nocturnal frontal lobe epilepsy
ADR	adverse drug reaction
AED	anti-epileptic drug
AHS	anticonvulsant hypersensitivity syndrome
APEC	atypical benign partial epilepsy of childhood
BCECTS	benign childhood epilepsy with centrotemporal spike
BCSSS	benign childhood seizure susceptibility syndrome
BOLD	blood oxygen level dependent
CAE	childhood absence epilepsy
cAMP	cyclic adenosine monophosphate
CI	confidence interval
CNS	central nervous system
CONSERT	Consolidated Standards for Reporting of Trials
CRMP	collapsin response mediator protein
CSE	convulsive status epilepticus
CSF	cerebrospinal fluid
CSTB	cystatin B
CSWS	continuous spike-and-wave during sleep
CT	computed tomography
CTS	centrotemporal spike
CVS	cyclic vomiting syndrome
CYP	cytochrome P450
DMS	*Diagnostic and Statistical Manual of Mental Disorders*
DRPLA	dentatorubral-pallidoluysian atrophy
EBM	evidence-based medicine
ECG	electocardiogram
EEG	electroencephalogram
EFS+	epilepsy with febrile seizures plus
EGTCSA	epilepsy with GTCS on awakening
EM-AS	epilepsy with myoclonic–astatic seizure
eMC	electronic Medicines Compendium
EMEA	European Medicines Agency
EMG	electromyography
EPC	epilepsia partialis continua
ERG	electroretinogram
ESES	extreme somatosensory evoked spike
EURAP	European and International Registry of Antiepileptic Drugs in Pregnancy
EUROCAT	European Surveillance of Congenital Anomalies
FDA	US Food & Drug Administration
FDG	[^{18}F]fluorodeoxyglucose
FLAIR	fluid-attenuated inversion recovery
FLTLE	familial lateral temporal lobe epilepsy
fMRI	functional magnetic resonance imaging
FMTLE	familial mesial temporal lobe epilepsy
FMZ	[^{11}C]flumazenil
FOS	fixation-off sensitivity
FS+	febrile seizures plus
GABA	Gamma-aminobutyric acid
GABA-T	GABA-transaminase
GEFS+	generalised epilepsy with febrile seizures plus
GEPR	genetically epilepsy-prone rat
GnRH	gonadotrophin-releasing hormone
GPSWD	generalised polyspike–wave discharge
GSWD	generalised spike–wave discharges
GTCS	generalised tonic–clonic seizure
GTC-SE	generalised tonic–clonic status epilepticus
HLA	human leukocyte antigen
HR	hazard ratio
IBE	International Bureau of Epilepsy
ICOE-G	idiopathic childhood occipital epilepsy of Gastaut
IGE	idiopathic generalised epilepsy

IL	interleukin
ILAE	International League Against Epilepsy
IM	intramuscular
IPOE	idiopathic photosensitive occipital lobe epilepsy
IPS	intermittent photic stimulation
IQ	intelligence quotient
IV	intravenous
JAE	juvenile absence epilepsy
JME	juvenile myoclonic epilepsy
LGI	leucine-rich, glioma-inactivated
LKS	Landau–Kleffner syndrome
LTLE	lateral temporal lobe epilepsy MAE epilepsy with myoclonic absences
MCM	major congenital malformation
MDVU	Movement Disorders Virtual University
MEG	magnetoencephalography
MEI	myoclonic epilepsy in infancy
MELAS	mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes
MERRF	myoclonus epilepsy with ragged-red fibers
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
MSA	multiple source analysis
MSI	magnetic source imaging
MSLT	multiple sleep latency test
mtDNA	mitochondrial DNA
MTLE	mesial temporal lobe epilepsy
MTLE-HS	mesial temporal lobe epilepsy with hippocampal sclerosis
nAChR	neuronal nicotinic acetylcholine receptor
NCL	neuronal ceroid lipofuscinosis
NEPE	non-epileptic paroxysmal event
NMDA	*N*-methyl D-aspartate
NREM	non-rapid eye movement
OPS	occipital seizures precipitated by photic stimuli
PAS	periodic acid–Schiff
PCR	polymerase chain reaction
PEHO	progressive encephalopathy with edema, hypsarrhythmia and optic atrophy
PET	positron emission tomography
PGTCS	primarily generalised tonic–clonic seizure
PI	package insert
PIL	patient information leaflet
PLED	pseudoperiodic lateralised epileptiform discharge
PMA	perioral myoclonia with absences
PME	progressive myoclonic epilepsy
PNEPE	psychogenic non-epileptic paroxysmal event
PPR	photoparoxysmal response
PPT	palmitoyl-protein thioesterase
PS	Panayiotopoulos syndrome
RBD	REM sleep behaviour disorder
RCT	randomised controlled trial
REM	rapid eye movement
SE	status epilepticus
SGTCS	secondarily generalised tonic–clonic seizure
SMA	supplementary motor area
SmPC	Summary of Product Characteristics
SMR	standardised mortality ratio
SPECT	single photon emission computed tomography
SSEP	somatosensory evoked potential
SUDEP	sudden unexpected death in epilepsy
SV2A	synaptic vesicle protein 2A
SWI	spike–wave index
TAS	typical absence seizures
TDM	therapeutic drug monitoring
TLE	temporal lobe epilepsy
TPP	tripeptidyl-peptidase
UGT	uridine diphosphate glucuronosyltransferase
VDU	visual display unit
VEP	visual evoked potential
VER	visual evoked response
VGSC	voltage gated sodium channel
VNS	vagus nerve stimulation
WEMOVE	Worldwide Education and Awareness for Movement Disorders
WHO	World Health Organisation

one

General aspects of epilepsies

Epileptic seizures and epileptic syndromes have high prevalence and incidence rates affecting all ages and all races of both sexes. They constitute an important part of the everyday clinical practice of general and specialist health care professionals.

Patients with epileptic seizures and their families are entitled to diagnosis, prognosis and management that are specific and precise.

Medical diagnosis is the identification of a disease by investigation of its symptoms and history, which provides a solid basis for the treatment and prognosis of the individual patient.

Accurate diagnosis is the golden rule in medicine and epilepsies should not be an exception to this. Current practice that limits the diagnosis to 'epilepsy' or 'seizures' is unsatisfactory to the patient and physician alike, and may result in avoidable morbidity and mortality. Such a non-specific diagnostic label fails to provide guidance on important items such as severity of disease, prognosis, short- and long-term therapeutic decisions, and genetics (research and counselling), which are all factors that crucially affect personal, family and social life, education and career choices of patients.

'Epilepsy' is not a single disease entity. Epilepsies are many syndromes and diseases that have a multitude of different manifestations and causes. Epileptic syndromes and diseases are now largely well defined and easy to diagnose. Defining the type of epilepsy should be considered mandatory because it offers the best guide to both management and prognosis. The short- and long-term management of epilepsies is syndrome related and differs markedly between the various syndromes, thereby emphasising the need for accurate diagnosis. The benefits of syndromic diagnosis over seizure/symptom diagnosis, or an inclusive diagnosis such as 'epilepsy', far outweigh any morbidity from miscategorisation that may arise in difficult cases.

Unspecified diagnosis in epilepsies commonly results in avoidable morbidity and sometimes mortality.

Important reminder

Traditional medical teaching and attitudes to the diagnosis and management of epilepsies often differ from those applied in other medical conditions. This should be corrected.

Physicians who rightly seek bedside confirmation of muscle fatigability in a patient with a clear-cut history of myasthenia gravis, should also request to view the seizures, which if frequent can be easily captured even by mobile phones.

Physicians who rightly emphasise the differential diagnosis between spinal muscular atrophies and limb girdle muscular dystrophy should give the same emphasis to the differentiation between absence seizures of idiopathic generalised epilepsies and complex focal seizures.

Major paediatric journals that often emphasise a rare disease should at least give the same space to highlighting the fact that childhood autonomic status epilepticus is a common and costly cause of misdiagnosis and mismanagement, adversely affecting thousands of children around the world (see page 81).

What is epilepsy? Definitions

The definition of epilepsies should be simple, brief, precise and unambiguous. However, this is not the case and there is no consensus.

The newly proposed ILAE definition is:

> Epilepsy is a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological and social consequences of this condition.[1]

This definition of epilepsy 'requires the occurrence of at least one epileptic seizure' with the pre-condition that this is 'in association with an enduring disturbance of the brain capable of giving rise to other seizures'.[1] It would not require 'at least two seizures' or that the seizure be 'unprovoked', which were prerequisites of previous definitions of epilepsy.

> The central concept in [this] definition is an enduring alteration in the brain that increases the likelihood of future seizures… A single epileptic seizure due to an enduring epileptogenic abnormality that increases the likelihood of future seizures would indicate epilepsy, and a single epileptic seizure in a normal brain would not.[1]

This definition also proposes that part of the epileptic condition can involve behavioural disturbances, psychological consequences for the patient and for the family, and social stigma, exclusion, restrictions, overprotection and isolation.

Comment on the new ILAE definition

This proposal has been rightly criticised by eminent epileptologists[2] with whom I share the following concerns.

First: What is 'enduring' and how long does this last? This word 'enduring' has created the same questions and problems when used in the definition of status epilepticus. Enduring (adj.) = lasting, continuing, durable, unceasing, abiding, imperishable; permanent, continuing or enduring without marked change in status or condition or place.

Second: Most patients do not have at least one of the preconditions 'cognitive, psychological and social consequences' attached to epilepsy.

Third: Why is the singular 'epilepsy' preferred to the plural 'epilepsies'? This contradicts the facts and I quote from the same report 'Epilepsy is not one condition, but is a diverse family of disorders, having in common an abnormally increased predisposition to seizures… Some writers prefer the plural term, "the epilepsies," but we will use the singular phrase while recognizing this diversity'.[1]

Certainly, there must be a better definition of what epilepsies are. The following would be my proposal:

> Epilepsies are disorders of the brain with a clinically manifested liability to epileptic seizures.

Other formal definitions of epilepsy

Epileptic disorder: A chronic neurological condition characterised by recurrent epileptic seizures.[3]

Epilepsies: Those conditions involving chronic recurrent epileptic seizures that can be considered to be epileptic disorders.[3]

Epilepsy: A condition characterised by recurrent (two or more) epileptic seizures, unprovoked by any immediate identified cause (operational definition for epidemiological purposes).[4,5] Multiple seizures occurring in a 24-h period are considered as a single event. An episode of status epilepticus is considered to be a single event. People who have had only febrile seizures or only neonatal seizures, as herein defined, are excluded from this category.[4,5] *Author's note:* in this definition the type of 'epileptic seizures' is not defined, but this probably refers to generalised tonic–clonic seizures (GTCSs).

'Active' epilepsy: A prevalent case of active epilepsy is defined as a person with epilepsy who has had at

least one epileptic seizure in the previous 5 years, regardless of anti-epileptic drug (AED) treatment. A case under treatment is someone with the correct diagnosis of epilepsy receiving (or having received) AEDs on prevalence day.[4,5]

Epilepsy in remission with treatment: A prevalent case of epilepsy with no seizures for ⩾5 years and receiving AED treatment at the time of ascertainment.[4,5]

Epilepsy in remission without treatment: A prevalent case of epilepsy with no seizures for ⩾5 years and not receiving AED treatment at the time of ascertainment.[4,5]

Making the correct diagnosis in epilepsies

The assessment of a patient referred for epileptic seizures should follow the same approach as any other disorder:

- medical history
- physical examination (and developmental assessment in children)
- presumptive diagnosis
- differential diagnosis
- comprehensive investigative procedures
- final diagnosis (which could be definite, probable, possible or undiagnosed)
- management (including that of the family).

Medical history

The diagnosis of epileptic or non-epileptic seizures is almost always based solely on the clinical history, which should be obtained in an expert way, often requiring lengthy interrogation(s) of the patient and witnesses. Children also (if verbal) have a surprising insight into their illnesses. In certain cultures children are often left outside the consultation process by overprotective parents, and this should be approached with sensitivity.

Inadequate history is the most common reason for misdiagnosis.

In taking the medical history, every piece of information should be patiently gathered in order to synthesise the whole pattern of these transient events from the time that they started to their end, and up to normality. The medical history should include:

- details of the paroxysmal events (not only the most dramatic ones) as they have been experienced by the patient and witnesses
- the circumstances under which the paroxysmal events occurred
- timing and circadian distribution
- position (standing, sitting or lying)
- leisure or occupation (at rest or during exercise)
- possible triggering, precipitating or facilitating factors
- personal and family medical history.

Circadian distribution (on awakening, nocturnal and diurnal) and precipitating factors (flickering lights, sleep deprivation, alcohol indulgence, stress and reading) often provide invaluable clues for the correct diagnosis and may also prompt the appropriate EEG procedure.

Useful clinical note

The presence or absence of a single symptom is not sufficiently diagnostic of a particular disease and may be misleading.

The clinical diagnosis is often easy and secured only if individual elements of clinical events are meaningfully synthesised with regard to quantity, quality, location, onset, chronological sequence, development, speed of progress and duration.

Lengthy medical interviews may seem to be 'luxury' medicine, but this is by far outweighed by the benefits to patients, their families and their physicians. Constraints on the physicians' time should not be an excuse for allowing misdiagnosis and mismanagement to occur. With experience the time taken for an appropriate medical history is significantly shortened. Personally, I devote more time to eliciting the events preceding a GTCS than detailing what happened during the convulsive phase (if I am satisfied that this was a genuine GTCS), and directing the witnesses to portray what they saw rather than allocating time to endless descriptions of how they felt and what they did (although I fully respect this).

A second interview frequently provides more observations and recollections after learning what is desired during the initial consultation.

Useful recommended practice

Asking the patient/guardian to complete a purposely designed questionnaire, which should be made available prior to consultation, has many advantages:

- it provides the patient/guardian with an understanding of the type of information needed and allows them time to collect such information
- written information is often more reliable than verbal communication during a time-limited and often emotionally loaded interview
- it provides the physician with a good insight of the case prior to the consultation.

'That's it!' phenomenon[6]

It is often necessary for the physician to imitate and demonstrate physically or, when in doubt, show video-taped examples of different epileptic or non-epileptic seizures to patients and witnesses. 'That's it' is their common reaction for the presentation that closely resembles the events under investigation.

Home-made video recordings

Sometimes the diagnosis is easy, based on clinical history alone. Home-made video recording should be routinely requested if diagnosis is uncertain. Videotaping the clinical events is the only practical means of demonstrating and objectively documenting the symptoms of paroxysmal disorders. Genuine epileptic seizures or non-epileptic paroxysmal events (NEPEs) are often frequent and sometimes predictable. They can be recorded by relatives or friends and sometimes by the patients themselves. Today this is easier with the availability of digital recording and mobile phones.

Laboratory diagnostic procedures

Laboratory procedures (blood and urine tests, ECG, EEG, brain imaging and others such as metabolic or toxicology screening, CSF analysis, molecular genetic testing) should be appropriately prioritised and tailored to the particular clinical problem and individual patient. The aim is to obtain supplementary evidence of the clinical suspicion, which may provide definite diagnosis of a specific disorder. Investigative procedures are more demanding in children than in adults, or in those in whom seizures are the presenting symptom of a disease than in those where the underlying disease has already been established.

The EEG, the most significant investigative procedure in the diagnosis of epilepsies, is often misunderstood, undermined and misused. Brain imaging, another top diagnostic procedure, provides *in vivo* visualisation of structural causes of epilepsy such as hippocampal sclerosis, malformations of brain development and tumours, as well as other brain diseases.

Blood, urine and sometimes CSF studies have an important role in the evaluation of the child with epilepsy.[7]

Genetic testing has become available for a growing number of hereditary disorders associated with epileptic seizures (see Chapters 14 and 17).

The significance and the role of the EEG and brain imaging in the diagnosis and management of epilepsies is outlined in Chapter 6. Other laboratory procedures are discussed when appropriate in the relevant chapters.

Differential diagnosis

Misdiagnosis in epilepsies, when considering their dimensions and consequences, is a colossal and costly medical problem. Common disorders and even normal phenomena may imitate epileptic seizures and, conversely, certain types of epileptic seizures may imitate symptoms of other diseases. Misdiagnosis has serious repercussions. Patients with non-epileptic disorders incorrectly diagnosed as having epileptic seizures are likely to be mistreated with AEDs and also denied specific and possibly life-saving treatment (Figure 1.1). Similarly, patients with epileptic seizures erroneously diagnosed as migraine, encephalitis or other NEPEs are likely to be mismanaged with inappropriate treatments and also deprived of specific therapies (Figure 1.2).

It should also be emphasised that serious and adverse consequences to patient management often arise from misdiagnosing one type of epileptic seizure for another, or one type of epileptic syndrome for another.

There are three important steps to take in order to make a correct specific diagnosis, which will determine prognosis and management:

1. *First step:* are the paroxysmal events epileptic seizures?
2. *Second step:* what type of epileptic seizures?
3. *Third step:* what is their cause and what is the epileptic syndrome or disease?

First step: Are the paroxysmal events epileptic seizures?

The first step towards the correct diagnosis of epilepsies is to establish whether a paroxysmal clinical event was actually an epileptic seizure or a non-epileptic paroxysmal event (NEPE). The differential diagnosis includes all causes of episodic impairment of awareness, aberrations of mental function, falls, sensory/motor phenomena and generalised convulsive movements, which are common presenting symptoms of epileptic seizures. This is often easy for physicians adequately trained in the recognition of the various forms of epileptic seizures, who are able to obtain a clear history of the events from the patient and witnesses. However, even the most experienced epileptologists repeatedly have great difficulties in reaching an unequivocal diagnosis for reasons such as atypical seizure presentations, inadequate historical data or overlapping symptom manifestations.

The differentiation between seizures and other causes of transient neurological disturbance and collapse is epitomised by the familiar theme 'fits, faints and funny turns'.[6,8] Distinguishing epileptic (*fits*) from paroxysmal symptoms of non-epileptic disorders, particularly syncopal (*faints*) or psychogenic attacks (*funny turns*), should be a core skill of all trained physicians as detailed in any medical textbook. However, this is often simplistic and frequently perpetuates certain myths such as that urinary incontinence or postsyncopal confusion are rare in syncopes (Figure 1.1) or tongue biting and injuries are exceptional features in psychogenic non-epileptic seizures, as further detailed in Chapter 4.

NEPEs that have been misdiagnosed as epileptic seizures affect as many as 20–30% of patients diagnosed with epilepsy; these patients have often received treatment for epilepsy for many years or have been admitted to tertiary care epilepsy units.[9–11] The problem is complicated by the fact that approximately 30% of patients with genuine epileptic seizures also suffer from non-epileptic, mainly psychogenic seizures. In one study, the mean time lapse between the first attack and the correct diagnosis of non-epileptic seizures was over 9 years.[12] In financial terms the annual cost of such a misdiagnosis was estimated at US$4 billion.[13]

NEPEs[14–16] are common and are numerous episodic clinical manifestations of diverse aetiologies that mimic or look like, but are not, epileptic seizures. These imitators of epileptic seizures are detailed in Chapter 4.

Epileptic seizures imitating non-epileptic attacks

Epileptic seizures may imitate syncope, psychogenic attacks, migraine, sleep disorders or sinister acute brain insults. Their diagnosis is also demanding, as documented by the fact that, until recently:

Man aged 34 with video-EEG/ECG-documented potentially life-threatening cardiogenic syncopes imitating epileptic convulsive seizures

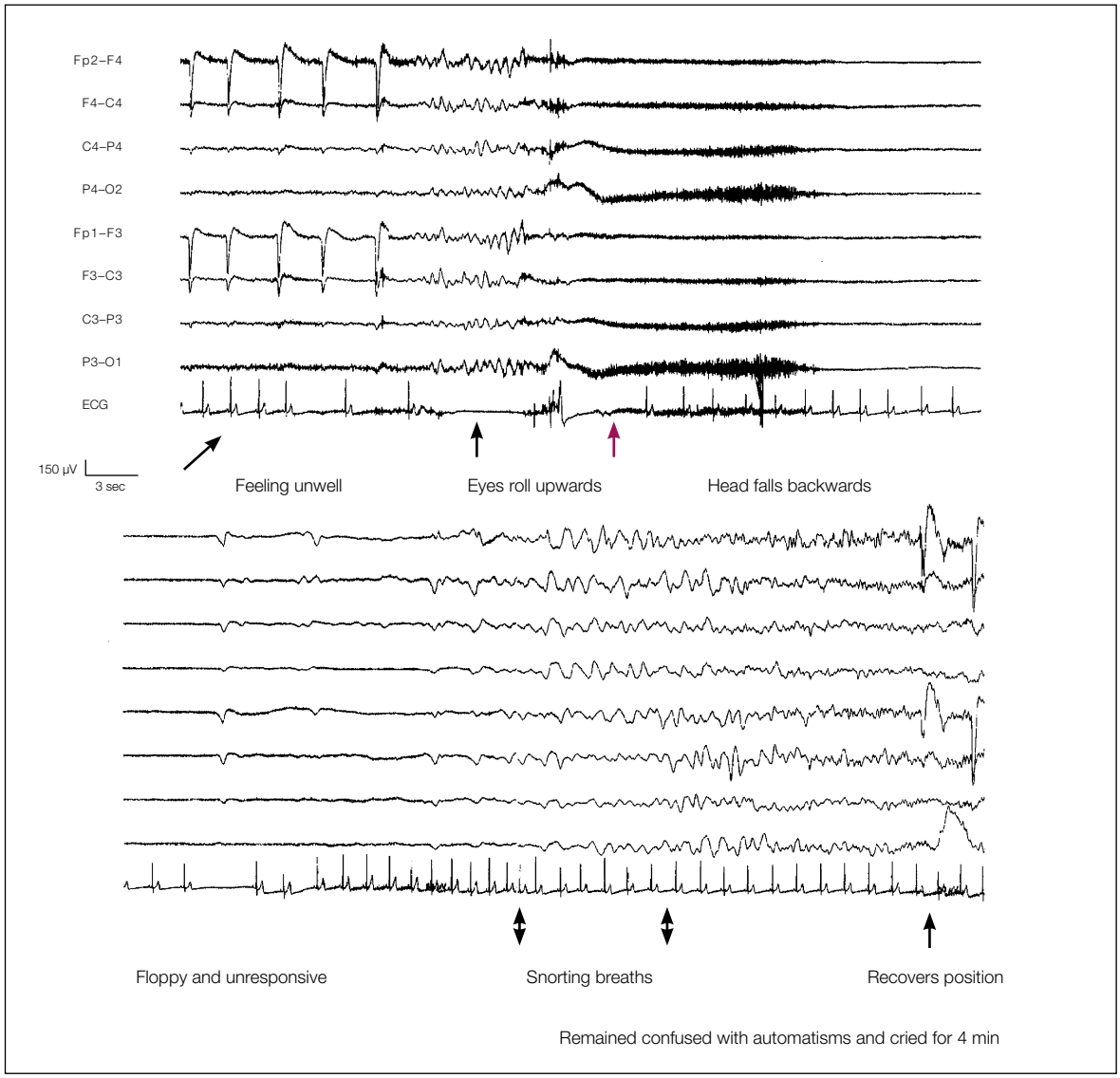

Figure 1.1 A 34-year-old man was referred for routine EEG because of 'two episodes of GTCSs in the last 2 months. The first occurred on his way home after work. He does not recall events until waking in the ambulance with the paramedics telling him that he had a seizure. He had no memory of the preceding 20 minutes. He did bite his tongue but there was no incontinence… This is likely to be generalised epilepsy… Treatment with valproate was initiated'. In accordance with our policy this was a video-EEG (page 155). A few minutes after the start of the recording he developed sinus bradycardia and then ventricular standstill for 9 s with one escape ectopic beat as documented with ECG (bottom trace). Clinically, at the oblique arrow the technician asked him if he felt okay and he said no. At the first vertical black arrow his eyes rolled slowly upwards to the extreme. At the red arrow, his head dropped backwards and he became flaccid and unresponsive. Some recovery started at the double-headed arrows when he took two snorting breaths. At the second black arrow, he resumed his position as before the syncope. Afterwards he was confused, he could not answer questions and, when asked again what happened to him, he was distressed and cried. He did not come back to normal until after more than 4 min from the start of the syncope. A cardiac pacemaker has been implanted and the patient remained well in the next 6 months of follow-up.

Cardiac asystole as an ictal symptom of right-sided temporal lobe seizures

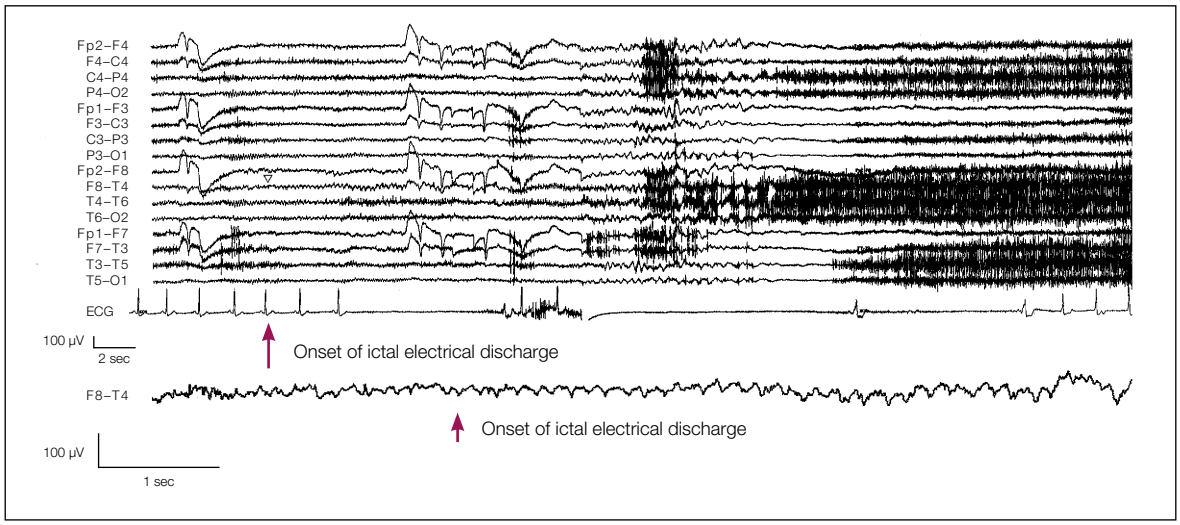

Figure 1.2 One day prior to this video-EEG a 60-year-old man said he felt unwell, went for a walk, but half an hour later became confused with repetitive questioning about his orientation and when the next meeting was to take place. On examination he was globally amnesic with a period of retrograde amnesia for about 1 month, which gradually shortened as he recovered after about 2 to 3 hours. His past medical history at that stage was thought to be unremarkable. He was known to have high cholesterol. There was a strong family history of early ischaemic heart disease. Physical and thorough neurological and cardiological examinations were normal. All relevant blood tests, ECG and brain MRI were normal. It was the video-EEG that established the diagnosis. He had three focal epileptic seizures with onset from the right temporal areas. The most severe one started with a rising epigastric sensation, which he retrospectively recalled as the same feeling that he had experienced the previous day. This led to almost immediate complete cardiac asystole for 26 s. During this seizure he became pale, lost consciousness and had a number of myoclonic jerks. He recovered without immediate need for cardiac resuscitation. The patient was treated with an appropriate AED and permanent cardiac pacemaker. He is well at follow up 6 months later. *Figure courtesy of Dr Michael Koutroumanidis, Department of Clinical Neurophysiology and Epilepsies, St. Thomas' Hospital, UK. Patient history courtesy of Dr Paul Holmes, Department of Neurology, St. Thomas' Hospital, London, UK.*

- frontal seizures from the supplementary sensorimotor area were considered to be sleep disorders (see page 459)
- ictus emeticus and autonomic status epilepticus, common in children, were dismissed as non-epileptic events or misdiagnosed as migraine or encephalitis (see page 355)
- visual seizures were confused with basilar migraine or migraine with visual aura (see page 125).

Simple focal seizures of epigastric aura and 'panic attacks' are unlikely to raise suspicion of epilepsy either by the patient or by the general physician (see Figures 1.2 and page 15.4). These patients are often investigated for gastroenterological and psychological disorders or hypoglycaemia, until more salient seizure features appear with the development of complex focal seizures and secondarily GTCSs (see page 451).

Second step: What type of epileptic seizures?

Having established that a paroxysmal event is genuinely epileptic, the next, but not the final, step is to define the type of seizure(s).

There are numerous types of epileptic seizures, as detailed in Chapter 2. Their features may be minor or dramatic, brief or long, frequent or sparse, or singular. Clinical manifestations of seizures range from the dramatic events of a GTCS to the mild myoclonic flickering of the eyelids or a focal numb-

ness of the thumb and mouth. The same patient may suffer from different types of minor and major seizures, independently or evolving from one to the other. Even if frequent, minor seizures are unlikely to raise concerns and promote a medical consultation. Conversely, a major seizure such as a GTCS invariably draws medical attention.

Minor seizures are more important than major ones for diagnostic procedures, correct diagnosis and appropriate management strategies.[17]

A single GTCS does not require medication, but if the patient also has other, even minor, seizures, treatment is usually mandatory (Figure 1.3). Similarly, it may be unwise to advise the withdrawal of medication for a patient with minor seizures even if free of convulsive seizures for many years.

Minor seizures should be thoroughly sought during the clinical evaluation (Figure 1.3). Patients are unlikely to report minor seizures because they do not appreciate that these are epileptic events or their significance. Minor seizures may go unnoticed for many years or be ignored as normal variations in a person's life. It is the physician's responsibility to detect and evaluate them. Patients may often suffer many minor seizures long before the reported 'first seizure' or long after what is considered to be their 'last seizure'.[17]

Useful reminder

Approximately three-quarters (74%) of patients with 'newly identified unprovoked seizures' (mainly GTCSs) had experienced multiple seizure episodes before their first medical contact.[18] Yet, studies on the prognosis and treatment of the 'first seizure' mainly refer to a GTCS, although this may not be the first seizure in the patient's life.

Third step: What is their cause and what is the epileptic syndrome or disease?

Having established that a paroxysmal event is epileptic, the next step is to establish an aetiological and syndromic diagnosis. The diagnosis by the non-specialist is often limited to excluding structural abnormalities of the brain or predisposing medical disease. However, simply diagnosing 'epilepsy' or 'seizures' is insufficient. Aetiology and syndromic diagnosis of epilepsies provides a firm foundation for short- and long-term therapeutic decisions and enables natural history, inheritance, treatment efficacy and prognosis of epilepsies to be studied scientifically. Chapter 5 discusses the classification of the epileptic syndromes.[19]

Imprecise syndromic diagnosis commonly results in avoidable morbidity and sometimes mortility.[20]

Important features of a syndrome include:

- the type of seizures, their localisation and frequency
- the chronological sequence of the events
- circadian distribution
- precipitating factors
- age at onset
- mode of inheritance
- physical and mental symptoms and signs
- response to treatment
- prognosis.

Although some symptoms predominate and may indicate the underlying disease, no single symptom or sign can be considered entirely pathognomonic. The process of differential diagnosis requires close scrutiny of the clinical data before a list of possible diagnoses can be drawn up and the final diagnosis reached. It should be realised that some epilepsies are easy to diagnose and some more difficult, but this is not unusual in medicine. Molecular genetics is already providing decisive discoveries in the identification of epilepsies (see Chapters 14 and 17).

A syndromic diagnosis of epilepsies is now a basic recommendation of good clinical practice.[10]

The delay in the general acceptance of this concept has led to significant time and resources being lost and patient safety being jeopardised. Just for the few readers who may still doubt the significance of the syndromic diagnosis of epilepsies, I refer again to the arguments utilised and emphasised on many occasions in the near past,[20–22] and to previous editions of this book.

Video-EEG of a 16-year-old girl referred because of a 'first generalised tonic–clonic seizure'

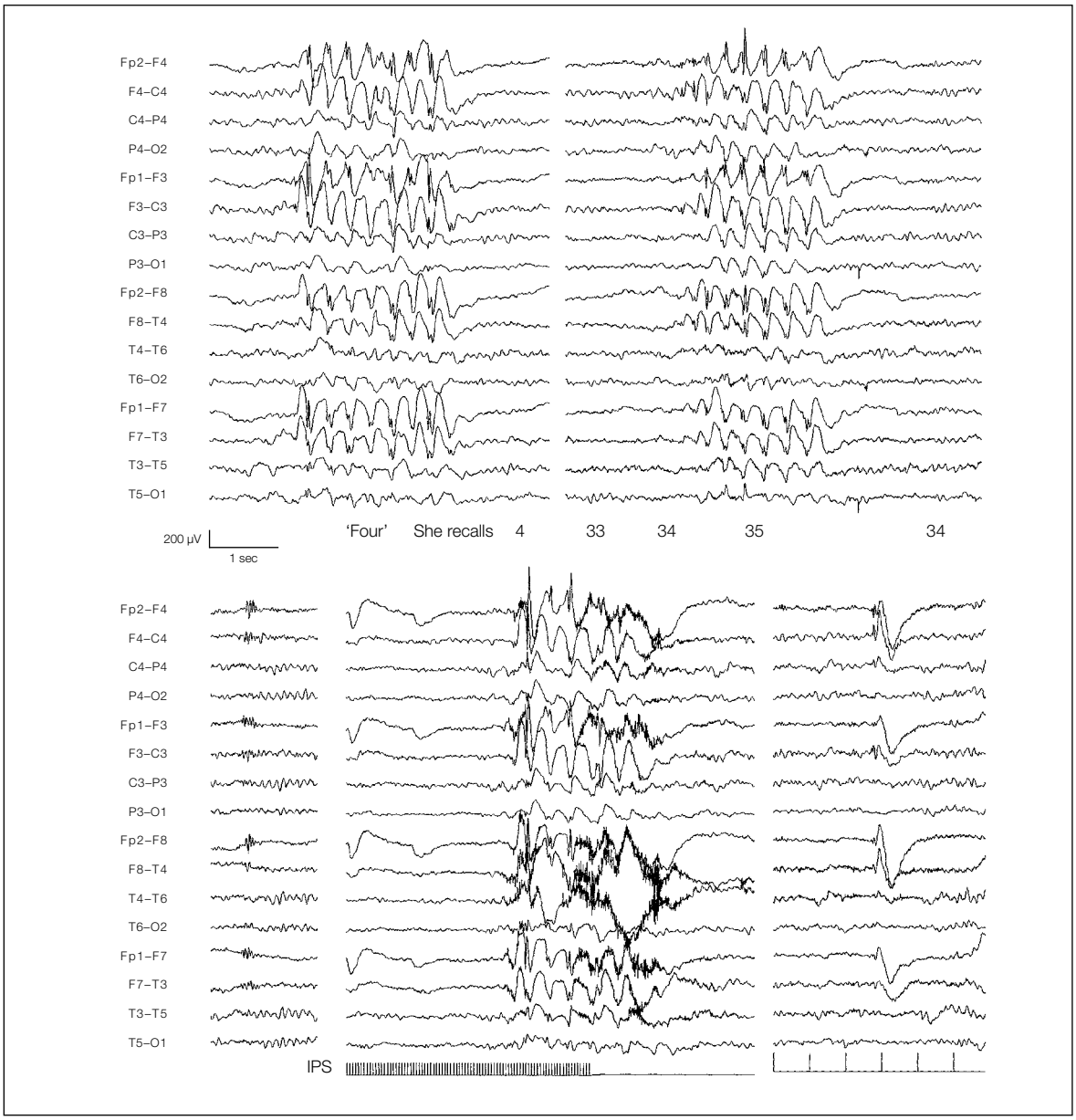

Figure 1.3 This girl had her first GTCS in the morning on her way to school for examinations. She suddenly became vague and nearly simultaneously fell on the ground with generalised convulsions. On questioning by the EEG technologist, it was revealed that 1 year before the GTCS she had mild jerks of the fingers in the morning interpreted as clumsiness. The EEG had generalised discharges of 3–4 Hz spike/multispike and slow wave. The girl recalled the number shouted to her during the discharge. However, breath counting during hyperventilation was disturbed during a similar discharge (annotated numbers). In addition, there were photoparoxysmal discharges. Brief frontal asymmetrical bursts of polyspikes or spike and slow wave could be erroneously interpreted as 'frontal lobe epilepsy with secondary bilateral synchrony'. On clinical and EEG grounds the diagnosis of JME was established and appropriate treatment was initiated because she had many more seizures (myoclonic jerks) prior and in addition to the single GTCS.

The results to be expected from the syndromic diagnosis of epilepsies can be compared to the advances that have accrued from the widespread acceptance of syndromic diagnosis of other medical disorders such as neuromuscular diseases.[20] If diagnosed on a few symptoms alone, distinction would be impossible even among the broad categories of muscular dystrophies, inflammatory myopathies and motor neurone diseases, which all manifest with muscle weakness and muscle atrophy. Similarly, in epilepsies, if diagnosed on a few symptoms alone, distinction would often be impossible even among the broad categories of focal and generalised, idiopathic and symptomatic epilepsies that all manifest with seizures.[20] Despite the occasional occurrence of 'overlap syndromes', syndromic classification allows the scientific analysis of the underlying disease processes and their specific clinicopathological features and genetics, and provides a framework for clinical trials aimed at optimising treatment.[23]

Some parts of the current ILAE classification[19,24] remain contentious and some syndromes are ill or broadly defined and require further clarification.[20–22] There are patients whose clinical and EEG features do not appear to fit neatly into any recognised category or erroneously appear to evolve from one syndrome to another. Some may represent new or 'overlap' syndromes, others may be unusual or atypical forms of known syndromes or cases where clinical history is misleading. However, many syndromes are common, well characterised and easily diagnosed.[20] An epilepsy syndrome can be diagnosed in most, even first-seizure, patients.[25] In one study, a generalised or focal epilepsy syndrome was clinically diagnosed in about half (47%) the patients. The addition of EEG data enabled a diagnosis for about three-quarters (77%) of the patients.[25]

Parents and patients often use the wide information provided on the internet to formulate their own opinion about diagnosis and management. They are entitled and should be encouraged to do so, in order to develop their awareness as part of their partnership with their healthcare professionals. Ultimately, they are the decision-makers.

Epilepsy or epilepsies?

The danger from a unified diagnosis of 'epilepsy' or a symptom diagnosis of 'seizures' is exemplified by common epileptic syndromes such as benign childhood focal seizures, juvenile myoclonic epilepsy (JME) and hippocampal epilepsy, which comprise more than a third of all epilepsies. They are entirely different in presentation, causes, investigative procedures, short- and long-term treatment strategies, and prognosis.

Benign childhood focal seizures are specific for children, manifest with focal seizures that may be solitary, remit within a few years of onset and may or may not require a short course of AED treatment, usually with carbamezapine.

JME is a lifelong idiopathic generalised epilepsy (IGE) syndrome that mainly manifests with myoclonic jerks and primarily GTCSs on awakening. Management of JME differs from standard medical practice for 'the treatment of epilepsy' in several important respects. Recommendations not to treat after the first seizure are usually inappropriate, many AEDs such as carbamazepine and phenytoin worsen JME, and withdrawal of appropriate AEDs after 2–3 years of being seizure free is inappropriate because relapses are inevitable.

Hippocampal epilepsy is a focal epileptic disorder of defined pathology that can be documented *in vivo* with high-resolution MRI in almost all patients. AED treatment may be ineffective, whereas neurosurgical treatment offers excellent and sustained benefit.

Even the most sceptical physicians, among those who doubt the clinical or practical significance of the syndromic diagnosis of epilepsies, have to accept that benign childhood focal epilepsies, JME and hippocampal epilepsy have nothing in common other than the fact that they may all be complicated by GTCSs, which are primarily GTCSs in JME and secondarily GTCSs in benign childhood focal epilepsies and hippocampal epilepsy. Furthermore, the short- and long-term treatment strategies are entirely different for each disorder: benign childhood focal seizures may or may not require medication for a few years, appropriate AED treatment is lifelong in JME, and neuro-

surgery may be life saving for patients with hippocampal type epilepsy. What is an effective drug for one type (carbamazepine for focal seizures) may be contra-indicated for another type of epilepsy (carbamazepine monotherapy in JME).

It should not be difficult to distinguish an intelligent child with benign focal seizures or childhood absence epilepsy from a child with Kozhevnikov–Rasmussen, Lennox–Gastaut, Down or Sturge–Weber syndrome, or a child with severe post-traumatic cerebral damage, brain anoxia or progressive myoclonic epilepsy of Unverricht or Lafora disease. Diagnosis of all these children as simply having epilepsy just because they have seizures offers no more benefit than a diagnosis of a febrile illness irrespective of cause, which may be a mild viral illness, bacterial meningitis or malignancy. Describing all these children as simply having epilepsy just because they have seizures is medically as unacceptable as a diagnosis of muscle atrophy, irrespective of whether it is localised or generalised, post-traumatic or genetically determined, static, reversible or progressive, or whether the underlying cause is in the muscle, nerve or spinal cord, and is treatable or untreatable.

The treatment of epilepsies will change, but their correct diagnosis will always be the golden rule. We should discourage RCTs that lump all patients with any type of seizures as a 'universe of epilepsy' or recommendations such as 'start with valproate and if this does not work change it to carbamazepine' or 'an EEG is not needed after the first seizure because treatment is after the second seizure' (not even specifying the type of seizure and the need to enquire specifically about minor fits).

Significant progress is expected if emphasis is directed at 'how to diagnose the epilepsies' rather than the current theme of 'how to treat epilepsy'.

Inappropriate generalisations in terminology, diagnosis and treatment is the single most important factor in the mismanagement in epilepsies.

The ILAE classification of epileptic seizures and epileptic syndromes

Outstanding achievements in the scientific and social aspects of epilepsies in the last 100 years should be largely attributed to the leaders and committee members of the ILAE. Two publications this year marked the 100th anniversary of the ILAE and Epilepsia, its official journal. Both publications are masterfully written by eminent epileptologists and ILAE protagonists. They are essential reading because they are part of the history of every one of us involved in the diagnosis and management of epilepsies.

The book *International League Against Epilepsy 1909–2009: A Centenary History*[26] is a painstaking and comprehensive history of the ILAE, including numerous illustrations of our past and present mentors. The March 2009 edition of Epilepsia, titled *History of epilepsy 1909–2009*, provides an excellent outline of 10 different aspects of epilepsy during this period, including the clinical concept of epilepsy, EEG, brain imaging, drug treatment and surgery.[27]

The ILAE standardised classification and terminology for epileptic seizures and syndromes provides a fundamental framework for organising and differentiating the epilepsies. This categorisation is essential in clinical practice, randomised controlled trials (RCTs) of AEDs and other therapies, epidemiology and research into these disorders. The efforts of the ILAE to devise classifications of the epilepsies has greatly improved communication among epileptologists and influenced both basic and clinical research.

The Classification of Epileptic Seizures (1981)[28] and Classification of Epilepsies and Epileptic Syndromes (1989)[19] are still the current valid formal ILAE classifications.

These classifications were made through lengthy and thorough assessments of the clinical, EEG, imaging, neurosurgical, neuropathological and other data then available. The Commissions explained their procedures and their reasoning behind their decisions at length. Further, they provided a brief definition of each epileptic seizure[28] and epileptic syndrome.[19] A dictionary of epilepsies had been published earlier in 1973.[29]

Subsequent advances in the clinical-EEG manifestations of epileptic seizures and syndromes, videoEEG information, functional and structural imaging, investigative procedures and genetics mandated a thorough and realistic revision of these classifications. Since 1997, members of the ILAE Task Force and the Commission on Classification and Terminology have invested tremendous work and time to incorporate these advances and introduce scientific principles and standards into the classification of the epilepsies – a challenging and difficult task. The subsequent recommendations and reports[24,30,31] given below are not a replacement for the 1981 Classification of Epileptic Seizures[28] and the 1989 Classification of Epilepsies.[19]

Recommended sources of ILAE information and classification

A recommended source of information is the ILAE website (www.ilae-epilepsy.org). The ILAE glossary and most epileptic seizures and epileptic syndromes can be found at www.ilae-epilepsy.org/Visitors/Centre/ctf/index.cfm. The newest report of the ILAE Commission on Classification and Terminology is posted at http://www.ilae-epilepsy.org/Visitors/Centre/ctf/ctfoverview.cfm and the ILAE member comments on this are available at http://www.ilae-epilepsy.org/Visitors/Centre/ctf/ctfcomments.cfm. The currently valid reports of the Classification of Epileptic Seizures (1981)[28] Epileptic Syndromes (1989)[19] are available free of charge on the Epilepsia website.

The ILAE Task Force on Classification and Terminology (Chair: Jerome Engel, Jr. 1997–2005) produced a report in 2001 as A Proposed Diagnostic

Proposed ILAE Task Force diagnostic scheme for people with epileptic seizures and with epilepsy[24]

Axis 1 involves a detailed description of ictal phenomenology using the glossary of descriptive ictal terminology. This can be extremely valuable for older patients with focal epilepsy who are being evaluated for surgical resection, but is not likely to be necessary in infants and young children, so it is optional

Axis 2 is the diagnosis of specific seizure type(s) that are detailed in Chapter 2

Axis 3 is the diagnosis of a specific syndrome as detailed in Chapter 5 and all other relevant chapters in this book. About half of these syndromes occur in infancy and early childhood, most of which are noncontroversial

Axis 4 is an aetiological diagnosis of 'diseases frequently associated with epileptic seizures' (see Chapter 17) or with epilepsy syndromes when possible, genetic defects (see Chapter 14) or specific pathological substrates for symptomatic focal epilepsies (see Chapter 15)

Axis 5 is an optional assessment of impairment taken from the WHO International Classification of Functioning, Disability and Health (ICIDH-2) classification. This axis is intended for application in older patients (see chapter 7, page 219)

Table 1.1 *Reproduced with permission from Engel (2000).*[24]

Scheme for People with Epileptic Seizures and with Epilepsy,[24] and this was updated and revised in 2006.[30] A glossary of descriptive terminology for ictal semiology has also been published.[3]

Table 1.1 shows the proposed ILAE diagnostic scheme to be used in the description of individual patients with epileptic seizures, syndromes and diseases for diagnostic studies and therapeutic strategies.[24] It takes into consideration the following:

- some patients cannot be given a recognised syndromic diagnosis
- seizure types and syndromes change as new information is obtained
- complete and detailed descriptions of ictal phenomenology are not always necessary
- multiple classification schemes can, and should, be designed for specific purposes (e.g. communication and teaching, therapeutic trials, epidemiological investigations, selection of surgical candidates, basic research, genetic characterisations).

The subsequent ILAE Commission on Classification and Terminology (Chair: Anne Berg, 2005–2009) have made their report, "Revised terminology and concepts for organization of the Epilepsies", available online on the ILAE website.[31] This report is an important document for consideration and reflection as it contains the thoughts of the leading authorities in the epilepsies. The authors should also be commended for their openness by establishing a forum for constructive debate with invitation for comments from ILAE member national chapters. Therefore, the report is not at its final form and it may be premature to discuss it at any length in this revision of the Guide (see page 15). Also, this is not a new classification: "rather we have provided new terminology and concepts which better reflect the current understanding of these issues. A guiding principle has been to strive for clarity and simplicity so that terms refer to single qualities and are not a mixture of different concepts and dimensions".[31] My own comments in response to the Commission's invitation can be found at http://www.ilae-epilepsy.org/Visitors/Centre/ctf/ctfcomments.cfm.

These newer ILAE proposals concentrate mainly on terminological and taxonomic issues. A significant drawback of these reports is that recognized epileptic seizures and epileptic seizures are listed by name only. There is no definition or brief description of what each of these should be in accordance with the advances made since 1981.

The attempts to provide a new classification for epileptic seizures and syndromes is to be continued by the newly appointed ILAE Commission on Classification and Terminology (Chair: Ingrid E. Scheffer, 2009–2011).

On classifications: concepts, clarifications and difficulties in reaching a consensus in the classification of epileptic seizures and syndromes

The different methodologies, approaches, targets and philosophies on classifications and their relevance to epilepsies have been authoritatively discussed in a multiauthor editorial in Epilepsia (January 2003) entitled Cabbages and Kings in the classification of seizures and the epilepsies.[32,33] More recently, a series of important essays appeared in Epilepsy Research (2007) that provides an excellent insight into what has been achieved so far and what is expected from future developments and proposals.[34–36]

Gardeners and botanists

Classifications in epileptological literature are often compared to the classification of plants for botanists and gardeners.[28,32] The botanists, like all scientists, need a systematic taxonomy based on scientific principles, whereas the gardeners, like all practising physicians, need a practical scheme that they can use in their daily work.

> There are two ways of investigating diseases, and two kinds of classification corresponding thereto, the empirical and the scientific. The former is to be illustrated by the way in which a gardener classifies plants, the latter by the way in which a botanist classifies them. The former is, strictly speaking, only an arrangement. The gardener arranges his plants as they are fit for food, for ornament, etc. One of his classifications of ornamental plants is into trees, shrubs, and flowers. His object is the direct application of knowledge to utilitarian purposes. It is, so to speak, practical. The other kind of classification (the classification properly socalled) is rather for the better organization of existing knowledge, and for discovering the relations of new facts; its principles are methodical guides to further investigation. It is of great utilitarian value, but not directly.
>
> John Hughlings Jackson (1874)[37]

In this sense, the currently valid classification of epileptic seizures (1981)[28] and epileptic syndromes (1989)[19] should be considered as pragmatic tools for gardeners, in accordance with which the ILAE Commission[28] quotes Jackson:

> Plainly enough, such an arrangement goes by what is most superficial or striking. The advantages of it are obvious. It facilitates the identification and the application of knowledge to utilitarian purposes, but it must not be trusted as a natural classification. However much of it may be further elaborated, it makes not even an approach to a scientific classification.
>
> John Hughlings Jackson (1874)[37]

The quest for a scientific classification of epilepsies useful for botanists has been a key point of attention in the newer ILAE reports.[24,30,31] Such a classification, applying the methods used in biology to determine separate species, is a noble and legitimate target but it appears to be very elusive.

> Phylogenetic systematics could provide an initial model worth studying in this context. While the classification of species cannot be directly applied to the classification of epilepsy syndromes, three general points can be appreciated. (1) In evolutionary biology, there is an operationalized definition of the end point (a species). There is no such definition of a syndrome. (2) There are rules and criteria for the type of evidence and how it is evaluated to determine whether an entity does or does not represent a separate species. There are currently no such rules or criteria for epilepsy syndromes. (3) There is an underlying model (evolution) that generates the diversity among species. With the possible and only partial exception of the idiopathic generalized epilepsies, there are no models to explain the diversity among the epilepsies.[35]

Therefore, and in view of the difficulties with finding a scientifically correct classification for botanists in epilepsies, the new ILAE proposals and reports mainly focus on terminological changes, aiming to "characterize seizures and epilepsies in dimensions that should represent useful, natural classes".[31] This may require significant compromises that they may not serve either the botanists or the gardeners.

> Finally, although new approaches need to be investigated, we should not suddenly abandon the work that has been done up until now. Not only did it inaugurate the field, but it also represents the observations of extraordinarily astute individuals who, in all likelihood have identified some very solid, biologically real entities, which, as they are put to the test will hold up under scrutiny. The evidence in support of this is the utility of the current syndromic classification especially for epilepsy in infancy and childhood. While we would like to do even better, we need to avoid doing worse. Ideally, the botanists' scientific classification and a gardeners' pragmatic arrangement are not incompatible, but there may be points when they seem worlds apart. For any endeavor, such as this, but especially one that represents such a major departure from previous practice, it will be essential to remain open-minded and self-critical at every stage. We will inevitably make mistakes despite our best efforts not to. A willingness and ability to recognize those errors and respond to them accordingly is essential. This is the essence of scientific inquiry.[35]