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Electroclinical Syndromes

Edited by
Hans Lüders and Ronald P. Lesser

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Hans Lüders, MD, PhD
Head, Section of Epilepsy and Clinical Neurophysiology, Department of Neurology, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44106, U.S.A.

Ronald P. Lesser, MD
Director of Adult Seizure Center, Department of Neurology, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44106, U.S.A.

Series Editors

John P. Conomy, MD
Chairman, Department of Neurology, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44106, U.S.A.

Michael Swash, MD, FRCP, MRCPath
Consultant Neurologist, Neurology Department, The London Hospital, Whitechapel, London E1 1BB

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Series Editors' Foreword

Epilepsy is among the most common scourges afflicting the health of humankind and perhaps the most terrifying. In one form or another, it is suffered by one in every one hundred people on earth, with a disproportionate prevalence at the early and late extremes of life. There is nothing sacred or sanctifying about it in spite of Hippocrates' terming epilepsy "The Sacred Disease" in a famous treatise. There is nothing ennobling about it despite its occasional designation as a "noble disorder" by virtue of its having affected the likes of Alexander of Macedon, Julius Caesar and other persons of royal lineage. From time to time, epilepsy is hailed as a condition which is artistically inspirational; Fyodor Dostoyevsky's dependence on his own personal experience with complex partial epilepsy as a source of imagery in the transfiguration scenes of *The Brothers Karamazov* and as a source of experience in *The Idiot* is often cited in this respect. In fact, for all its victims in human history, epilepsy has been a sad burden which has disrupted and shortened life, causing suffering and castigation for the duration of their terrestrial journey. Throughout the recorded history of epilepsy, now about 5000 years in the writing, men and women have experienced what Fernand Braudel and Emmanuel LeRoy Baudrie have termed *L'Histoire Immobile*, or unchanging history. Only in the last century have the increasingly powerful tools of neuropharmacology and electrophysiologic diagnosis been developed to allow epilepsy to be precisely diagnosed and effectively treated. Even more recently have the techniques been developed to allow surgical treatment of a small but important group of epileptic persons.

This volume, the second in the *Clinical Medicine and the Nervous System* series, deals with epilepsy in a newer but very important nosology. Doctors Lüders and Lesser have organized the entire issue of epilepsy about the denominator of electrophysiology. Together with an outstanding group of contributors, they have defined the

clinical presentation, natural history, genetics, risk factors and treatment of the epilepsies based on a diagnostic method which itself illuminates the fundamental pathology of the epilepsies, and which provides a rational basis for treatment. Illustrations are abundant in this text and are in every instance presented in the context of clinical problems. We asked the authors to produce a textbook of practical use to clinicians, novice or expert. We feel they have far exceeded that request and have produced a work of practical benefit to the scholar, scientist and clinician which will be of value for many years to come.

Cleveland, Ohio — John P. Conomy
London — Michael Swash

Preface

The development of electroencephalography marked the beginning of a new era in epileptology. Early on, relatively specific markers for epilepsy were described. Interestingly, and probably also unexpectedly, these markers were not only present during ictal episodes but also inter-ictally and not infrequently could be easily detected by a short 20-min sample of scalp EEG activity. The EEG test became, therefore, a routine test in the evaluation of all epileptics. Of great importance, the EEG abnormality was different in the different epileptic syndromes so that it could be used to define the type of epilepsy a patient was suffering. The prominent position which electroencephalography plays in the International Classification of Seizures, as also in the recently proposed International Classification of Epileptic Syndromes, clearly underlines this point. Finally, electroencephalography has been one of the most important tools in advancing our understanding of the pathophysiology of epileptic seizures.

Both editors were orginally trained as "pure" electroencephalographers but eventually also became epileptologists. This transition gave us an opportunity to apply the facts we had learned as electroencephalographers to the clinical management of patients with epilepsy. It also made us realize the close relationship between, and the importance of integrating, the two specialties of electroencephalography and epileptology.

This book follows the same philosophy. Each chapter is written either by authors specialized in both fields or by an epileptologist matched with an electroencephalographer of the same institution, who worked in close collaboration to produce a balanced chapter. The plan was to discuss the main epileptic syndrome from an electroclinical point of view.

In addition, this book contains one chapter which discusses the problem of classification of epilepsies in an attempt to relate the

subsequent specific syndromes with the entities identified by the International Committee. We hope that this book will contribute to a better understanding of epileptic syndromes and, particularly, that it will make a contribution to closer interaction between electroencephalographers and epileptologists.

Cleveland, Ohio

H. Lüders
R. P. Lesser

Contents

Contributors

Warren T. Blume, MD, FRCP(C)
Co-Director, Epilepsy Unit, Director, EEG Department, University Hospital, University of Western Ontario, London, Ontario, Canada N6A5A5

Antonio V. Delgado-Escueta, MD
Professor of Neurology, VA Epilepsy Center (1278), VA Wadsworth Medical Center, Wilshire & Sawtelle Blvds., Los Angeles, CA 90073

Dudley S. Dinner, MD
Section of Epilepsy and Clinical Neurophysiology, Department of Neurology, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44106

Gerald Erenberg, MD
Pediatric Neurologist, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44106

Manuel R. Gomez, MD
Professor of Pediatric Neurology, Mayo Medical School, Mayo Clinic, 200 First Street Southwest, Rochester, Minnesota 55905

Peter Kellaway, PhD
Professor of Neurology; Head, Section of Neurophysiology; Director, Epilepsy Research Center, Baylor College of Medicine, Fondren-Brown Building, The Methodist Hospital, 6565 Fannin, Houston, Texas 77030

Ronald P. Lesser, MD
Director of Adult Seizure Center, Department of Neurology, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44106

Hans Lüders, MD, PhD
Head, Section of Epilepsy and Clinical Neurophysiology, Department of Neurology, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44106

Eli M. Mizrahi
Assistant Professor, Departments of Neurology and Pediatrics, Baylor College of Medicine, One Baylor Plaza, Houston, Texas 77030

Harold H. Morris III, MD
Section of Epilepsy and Clinical Neurophysiology, Department of Neurology, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44106

Timothy A. Pedley, MD
Professor and Vice-Chairman, Department of Neurology, Columbia University of Physicians and Surgeons, The Neurological Institute, 710 West 168th Street, New York, N.Y. 10032

Roger J. Porter, MD
Chief, Medical Neurology Branch, National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, Clinical Center, Room 5N-248, Bethesda, MD 20205

A. David Rothner, MD
Head, Section of Child Neurology, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44106

Frank W. Sharbrough, MD
Professor of Neurology, Mayo Medical School, Mayo Clinic, 200 First Street Southwest, Rochester, Minnesota 55905

Hiroshi Shibasaki, MD
Associate Professor, Department of Internal Medicine, Saga Medical School, Nabeshima, Saga City 840-01, Japan

Barbara F. Westmoreland, MD
Professor of Neurology, Mayo Medical School, Mayo Clinic, 200 First Street Southwest, Rochester, Minnesota 55905

Chapter 1

The Classification of Epileptic Seizures and Epileptic Syndromes

Roger J. Porter

Introduction

The epilepsies are a heterogeneous group of symptom complexes, mostly empirically determined, whose common feature is the recurrence of seizures caused by abnormal neuronal discharge, usually arising from the cortex of the brain. The disorders are, of course, paroxysmal and often unpredictable; clear definition of even the seizures themselves has not proved easy, let alone the possible epileptic syndromes in patients.

A major improvement in our understanding of the epilepsies became possible when epileptic seizures could be recorded on reusable videotape, allowing comparison of the various seizure types and permitting a clinically meaningful classification of epileptic seizures. A classification of these finite, recordable events is pivotal to an understanding of epilepsy in general and is specifically necessary before one can classify epileptic syndromes.

This introductory chapter will review the evolution of the classification of epileptic seizures as the most important single element in the syndromic classification of the epilepsies, discuss difficulties inherent in such syndromic classifications, and finally consider the most recent Classification of the Epilepsies of the International League Against Epilepsy.

The Classification of Epileptic Seizures

Although classifications of seizures had been previously attempted, the first to be internationally accepted was published in *Epilepsia* in 1970 (Gastaut 1970), a result of many long years of effort and persistence. The classification emphasized the

primary importance of describing the clinical seizure but also included other criteria, such as the ictal EEG pattern, the interictal EEG pattern, the age of the patient, the etiology of the seizures, and the anatomical substrate. One of the most important contributions of the 1970 classification was the subdivision of seizures into those with a localized onset—partial seizures—and those in which no localization of onset was possible—generalized seizures; although this concept was not new, it was effectively popularized by the publication of the 1970 classification. Another very important concept inherent in the 1970 classification of epileptic seizures was the distinction between the classification of epileptic seizures and that of epileptic syndromes or "the epilepsies." Even though the 1970 seizure classification was still burdened with certain aspects of syndromic classification—such as age and etiology—the foundation was provided for a more definitive separation of these two concepts in the decade to come. A summary of the 1970 seizure classification is found in Table 1.1. A full description of each seizure type did not accompany the classification; such descriptions were included in the WHO *Dictionary of Epilepsy* published in 1973 (Gastaut 1973).

The 1970 classification, by its own admission, was "tentative" and "subject to change with every advance in the scientific understanding of epilepsy." Changes were soon made possible by the videotape recording of seizures, enabling a data-generated evaluation of the actual appearance and form of epileptic seizures. Video workshops were held in 1975, 1977, and 1979. The resulting 1981 revision

Table 1.1. The 1970 International Classification of Epileptic Seizures (abstracted from Gastaut 1970)

I. Partial seizures (seizures beginning locally)
   - A. Partial seizures with elementary symptomatology (generally without impairment of consciousness)
     1. With motor symptoms (includes jacksonian seizures)
     2. With special sensory or somatosensory symptoms
     3. With autonomic symptoms
     4. Compound forms
   - B. Partial seizures with complex symptomatology (generally with impairment of consciousness) (temporal lobe or psychomotor seizures)
     1. With impairment of consciousness only
     2. With cognitive symptomatology
     3. With affective symptomatology
     4. With "psychosensory" symptomatology
     5. With "psychomotor" symptomatology (automatisms)
     6. Compound forms
   - C. Partial seizures secondarily generalized

II. Generalized seizures (bilaterally symmetrical and without local onset)
   1. Absences (petit mal)
   2. Bilateral massive epileptic myoclonus
   3. Infantile spasms
   4. Clonic seizures
   5. Tonic seizures
   6. Tonic–clonic seizures (grand mal)
   7. Atonic seizures
   8. Akinetic seizures

III. Unilateral seizures (or predominantly)

IV. Unclassified epileptic seizures (due to incomplete data)

Table 1.2. The 1981 International Classification of Epileptic Seizures[a] (abstracted from Commission on Classification and Terminology of the International League Against Epilepsy 1981)

I. Partial seizures (seizures beginning locally)
  A. Simple partial seizures
     (consciousness not impaired)
     1. With motor symptoms
     2. With somatosensory or special sensory symptoms
     3. With autonomic symptoms
     4. With psychic symptoms
  B. Complex partial seizures (with impairment of consciousness)
     1. Beginning as simple partial seizures and progressing to impairment of consciousness
        a. With no other features
        b. With features as in A.1-4
        c. With automatisms
     2. With impairment of consciousness at onset
        a. With no other features
        b. With features as in A.1-4
        c. With automatisms
  C. Partial seizures secondarily generalized

II. Generalized seizures (bilaterally symmetrical and without local onset)
  A. 1. Absence seizures
     2. Atypical absence seizures
  B. Myoclonic seizures
  C. Clonic seizures
  D. Tonic seizures
  E. Tonic–clonic seizures
  F. Atonic seizures

III. Unclassified epileptic seizures (inadequate or incomplete data)

[a] This classification was approved by the International League Against Epilepsy in September 1981.

(Commission on Classification and Terminology of the International League Against Epilepsy 1981) was an astonishing reaffirmation of the basic structure of the 1970 classification (Table 1.2). Certain changes were undertaken in the 1981 revision; the most important of these are as follows:

1. *Limitation of the criteria for seizure classification to empirical data regarding the seizure itself with its accompanying ictal electroencephalogram.* The 1970 criteria included data, such as anatomical substrate and etiology, which are often speculative or unavailable in any given patient, and which more appropriately relate to epileptic syndromes than to an empirical classification of seizures. The 1981 limitation strengthens the data orientation of the seizure classification, as all of the information related to a seizure may be directly viewed—either on videotape or in the ictal EEG.

2. *Definition of the subdivisions within the partial seizures as a function of preservation of consciousness (responsiveness).* Many have thought it best to define simple partial seizures as those attacks involving only a certain, limited portion of the brain and complex partial seizures as involving "higher cortical integrative functions." Such distinctions, however, are extraordinarily difficult, usually untestable and unverifiable, and involve speculation regarding anatomical involvement of the brain. If one uses a purely operational definition of consciousness—the ability to respond to exogenous stimuli—a highly testable differentiation is

possible. Evaluation of responsiveness thereby becomes an entirely empirical process, completely consistent with the empirical nature of the seizure classification. Although speculation is possible regarding the anatomical substrate of simple versus complex partial seizures (Porter 1984), such speculation is completely unnecessary for the purposes of the classification. Evaluation of responsiveness can be relatively simple, such as asking questions of the patient during the seizure, or can utilize more sophisticated techniques, such as reaction time (Porter et al. 1973).

3. *Provision for the progression of epileptic seizures.* The only progression clearly recognized by the 1970 classification was the progression of partial seizures to generalized seizures (tonic, clonic, or tonic–clonic). The most obvious omission in this regard is the progression of simple partial seizures to complex partial seizures. Table 1.3 outlines the partial seizure progression possibilities, which total six and which are included in the 1981 revision. More recently, the progression of seizures such as absence or clonic seizures to generalized tonic–clonic seizures has been recognized, creating complicated semantic difficulties (Porter and Sato 1982; Porter 1984); these seizures are unfortunately not included in the 1981 classification.

Table 1.3. Possible progression of partial seizures (Porter 1984)

Seizure progression	Seizure name
SP	Simple partial seizures
SP→CP	Complex partial seizures (with SP onset)
CP	Complex partial seizures
SP→GTC	Partial seizures secondarily generalized—generalized tonic–clonic seizures
CP→GTC	Partial seizures secondarily generalized—generalized tonic–clonic seizures
SP→CP→GTC	Partial seizures secondarily generalized—generalized tonic–clonic seizures

Abbreviations: SP, simple partial; CP, complex partial; GTC, generalized tonic–clonic.

4. *Allowance for overlap of symptomatology of simple and complex partial seizures.* Although clonic jerking is not very common as a manifestation of complex partial seizures, it does occur (Theodore et al. 1983). Provision is made in the 1981 revision such that all phenomena which accompany simple partial seizures may also occur in complex partial seizures. Automatisms, however, are unique to seizures such as complex partial or absence in which an alteration of consciousness occurs, and therefore cannot occur in simple partial seizures.

5. *Elimination of groups entitled "compound forms."* With the addition of the concept of seizure progression, there was no longer a need to lump seizures (or seizure phenomena) together as compound forms. This deletion was beneficial to the more widespread use of the classification, as the term "compound forms" was never used by clinicians (it conveyed no real information about the seizure).

6. *Elimination of akinetic seizures as a distinct entity.* The widespread but mistaken use of the term "akinetic" (without motion) in place of "atonic" has contributed much to the confusion of seizure types and epileptic syndromes. Many seizures are characterized by motionlessness, and this phenomenon is not unique to any specific seizure type (Porter 1984).

7. *Removal of "infantile spasms" from the seizure classification.* The syndrome of infantile spasms is not a specific seizure type and does not belong in an empirical seizure classification. It is included in the proposed classification of epileptic syndromes.

Certain other changes undertaken by the commission were less dramatic, e.g., the addition of a grouping for atypical absence (with appropriate definitions), the addition of myoclonic as distinct from clonic, and the deletion of bilateral massive epileptic myoclonus and unilateral seizures. The result is a highly relevant, clinically applicable classification of epileptic seizures, valuable for both the practicing physician and the clinical investigator. This classification was accepted by the International League Against Epilepsy in 1981.

The Classification of Epileptic Syndromes

The classification of epileptic seizures is exceedingly useful in the diagnosis and treatment of patients with epilepsy. In isolation, however, the seizure type gives only limited information regarding prognosis and long-term therapeutic decisions. Much more useful would be a coherent grouping of epileptic patients into known etiologies, anatomical involvement, physiological origin, and spread of the seizure discharge. Also useful would be a comprehensive grouping of the case histories, neurological findings, psychological studies, and imaging techniques into meaningful patterns that would allow categorization of patients with epilepsy—as opposed to the mere grouping of epileptic seizures. It is the grouping together of patients that we call the *classification of the epilepsies*, or *electroclinical syndromes*.

Although the classification of epileptic syndromes is clinically more desirable than the classification of seizures, the creation of a useful and meaningful classification of syndromes is much more difficult. Seizures themselves can be recorded, reviewed, and re-reviewed, and classification differences eventually resolved. Better recordings of seizures and their accompanying ictal electroencephalograms will provide more objective, data-generated improvements in the seizure classification. Epileptic syndromes, on the other hand, are much more dependent on a wide variety of impressions gained by a number of talented physicians who are attempting to establish some sort of order in our understanding of the epilepsies. What forms a syndrome in the mind of one physician forms a different syndrome in the mind of the next investigator, and data may not be readily available to resolve the issue. On occasion, the power of persuasion, in the absence of obvious data, becomes quite important in the creation of a classification of syndromes regardless of the validity of the expressed point of view. Nevertheless, clinical investigators must make an effort to create a syndromic classification. Such efforts will be frustrating and time-consuming, and many, many revisions will be necessary, probably over several decades.

The 1970 Classification

One of the major contributions to epilepsy made by the International League Against Epilepsy has been the activities of the Commission on Classification and Terminology. This group, which changes in membership every few years, has been the major force in stimulating classification efforts. The focus was originally on seizure classification, but more recently the Commission has emphasized classification of the epilepsies. The 1970 classification of epileptic seizures was accompanied by a first effort to classify epileptic syndromes (Tables 1.4, 1.5). Many of the criteria important for such a classification were outlined therein (Merlis 1970):

1. The approach is necessarily phenomenological, based on a collection of criteria.
2. The syndromic classification must be consistent with the seizure classification.
3. The classification should be usable by the average physician and should reflect the approach of the physician to the patient.

Table 1.4. The 1970 International Classification of the Epilepsies (abridged)[a] (abstracted from Merlis 1970)

I.	Generalized epilepsies
	1. Primary generalized epilepsies (includes petit mal and grand mal seizures)
	2. Secondary generalized epilepsies
	3. Undetermined generalized epilepsies
II.	Partial (focal, local) epilepsies (includes jacksonian, temporal lobe, and psychomotor seizures)
III.	Unclassified epilepsies

[a] This table of the 1970 Classification of the Epilepsies should be compared with Table 1.6, the 1984 revision.

The major criteria for the 1970 classification of the epilepsies were (a) seizure form, (b) neurological/psychological brain abnormalities, (c) age of onset, (d) etiology, (e) ictal EEG, and (f) interictal EEG. Other criteria thought to be important were (a) response to medication, (b) genetic factors, and (c) presumed pathophysiology.

The 1970 classification is divided into the two major categories, generalized and partial epilepsies—just as epileptic seizures are categorized as generalized or partial. The subclassification of the generalized epilepsies but not of the partial epilepsies depends on whether the seizures are "primary," i.e., without known cause, or "secondary," i.e., with evidence of underlying brain disease. The partial epilepsies are all assumed to be secondary. Below this level a minor effort toward specificity was attempted, but its utility was conceded to be minimal.

Table 1.5. The 1970 International Classification of the Epilepsies[a]

I. Generalized epilepsies
1. Primary generalized epilepsies
A. Clinical criteria
1. Seizures
Seizures which are generalized from the onset in the form of absences, bilateral myoclonus, and tonic–clonic seizures. One or more of these types of seizure can occur in the same patient.
2. Neurological status
The usual absence of neurological or psychological evidence of cerebral abnormality.
3. Age of onset
Onset in childhood and adolesence, although they are liable to persist to, and may even begin at, any age.
4. Etiology
Lack of clear etiology.
B. Electroencephalographic criteria
1. Interictal EEG
The presence (usually) of bilaterally synchronous spikes, polyspikes, spike and wave, or polyspike–wave complexes. These may occur singly or rhythmically, at about 3/s. They are spontaneous or are induced by hyperventilation, intermittent photic stimulation, or sleep.
2. Ictal EEG
The occurrence (usually) of synchronous and symmetrical discharges with a given type of seizure (rhythmic at about 3 spike and wave complexes per second during absences; polyspike–wave complexes during bilateral myoclonus; "recruiting" rhythms at about 10/s followed by rhythmic polyspike–waves during tonic–clonic seizures).
2. Secondary generalized epilepsies
A. Clinical criteria
1. Seizures
Seizures which are generalized from the onset in the form of absences; bilateral myoclonus; tonic or atonic seizures; or tonic–clonic seizures. One or more of these seizures can occur in a single patient.
2. Neurological status
The presence (usually) of neurological or psychological signs (i.e., mental deficiency or deterioration), or both, indicative of diffuse cerebral pathology.
3. Age of onset
Onset at any age; most frequent in childhood.
4. Etiology
May be ascribed (usually) to diffuse or multifocal cerebral lesions.
B. Electroencephalographic criteria
1. Interictal EEG
Slow background activity with sharp- and slow-wave complexes, usually symmetrical and synchronous, or asymmetrical or even asynchronous. These are less frequently induced by hyperventilation and photic stimulation. Sleep may be effective.
2. Ictal EEG
Ictal patterns which may contain diminution in amplitude of background EEG activities, a low-voltage rapid discharge, a "recruiting" rhythm at about 10/2, sharp- and slow-wave discharges at about 2/s, and spike and wave or polyspike–wave discharges. The sharp- and slow-wave discharges are less synchronous and symmetrical and are more variable in topographical distribution than the other discharge types and than those in primary generalized epilepsy. The correlation between these ictal EEG patterns and the seizure types is not as good as in primary generalized epilepsy.
3. Undetermined generalized epilepsies

Using the criteria above, the information available concerning a given patient with a generalized epilepsy may not be adequate to determine whether it is primary or secondary. The patient will then be classified as generalized epilepsy, undetermined.

Table 1.5 continues on p. 8

Table 1.5 (*continued*)

II. Partial (focal, local) epilepsies
A. Clinical criteria
1. Seizures
Partial seizures (of local onset) with or without generalization whose manifestations (chiefly initial) are of many forms as detailed in the International Classification of Epileptic Seizures. Postictal focal neurological deficit may be present.
2. Neurological status
The presence (frequently) of neurological signs related to the epileptogenic lesion.
3. Age of onset
Onset at any age.
4. Etiology
Associated (usually) with brain damage.
B. Electroencephalographic criteria
1. Interictal EEG
Occurrence of local spikes or spike and wave complexes (usually). Sleep, hyperventilation, and photic stimulation are less effective activators than in other types of epilepsies. The site of the epileptogenic focus should correspond to the clinical symptoms of the seizures.
2. Ictal EEG
Local discharges related to the lesion. In many cases, these may be diffuse; they may even be absent. Postictal focal abnormalities may be present.

III. Unclassifiable epilepsies
This group comprises all those epilepsies which cannot be classified in one of the above-mentioned generalized or partial groups, either because they are atypical or because data are insufficient. The epilepsy with "erratic seizures" in the newborn and the unilateral seizures of childhood may have to be included in this category.

The above groups may differ significantly in cyclic characteristics, response to medication, prognosis, and so forth. As our understanding of the basic mechanisms of the epilepsies increases, modification of this classification will undoubtedly be necessary.

[a] This 1970 classification of the epilepsies should be compared with Table 1.7, the 1984 revision.

The 1984 Classification

Since acceptance of the revised classification of epileptic seizures in 1981, the Commission on Classification and Terminology has been meeting in an effort to formulate a better classification of epileptic syndromes under the leadership of Dr. Peter Wolf of Berlin. In late 1984, Dr. Wolf circulated a draft document to the National Chapters of the International League Against Epilepsy, proposing a new, much more detailed and specific syndromic classification. Although this document is a draft, and a more final form will clearly be published later, the fundamentals are worthy of review and consideration.

The 1984 proposed classification maintains the basic structure of the 1970 classification (Table 1.6). The Commission again agreed that localization or nonlocalization of the onset of the seizure is the single most important dichotomy and has the highest likelihood of contributing to the physician's decisions regarding diagnosis and therapy. The terminology is slightly changed ("partial" is replaced by "localization-related") and the order has been reversed such that the generalized epilepsies come second (as in the seizure classification), but otherwise the differences are minimal. The 1984 revision adds a new category "special

Table 1.6. The 1984 Proposed International Classification of Epilepsies (abridged)[a]

1. Localization-related epilepsies
   1.1 Idiopathic
   1.2 Symptomatic
2. Generalized epilepsies
   2.1 Idiopathic
   2.2 Symptomatic
3. Epilepsies undetermined whether focal or generalized
4. Special syndromes

[a] This table is the 1984 revised version of the 1970 classification (Table 1.4). One substantive change from 1970 is the provision for idiopathic epilepsies in the localization-related (partial) group.

Table 1.7. The 1984 Proposed International Classification of Epilepsies[a]

I. Localization-related epilepsies
   1. Idiopathic (age-related)
      - Benign childhood epilepsy with centrotemporal spikes
      - Benign childhood epilepsy with occipital paroxysms
   2. Symptomatic
      a. Epilepsies involving the limbic system
      b. Epilepsies not involving the limbic system
      Various further subdivisions are possible and will depend on the purpose of classification:
      - etiological (perinatal brain damage, cerebral trauma, brain tumor, toxic and metabolic, inflammatory, cerebrovascular, degenerative process)
      - according to cardinal symptoms (e.g., epilepsia risoria, epilepsy with running fits)
      - according to anatomical localization, if known
      -- frontal
      --- supplementary motor
      --- cingular
      --- orbitofrontal
      --- dorsolateral
      -- temporal
      --- hippocampal
      --- amygdalar
      --- lateral posterior
      --- opercular
      -- central
      -- parietal
      -- occipital

II. Generalized epilepsies
   1. Idiopathic (age-related)
      - Benign neonatal familial convulsions
      - Benign neonatal convulsions
      - West syndrome (idiopathic cases)
      - Epilepsy with myoclonic–astatic seizures (idiopathic and familial cases of Lennox-Gastaut syndrome)
      - Childhood absence epilepsy (pyknolepsy)
      - Epilepsy with (myo)clonic absences
      - Juvenile absence epilepsy
      - Benign juvenile myoclonic epilepsy (impulsive petit mal)
      - Epilepsy with generalized tonic–clonic seizures on awakening

Table 1.7 continues on p. 10

Table 1.7 (*continued*)

2. Symptomatic
   a. Nonspecific etiology (age-related)
      - Neonatal seizures
      - Early myoclonic encephalopathy
      - West syndrome (infantile spasms, Blitz-Nick-Salaam-Krampfe)
      - Lennox-Gastaut syndrome
   b. Specific etiology
      - Unverricht's disease
      - Lafora's disease
      - Lundborg-Hartung disease
      - Ramsay-Hunt syndrome
      - Kufs' disease
      - Zeman's disease
3. Epilepsies undetermined whether focal or generalized
   a. With both generalized and focal features
   b. Without unequivocal generalized or focal features
      - Sleep grand mal without more precise classification
      - Severe myoclonic epilepsy in infancy
4. Special syndromes
   a. Occasional seizures
      - Febrile convulsions
      - Nonfebrile convulsions
      -- in infancy
      -- in adolescence
      - Occasional partial seizures of adolescents
   b. Epilepsies characterized by specific modes of seizure precipitation
   c. Syndromes of chronic neuropsychological suffering with status-like EEG-activity
      1. Syndromes of limited course
         - Acquired epileptic aphasia (Landau-Kleffner syndrome)
         - Epilepsy with continuous spike-waves during slow sleep
      2. Progressive syndromes
         - chronic progressive epilepsia partialis continua of childhood

[a] This table was sent as a draft to the National Chapters of the ILAE. The document was not intended to be final. It can be compared to the 1970 version (Table 1.5). A revised version of this document was published in Epilepsia 26: 268–278 (1985). This revision was not available at the time of writing.

syndromes," a group certain to be controversial, which in some cases clearly overlaps with the partial or generalized epilepsies. The second tier of the classification is likewise virtually unchanged, with classic emphasis on whether or not the cause of the epilepsy is known or unknown. Again, the terminology is changed, but the overall structure is not. "Primary" has been replaced by "idiopathic" and "secondary" (which indeed has often been confused with secondary generalization of epileptic seizures—see discussion by Porter 1984) by "symptomatic."

It is in the expansion beneath the major terms related to localization/nonlocalization and cause-known/cause-unknown that the 1984 proposed syndromic classification makes its unique contribution (Table 1.7). Efforts are made to include syndromes in epilepsy based on criteria similar to those utilized in the 1970 version: patient history, seizure types, modes of seizure recurrence, neurological/psychological findings, EEG, radiographic (including CT), and magnetic resonance imaging findings, etc. As might well be expected, these criteria are applied in each proposed syndrome when relevant and when data are available. Under the very first group—localization-related epilepsies—one may find, for example, epilepsies whose major

distinguishing characteristics are primarily related to the seizure type and the EEG (e.g., benign childhood epilepsy with centrotemporal spikes); in others, more specific anatomical localization is possible and the most common etiologies are listed (e.g., orbitofrontal epilepsy). Such variability and flexibility of the application of the fundamental criteria is necessary in any empirical classification—including the classification of epileptic seizures; unfortunately, this variability weakens the clinical utility of the classification.

Nevertheless, the classification makes a concerted effort to define specific syndromes. An explanation of the terminology employed is appended to the classification, a testimony to the openness of the scientific thoughts of the classification committee. A critique of this proposed classification[1] is beyond the scope of this chapter and is not even appropriate; the committee is still actively seeking opinions before publishing a "final" version.

The classification of the epilepsies will continue to be a difficult task. The effort will be greatly assisted if new data-oriented methods of improving the classification can be created. The original aims of the 1970 classification remain valid, and those of us who wish to create a new order would be well advised to remember that the practicing physician and clinical investigator are the foremost targets of the effort.

[1] A revised version of this document was published in Epilepsia 26: 268–278 (1985). This revision was not available at the time of writing.

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Chapter 2

Neonatal Seizures

Peter Kellaway and Eli M. Mizrahi

Introduction

The world literature concerning neonatal seizures is not extensive, but it is sometimes confusing and often contradictory because of marked differences among authors as to the clinical phenomena considered to be seizures. This lack of uniformity is compounded by the fact that the methods of observation of the phenomena and the determination that they were seizures have varied with different authors and in different periods of time. First-hand observation and characterization of the clinical phenomena have been the exception rather than the rule, and many studies have been retrospective or dependent only on the observations and assessments of others not only for establishing that a seizure occurred but also for its characterization. The limitations of this type of study are obvious. In daily practice and in the literature, newborn infants are often described as having had a generalized tonic–clonic seizure, in spite of the fact that seizures of this type do not occur in infants until sometime after the third postnatal month. A quite recent publication concerned with the relationship between ischemic brain lesions in the newborn and epileptic seizures asserts that one of the most common seizure types in this condition is generalized tonic–clonic. If the phenomena that are the subject of the study are not precisely characterized, how reliable can the data be which are being reported?

Semiology

Over the past three decades, clinical investigators have attempted to develop a comprehensive classification of neonatal seizures (Table 2.1). However, the science of developmental physiology, the knowledge of epileptogenesis in the immature central nervous system (CNS), and the methodology and criteria of neonatal electroencephalography (EEG) have undergone many changes during this time. In addition, the technology and strategies applied to the study of clinical behavior thought to be neonatal seizures have changed.

Clinical phenomena designated as seizures of the newborn have varied, depending on techniques used to characterize these events and the points of view of the investigators. The current classification of neonatal seizures is best understood in the light of previous efforts to characterize seizures of the newborn.

The initial period of investigation emphasized the motor and behavioral changes thought to be seizures. Techniques varied: clinical observation only (Burke 1954; Craig 1960; Keen 1969; McInerny and Schubert 1969); correlation of clinical observation with interictal EEG (Prichard 1964; Schulte 1966; Massa and Niedermeyer 1968); clinical observation of seizures during EEG recording (Cadilhac et al. 1959; Harris and Tizard 1960; Passouant and Cadilhac 1962); and the first investigation in newborns which utilized combined EEG and cinematography (Dreyfus-Brisac and Monod 1964). Early investigators referred to all neonatal seizures as "convulsions" or "muscular twitching" (Burke 1954). But it was soon recognized that seizures of the newborn were not like those of older children or adults. Generalized tonic seizures and focal and multifocal clonic seizures were identified early as epileptic phenomena of the newborn. Generalized tonic–clonic seizures were considered to be rare or nonexistent in this age group (Minkowski et al. 1955; Ribstein and Walter 1958; Cadilhac et al. 1959; Dreyfus-Brisac and Monod 1964; Schulte 1966). However, bilateral but asynchronous clonic movements of the extremities, resembling a generalized clonic seizure, were appreciated by early investigators (Craig 1960; Harris and Tizard 1960; Passouant and Cadilhac 1962; Dreyfus-Brisac and Monod 1964). The spread of a clonic seizure was originally thought to be jacksonian (Harris and Tizard 1960), but it was soon recognized that this was not the case.

From the late 1950s to the mid 1960s, the following signs were identified as epileptic in the newborn: apnea with cyanosis or hypotonia (Cadilhac et al. 1959); staring, pallor, hypotonia, and alternating "warding off" movements of the arms (Harris and Tizard 1960); upward eye deviation, cyanotic apnea, slight finger contractions, sudden awakening with crying (Passouant and Cadilhac 1962); eye opening, paroxysmal blinking, nystagmus, vasomotor changes, chewing, limb movements "resembling swimming, rowing, and pedaling" (Minkowski and Sainte-Anne-Dargassies 1956; Dreyfus-Brisac and Monod 1964); and abrupt changes in respiration and skin color, salivation, and alerting behavior (Schulte 1966).

In 1964, Dreyfus-Brisac and Monod discussed their observations of neonates having clinical seizures and reviewed the investigations performed in their laboratory over a 10-year period (Sainte-Anne-Dargassies et al. 1953; Minkowski et al. 1955; Dreyfus-Brisac and Monod 1960). Their conclusions summarized this initial period in the development of the semiology of seizures of the newborn and indicated the direction that further clinical research efforts in this field should take:

Table 2.1. Summary of methodologies employed and clinical features of neonatal seizures recognized by various investigators since 1959

Investigators	Year	Methodology					Clinical features															
		Observation without EEG	Observation + interictal EEG	Observation + ictal EEG	Observation + ictal EEG/polygraph	Video + ictal EEG/polygraph	Focal clonic	Multifocal clonic	Tonic	Myoclonic	Hypotonia	Flushing, pallor, cyanosis	Apnea, dyspnea, hyperpnea	Staring, nystagmus, eye deviation, blinking	Arousal	Salivation, drooling	Oral–buccal–lingual	Swimming, rowing, pedaling	Change in heart rate	Change in blood pressure	Rise in intracranial pressure
Cadilhac et al.	1959			×			×	×	×		×	×	×								
Craig	1960	×					×	×	×		×										
Harris and Tizard	1960		×	○			×	×	×		×	×		×							
Passouant and Cadilhac	1962			×			×	×	×			×		×	×						
Dreyfus-Brisac and Monod	1964			×		○	×	×	×			×	×	×		×	×	×			
Schulte	1966		×	○			×	×	×				×								
Massa and Niedermeyer	1968	×	○				×		×												
Keen	1969	×					×	×													
Rose and Lombroso	1970		×	○			×	×	×	×			×	×		×	×				
Brown	1973	×					×	×	×												
Volpe	1973	×	○	○			×	×	×	×			×	×		×	×				
Knauss and Marshall	1977	×	○				×	×	×	×											
Volpe	1977	×	○	○			×	×	×	×			×	×		×	×	×			
Watanabe et al.	1977				×		×	×	×	×			×	×			×	×	×		
Fenichel et al.	1979				×								×								
Lou and Friis-Hansen	1979	×	○				×		×	×											×
Goldberg et al.	1982				×															×	×
Kellaway and Hrachovy	1983				×		×	×	×	×		×	×	×		×	×	×			
Perlman and Volpe	1983	×	○	○															×	×	×
Mizrahi and Kellaway	1984–1985					×	×	×	×	×		×	×	×	×	×	×	×			

[a] In methodology section, "×" denotes primary means of investigation; "○" indicates that some infants were also studied by the additional technique.

"Clinical and electrographic studies of status epilepticus and convulsions in newborn infants have revealed their polymorphic and atypical character in comparison with those of adults. ... Combined use of cinematography and electroencephalography has been of great help in the analysis of the clinical and electrographic manifestations of [neonatal] seizures."

The next period was characterized by the consolidation and confirmation by others of data generated principally by the French workers. Rose and Lombroso (1970) confirmed the findings of the various seizure types identified by Dreyfus-Brisac and Monod, including a group of behaviors they considered "difficult to classify because the peripheral phenomena were very slight". These behaviors (changes in respiration, slight posturing of limbs, tonic eye deviation, chewing, sucking, or drooling) were eventually referred to by Lombroso (1974) as a "minimal seizure pattern." Rose and Lombroso (1970) also identified myoclonus as a clinical seizure of the newborn. Freeman (1970) suggested that "the occurrence of any type of bizarre or unusual transient event" should raise the suspicion of a clinical seizure.

In 1973, Volpe proposed that some of the "atypical and anarchic" seizures described by the French group in the 1950s and the "slight" seizures described by Rose and Lombroso (1970) should be classified as "subtle." The remainder of his classification system included multifocal clonic, focal clonic, tonic, and myoclonic seizures. Although initially behaviors such as swimming, pedaling, or rowing movements were not included in Volpe's characterization of subtle seizures, by 1977 these behaviors became a part of his classification scheme. Although others (Knauss and Marshall 1977; Watanabe et al. 1977) presented similar classification systems, most clinical investigations of neonatal seizures refer to the Volpe classification, which was recently updated (Volpe 1981).

The next phase in the development of the semiology of neonatal seizures was marked by a study by Watanabe et al. (1977) characterizing 496 clinical seizures observed in 62 infants during EEG and polygraphic recordings. Multifocal clonic, focal or hemiconvulsive clonic, tonic, and myoclonic seizures were observed in addition to four groups of other paroxysmal behaviors: body/limb movements (swimming, rowing, pedaling, fencing); oral movements (chewing, sucking, mouthing); respiratory changes (apnea, dyspnea); and ocular changes (staring, eye opening, eye deviation, nystagmus, blinking). The basic concept of this investigation was to characterize any behavior as a seizure if accompanied by seizure activity in the EEG. Polygraphic parameters were recorded simultaneously with the EEG in order to characterize changes in respiration and heart rate associated with seizures.

The studies by Watanabe et al. (1977) and the general application of routine monitoring techniques to critically ill neonates initiated a phase in which autonomic changes associated with neonatal seizures were scrutinized. For example, Lou and Friis-Hansen (1979) described increases in mean arterial blood pressure during generalized and focal motor seizures in the newborn. Fenichel et al. (1979) recorded heart rate and respiration in order to characterize convulsive apnea, as did Watanabe et al. (1982). Goldberg et al. (1982) observed a group of infants paralyzed with neuromuscular blocking agents and demonstrated tachycardia, systemic hypertension, and increased pO_2 during EEG seizure activity. Perlman and Volpe (1983) showed that there were increases in cerebral blood flow velocity, systemic blood pressure, heart rate, and intracranial pressure during clinical seizures.

The recording of these parameters confirmed the observations of earlier investigators (Passouant and Cadilhac 1962; Dreyfus-Brisac and Monod 1964; Rose and Lombroso 1970; Volpe 1973) that the autonomic nervous system may be involved as an integral aspect of neonatal seizures. However, the frequency of occurrence of autonomic changes as epileptic events and their relationship to other seizure phenomena have not been determined. In a study utilizing bedside observation during EEG and polygraphic recording, Kellaway and Hrachovy (1983) differentiated two types of tonic seizure according to their association with autonomic changes. Eighty-five per cent of the newborns with tonic seizures had no accompanying autonomic features and no associated seizure activity in the EEG. The 15% of tonic seizures that were accompanied by electrical seizure activity were indistinguishable from those that were not, except that they were more often associated with autonomic changes. These findings raised two important issues in the development of the semiology of neonatal seizures and set the stage for the current period of investigation. First, neonates may demonstrate identical behaviors both with and without accompanying EEG seizure activity. Second, in some instances, autonomic signs associated with paroxysmal behaviors in the newborn may be the only clinical marker of the occurrence of electrical seizure activity in the brain.

Despite these efforts to identify and characterize seizures of the newborn, a consensus has not yet been reached as to the phenomena that are truly epileptic, and a uniform classification system has not been developed. As a result, published investigations concerned with etiology, prognosis, and treatment of seizures in the newborn often do not specify the precise nature of the phenomena regarded as seizures. Investigations utilizing the most modern techniques of pharmacological assay (Painter et al. 1978, 1981; Lockman et al. 1979; Fischer et al. 1981; Gal et al. 1982; Bourgeois and Dodson 1983), statistical analysis (Ellison et al. 1981; Holden et al. 1982; Mellits et al. 1982), or state-of-the-art radiographic and sonographic methodology (Chaplin et al. 1979; Dubowitz et al. 1981; Mannino and Trauner 1983; Bergman et al. 1985; Levy et al. 1985) are limited in value insofar as they employ seizure terminology or characterizations that are imprecise.

In recent years, intensive EEG/polygraphic monitoring techniques have been utilized effectively to characterize and quantify various seizure disorders, particularly absence seizures (Penry and Dreifuss 1969; Penry et al. 1975), complex partial seizures (Escueta et al. 1977; Belafsky et al. 1978; Delgado-Escueta 1979), and infantile spasms (Frost et al. 1978; Kellaway et al. 1979). [For a complete review, see Gotman et al. (1985).] Until recently, these techniques were not available for the investigation of seizures at cribside in the nursery. Now, however, a portable, time-synchronized EEG/polygraphic/video system has been designed and fabricated which permits intensive monitoring at the bedside (Mizrahi and Kellaway 1984a,b, 1985a,b; Kellaway and Frost 1985).

Application of intensive monitoring should afford a precise characterization and better understanding of the paroxysmal behaviors and autonomic changes that are signs of altered brain function in the neonate. As Volpe (1981) said, "... there is considerable need for further definition of the nature, frequency, and duration of various clinical manifestations of seizures in newborns. Similarly, delineation of the precise relations of seizure type to gestational age, etiology, response to therapy, and outcome awaits future clinical research."

The information in the next section is derived from two sets of studies: (a) personal observation of neonatal seizures during recording of the interictal and

ictal EEG (420 neonates), and (b) intensive cribside EEG/video/polygraphic monitoring using a newly developed portable time-synchronized system (134 neonates).

Electroclinical Correlations

In terms of the definition and classification of seizures we have employed in this chapter, it is important to recognize that there are neonatal seizures that (a) have a consistent relationship to EEG seizure activity, (b) have an inconsistent relationship to such activity, and (c) have no accompanying EEG seizure activity.

Seizures Having a Consistent Electrical Signature

Focal Clonic Seizures

Focal clonic seizures consist of rhythmic twitching of one side of the face or of an extremity; each twitch has a consistent, time-synchronized relationship to focal rhythmic sharp-wave discharges in the central region of the opposite hemisphere. Figure 2.1 shows the typical seizure discharge associated with this type of seizure. In this particular case, the seizures were consequent to hypocalcemia.

Focal clonic seizures are, of all seizures, the most easily recognized as being epileptic, but then they have features that are not typically seen in older children and adults:

1. *Alternation.* A focal clonic seizure involving one extremity may be followed in quick succession by a focal clonic seizure of the opposite homologous extremity; indeed, the seizures may overlap so that both extremities jerk at the same time, but asynchronously.
2. *Migration.* Focal motor seizures in neonates do not show a typical jacksonian march but may change abruptly from focal jerking confined to, for example, the hand, to focal jerking of the foot. Electrographically, this is associated with a change in the locus of the epileptogenic discharge, as shown in Fig. 2.2.
3. *Hemiconvulsion.* A seizure that may initially be confined, for example, to the hand on one side may abruptly involve the face and upper and lower extremities without an intervening jacksonian march. Electrographically, this is associated with a marked increase in the size of the field of the focus and an increase in the duration, and sometimes the complexity, of the focal sharp-wave discharge in the opposite hemisphere.

Tremor and clonus are often mistaken for clonic seizures. Although these are important neurological signs, they are not epileptic and have an entirely different pathophysiological basis. Epileptic clonic seizures characteristically have a slow rate of movement; the jerking of the limb or the twitching of the face is consistently rhythmic and slow compared with clonus or tremor, and if the limb is physically

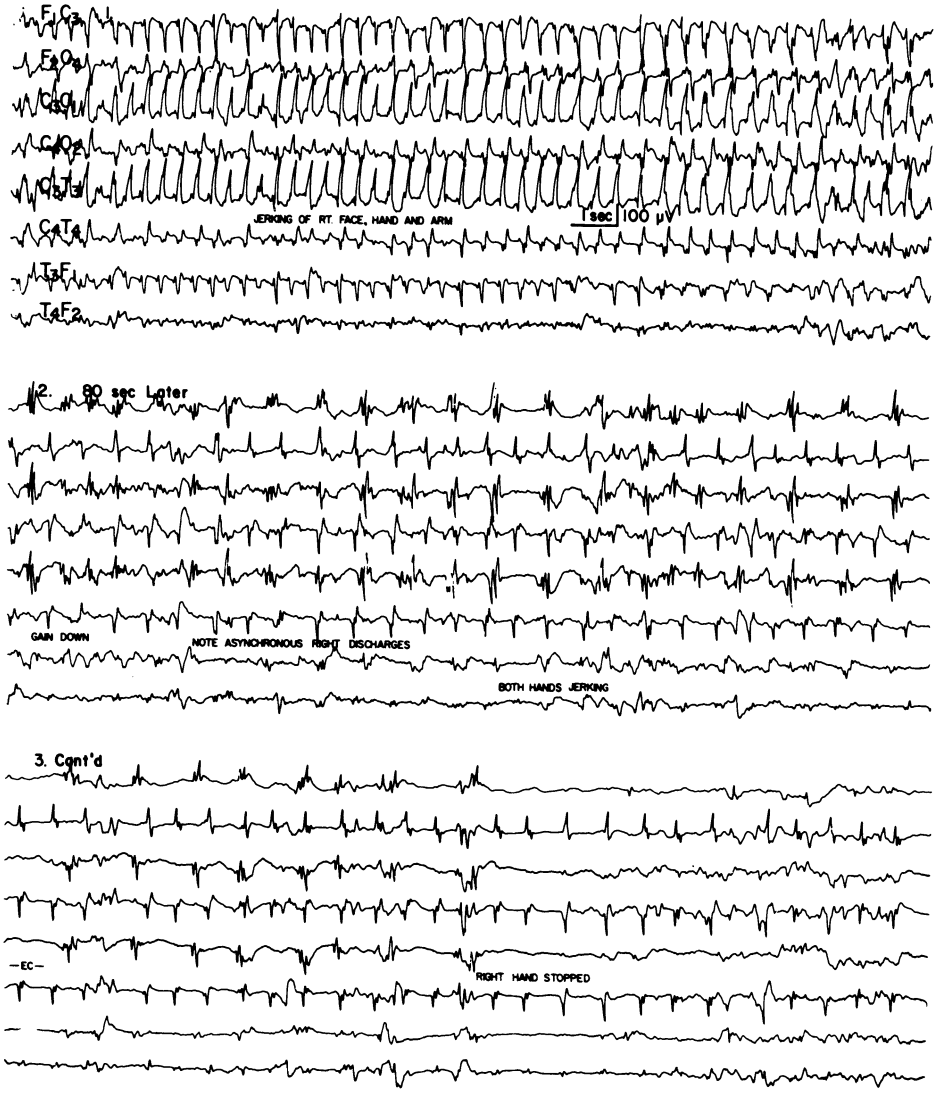

Fig. 2.1. This seizure was recorded in a term infant who developed focal motor seizures 14 days after birth. Between seizures, the EEG showed normal background activity and no interictal focal spikes or sharp waves. In this particular seizure, the jerking began in the right hand and arm and quickly involved the face. The focal sharp-wave activity began at C_3 and soon was reflected at lower voltage in C_4 and in the midtemporal derivation bilaterally. After approximately 120 s, the rate of the discharge began to decrease and independent (asynchronous) focal spike activity began to appear in the right central region. At this point, there was jerking of the hands bilaterally but asynchronously on the two sides. Finally, the jerking of the right hand ceased, as did the repetitive discharge in C_3. The spike discharges continued in C_4, as did the jerking of the left hand, for another 37 s. Occasionally, at the height of bilateral spiking, the activity of the two sides may, for a time, be synchronized. Probably, it is this phenomenon which has led some authorities to insist that neonates can have generalized clonic seizures.

This is a case of primary hypocalcemia, a condition only rarely seen in the modern nursery. In primary hypocalcemia (late neonatal hypocalcemia), the electrical seizure discharges are always high in voltage and the spikes have a repetition rate of about 2–3/s. The focal jerking of the limb is strong and occurs synchronously with the focal seizure discharges in the EEG. In secondary hypocalcemia (early NHC), the background EEG is usually abnormal and the infant may also be depressed and obtunded, depending upon the severity of the primary brain insult (e.g., hypoxia).

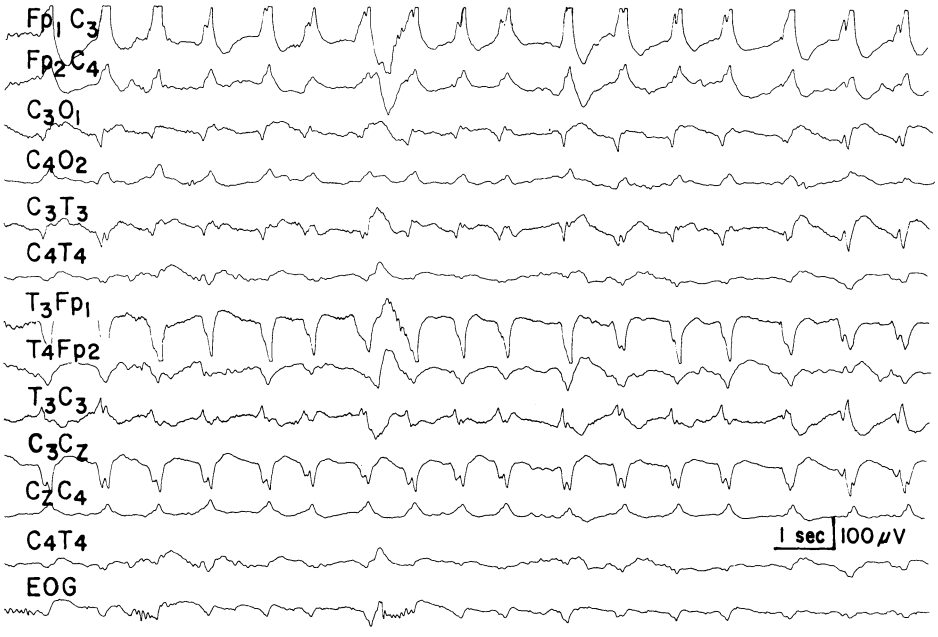

Fig 2.2a

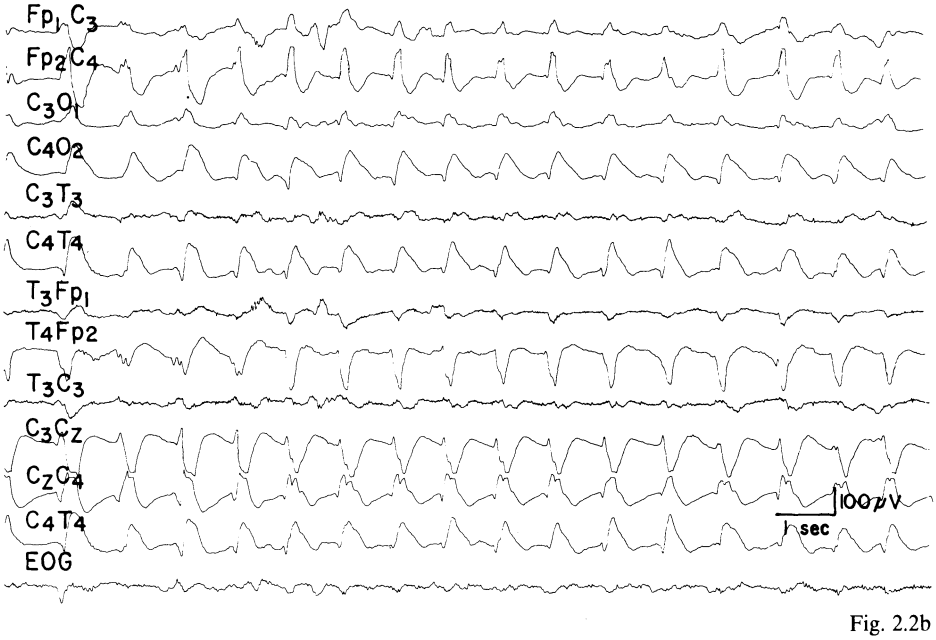

Fig. 2.2b

Fig. 2.2. This term infant, aged 31 days, shows, in **a**, focal high-voltage sharp waves occurring with a repetition rate of about 1/s in the left frontal region, associated with deviation of the eyes to the right and twitching of the right face. **b** The discharge 110 s later switched to the right frontocentral region, and the clinical seizure changed to twitching of the left hand. **c** Fifty seconds later the repetitive sharp-wave discharge was confined to the midline central region, Cz, and was associated with slow twitching of the left foot. Diagnosis: asphyxia, hypoglycemia, subarachnoid hemorrhage.

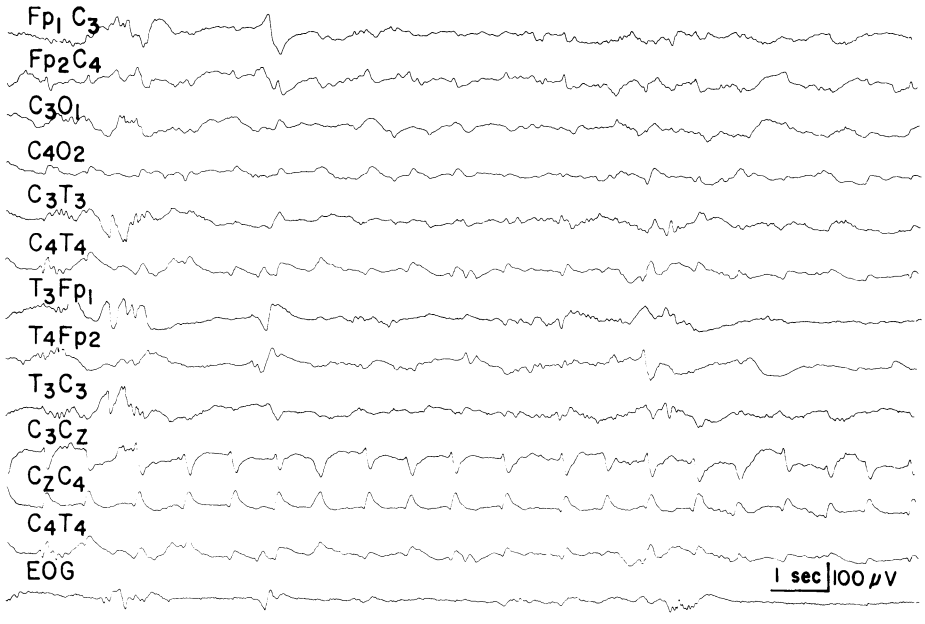

Fig. 2.2c

restrained, the muscular twitches can still be felt. Tremor is faster, and the limb excursion is smaller and will stop when the limb is restrained. Clonus may stop simply upon repositioning of the limb. Epileptic clonic activity usually has a rate of about 1–3 jerks per second; the rate usually shows a progressive decline toward the end of the seizure. More rarely, a faster rate of 3–4 jerks per second may occur, but in this case, clonic movements are confined to a quite circumscribed muscle group, e.g., the fingers of one hand. Because the excursion of the movement may be quite small, it may be mistaken for tremor.

Before the end of the 1960s, clinical focal seizures were the most common type of seizure recognized, and the most common cause was hypocalcemia. Currently, the most common cause is subarachnoid hemorrhage, but there are many cases in which the cause is not established. In the latter, the generally favorable outcome and the otherwise normal neurological status of the infant and typically normal background activity in the EEG suggest that the seizures may arise as a consequence of metabolic abnormalities yet to be recognized. In view of recent histological studies of tissue removed during surgery from patients with complex partial seizures, cortical ectopia may also be a cause of this kind of seizure (Bruner et al. 1983).

Myoclonic Seizures

Myoclonic jerks of individual extremities or of circumscribed muscle groups occur coincident with focal sharp-wave discharges in the EEG. Flexor muscles are predominantly involved, and, electrographically, each myoclonic jerk is associated with a high-voltage sharp wave of long time course and extensive electrical field in the central region (Fig. 2.3). An individual infant may show only this type of seizure, but there are also cases in which the random flexor jerks evolve into a focal clonic seizure. This change is associated, electrographically, with the appearance of rhythmic sharp-wave discharges of lower voltage and shorter time course (Fig. 2.4).

Bilateral, "slow" myoclonic jerks, occurring in isolation or in a very slow rhythmic series, also occur in neonates and are associated, electrographically, with quite slow, extremely high-voltage, sharp-wave transients occurring bilaterally but slightly asynchronously on the two sides (Fig. 2.5). The myoclonic jerks also are slightly out of phase on the two sides. This type of seizure is seen only in severe encephalopathies—primarily hypoglycemia and hypoxia.

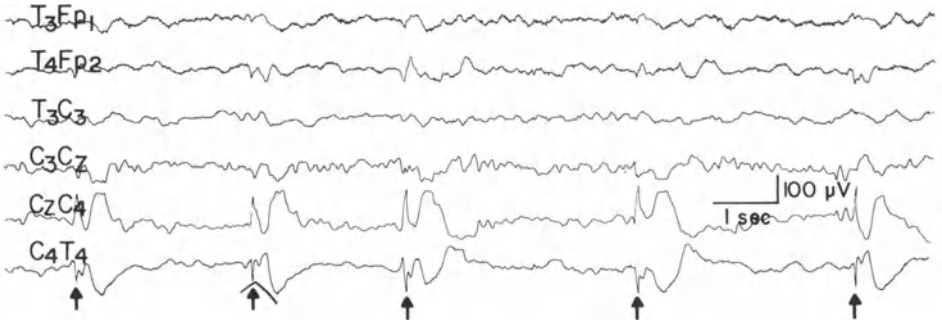

Fig. 2.3. Random or semiperiodic jerks of an extremity or a single muscle group may occur in synchrony with high-voltage sharp- and slow-wave complexes in the central region of the opposite hemisphere. This term infant showed myoclonic jerks of the proximal muscles (shoulder) of the left upper extremity (marked with an *arrow*) with each sharp- and slow-wave complex in the right central region. Diagnosis: undetermined.

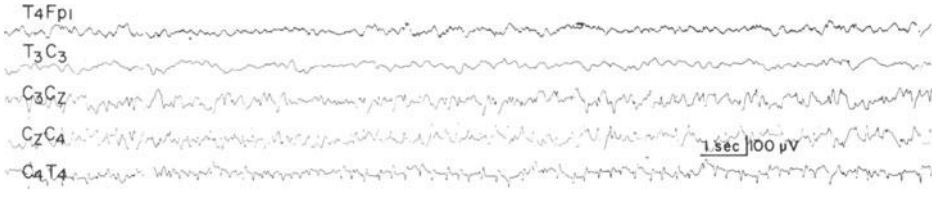

Fig. 2.4. This recording is from the same infant as in Fig. 2.3, about 20 min later. It shows the onset of a clinical seizure consisting of rhythmic flexion of the fingers of the left hand at a rate of 4–5/s. Spike discharge rates this high have not been seen in infants before the 4th week post-term.

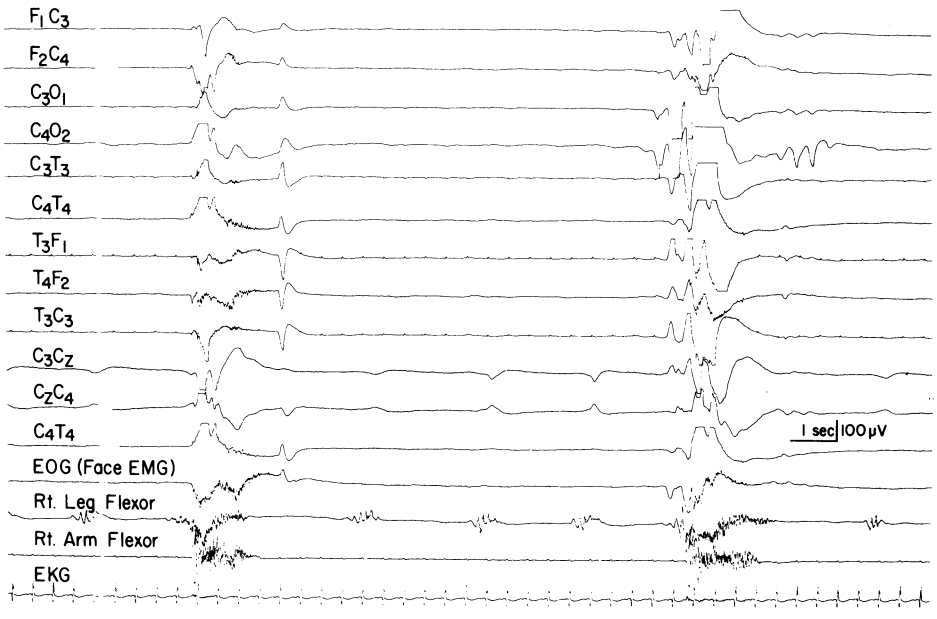

Fig. 2.5. Bilateral, "slow" myoclonic jerks of flexors of the arms, legs, and abdomen are accompanied, as in this example, by a paroxysmal generalized complex of slow waves. The onset of the muscle potentials in the flexor muscles precedes the onset of the EEG event. Shown are two bilateral myoclonic jerks. The muscular contraction, as evidenced by the EEG channel, lasts from 2 to 2.5 s, hence the term "slow" myoclonus. Also shown are a series of three slight myoclonic contractions confined to the flexors of the right leg. Each of these is followed by a low-voltage slow transient appearing only at Cz (the midline central derivation). Preterm 26 weeks; conceptional age at EEG, 40 weeks. Diagnosis: grade IV left intraventricular hemorrhage and hydrocephalus. Pathology: periventricular leukomalacia, large cavitation of centrum ovale on the left, subarachnoid hemorrhage of cerebellum and brain stem.

Seizures Having No Association or a Variable Association with EEG Seizure Activity

All the other types of neonatal seizure, including some myoclonic seizures, may occur with no associated electrical seizure activity or with only a variable association with such activity, if present. That is, they may occur in an individual infant who shows no electrical seizure activity and also in infants who do show such activity, but the clinical seizures occur sometimes with and sometimes without the electrical events.

Motor Automatisms

Examples of motor automatisms are oral–buccal–lingual movements, ocular signs, progression movements of the extremities, and thrashing and struggling movements. All of these behaviors, currently referred to as subtle seizures (Volpe 1981), may occur in the absence of any electrical seizure activity. The movements are

quite stereotyped in a given infant and are similar in different infants. They occur in infants who are obtunded and who otherwise show paucity of spontaneous movement. The EEG is depressed and undifferentiated; that is, the activity is low in voltage and characterized by an attenuated frequency spectrum compared with the EEG of the normal full-term newborn.

1. *Oral–buccal–lingual movements.* Repetitive puckering, sucking, or grimacing of the mouth, and tongue protrusion may occur in the absence of any EEG seizure activity. When electrical seizure activity is present, the same movements may occur either in a variable or a consistent relationship to it. Rhythmic tongue protrusion sometimes occurs in a time-locked relationship to repetitive seizure discharges in the EEG, but in this situation there is also involvement of the face or upper extremity on one side.

2. *Eye opening, nystagmus, oscillatory eye movements.* These also occur in the absence of electrical seizure activity in neonates with depressed and undifferentiated EEGs.

3. *Progression (locomotor) movements.* These consist of swimming movements of the upper extremities or pedaling or stepping movements of the lower extremities. The movements are usually bilateral but may be confined to one side or be of greater amplitude on one side.

4. *Complex purposeless movements.* These may be characterized by repetitive moving of the head from side to side, thrashing about, or struggling movements. They are the rarest type of paroxysmal motor automatism and occur in very obtunded infants who otherwise have a paucity or absence of spontaneous movement.

Tonic Seizures

Tonic seizures may be bilateral, unilateral, or bilateral but asymmetrical. They may be extensor or flexor, or mixed extensor–flexor. There may be tonic version of the trunk to one side and head turning, or turning of the head and extension of the neck (Fig. 2.6). Deviation of the eyes to one side and nystagmus may also be present, and there may be associated apnea, grunting respirations, pupillary constriction or dilatation, abrupt changes in heart rate, and increased blood pressure (see Autonomic Features, below).

Bilaterally symmetrical tonic seizures consist primarily of hyperextension of the upper and lower extremities or hyperextension of the lower extremities and flexion of the arms. There may also be hyperextension of the torso and of the neck. Tonic flexion of the trunk and of the extremities is rare, and when it does occur it is usually asymmetrical, with the trunk pulling down and to one side.

Tonic seizures are distinguished from infantile spasms by their relatively slow execution. They do not have the quick phasic component of the flexor or extensor seizures of infantile spasms. Symmetrical tonic posturing is seen most often in infants with depressed or undifferentiated EEGs with no electrical seizure activity.

Asymmetrical tonic posturing most often occurs in infants who show electrical seizure activity, and it is often difficult to determine whether the associated features of the seizure, e.g., eye turning or nystagmus, or the autonomic changes are directly related to the electrical seizure discharges.

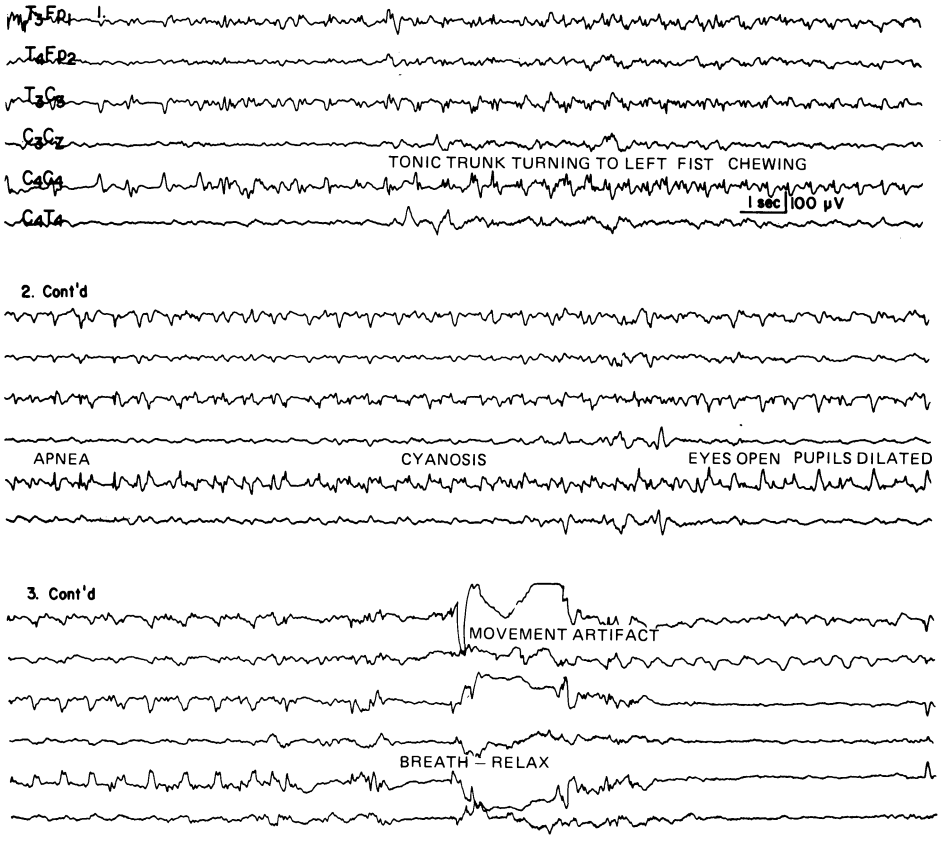

Fig. 2.6. Tonic posturing of the trunk, fisting, chewing, and apnea, followed by the eyes opening wide and dilation of the pupils, occurred in this infant, with and without electrical seizure activity of the type shown.

Tonic seizures and motor automatisms may be elicited in most cases by sensory stimulation. This effect is commonly observed when the infant is suctioned or even repositioned in the course of routine care. Painful stimulation such as pinching of a toe may also be effective, and an important phenomenon from the standpoint of the putative pathophysiological mechanism involved is that the more intense or repetitive the stimulus, the greater the response in terms of both the magnitude of the movement and the degree of irradiation of the response.

Autonomic Features

Autonomic changes are rarely the sole expression of a seizure but are common accompaniments of motor seizures. They do not appear to be secondary to the motor activity, however, because they may be present in clinically paralyzed infants. Paroxysmal increases in blood pressure and, more rarely, pupillary dilatation may signal that seizure activity is occurring in the paralyzed infant, as verified subsequently by EEG and polygraphic recording (Fig. 2.7).

Apnea as the *sole* clinical manifestation of a seizure must be extremely rare if, indeed, it occurs at all (we have not seen it). When apnea occurs in association with EEG seizure activity, it is generally also associated with other clinical signs such as tonic posturing, tonic eye deviation, and so forth. Central apnea due to maturational or other factors is much more common than epileptic apnea, and the latter should not be considered likely unless other clinical seizure phenomena occur concurrently.

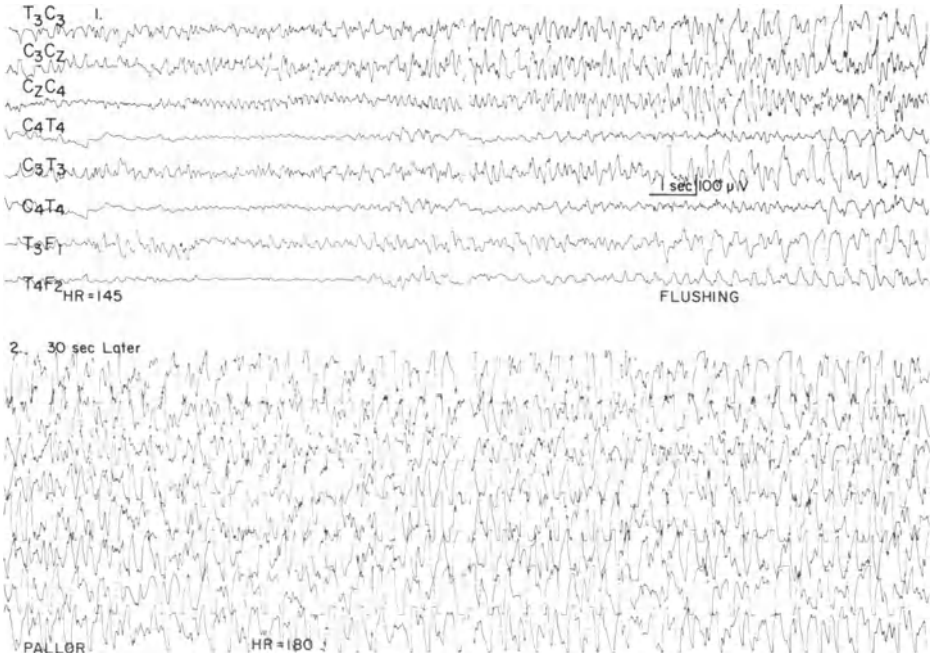

Fig. 2.7. Term neonate asphyxiated at birth, started on Pavulon. Noted to have recurrent episodes of increased heart rate and blood pressure. EEG showed that these were associated with electrical seizure activity beginning focally in the left centrotemporal region. Electrical seizures occurred every few minutes and lasted from 50 to 250 s. Recurrent transient episodes of elevated blood pressure and/or heart rate may be evidence of electrical seizure activity in the infant receiving Pavulon.

EEG Correlates of These Seizure Types

The EEG in neonates who show paroxysmal motor automatisms is diffusely depressed and undifferentiated, and electrical seizure activity, if present, has some special features that are characteristic of this state.

The voltage of the electrical discharge is relatively low and may show little or no augmentation as the discharge progresses. It usually consists of slow- and sharp-wave complexes that increase in wavelength toward the end of the discharge (Fig. 2.8). Because of their attenuated appearance and their characteristic association with depressed and undifferentiated background EEG activity, we have called these "depressed brain seizure discharges."

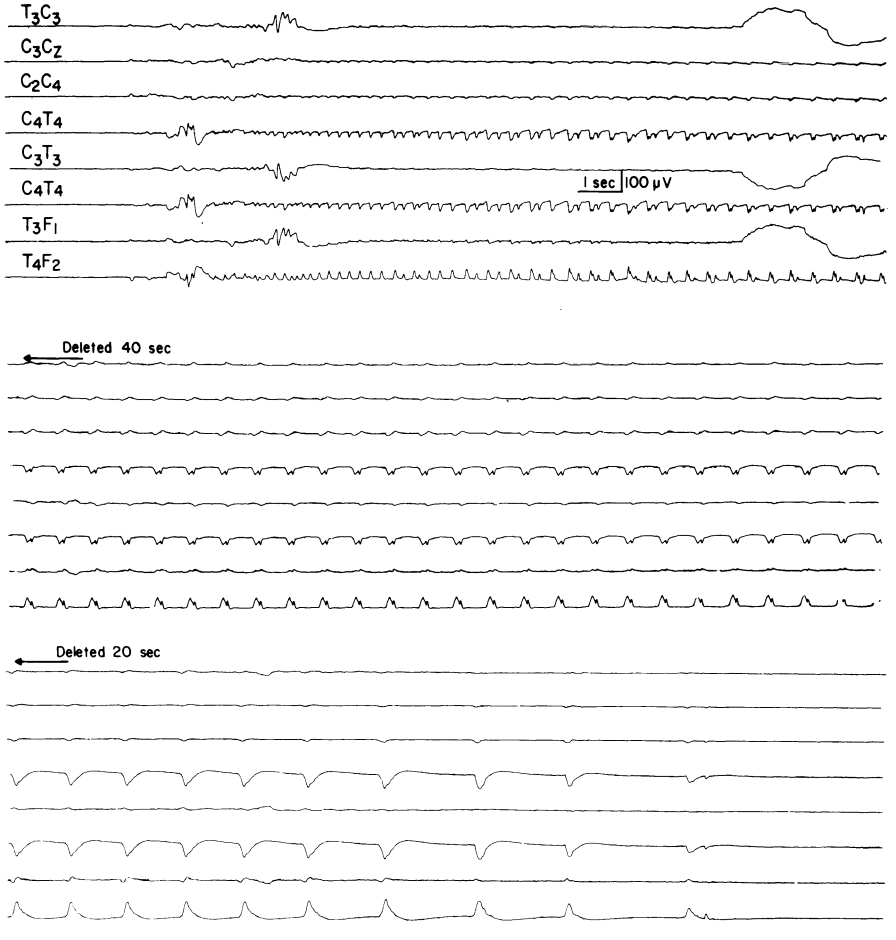

Fig. 2.8. Example of "depressed brain electrical seizure." In infants who have depressed and undifferentiated electroencephalograms, focal electrical seizures may occur which are low in voltage and, although they may last for a minute or more, show little increment in voltage. The individual sharp waves of the electrical seizures progressively decrease in frequency and then cease. There are usually no interictal focal spikes or sharp waves.

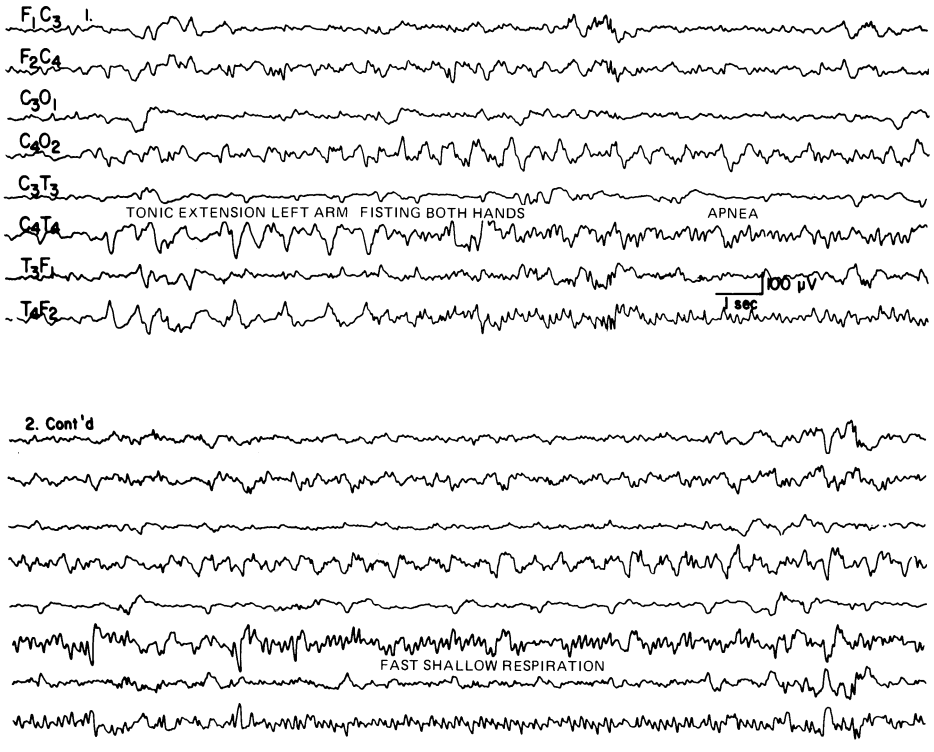

Fig. 2.9. Example of alpha-frequency activity at onset of focal electrical seizure arising in the right temporal region. Clinical seizures consisting of tonic extension of the left arm, fisting of both hands, and then apnea, followed by fast shallow respiration, occurred, as shown in the figure, not only in association with electrical seizure activity but also when no such activity was present. Diagnosis: asphyxia, hypoglycemia.

A particular EEG pattern seen only in infants with depressed and undifferentiated EEGs consists of rhythmic trains of 8–10 Hz activity that appear chiefly on one side, usually in the centrotemporal region, persist for a few to as many as 40 s, and abruptly disappear (Fig. 2.9). Interspersed with the abnormal alpha-frequency activity there may be some repetitive low-voltage sharp- and slow-wave complexes, or sharp- and slow-wave serials may ultimately replace the alpha-frequency activity when it ceases (Fig. 2.9).

The relationship of this alpha-frequency activity to repetitive sharp- and slow-wave complexes and its apparent association with clinical seizures are the basis for considering it to be a unique form of electrical seizure discharge.

Etiology

At no time in life is the brain subject to so many possible hazards for injury and dysfunction and in so concentrated a period as from conception to the end of the first 4 weeks of postnatal life. The factors causing injury or dysfunction may be

present either prior to or following birth, and the degree and character of the injury or dysfunction will depend, in part, on the maturational development of the brain at the time these factors are operant. The influence of the maturational state of the brain in determining the effects and clinical expression of various types of insult or metabolic dysfunction is not well understood, and no attempt will be made in this chapter to discuss this subject in detail. It is clear, however, that certain insults and dysfunction produce different patterns of response in the immature than in the more mature organism. For example, premature infants, who may be said to be born in calcium debt, tolerate levels of 5.0 mg per 100 ml or less without having seizures, whereas term infants will have clonic seizures when the calcium level is only a little less than 7.4 mg per 100 ml (Kellaway and Prakash 1974). Similarly, the premature infant appears to tolerate more severe degrees of hypoxia than does the full-term neonate without having seizures of any kind. The degree to which this reflects a greater cellular resistance to hypoxia or a lack in the immature brain of the neuronal substrate necessary for the elaboration of certain types of seizure has not been determined.

In this discussion of etiology, the changes that have taken place during the past 25 years in the relative incidence and importance of various etiological factors will be reviewed so that current concepts concerning etiology and prognosis can be more easily understood. Only the major etiological factors will be discussed in detail; the less common factors have merely been noted and listed (Table 2.2).

Table 2.2. Detailed etiological factors in order of current incidence

I. Perinatal asphyxia

II. Infection
- A. Septicemia
- B. Meningitis
  1. Group B β-streptococcus
  2. *E. coli*
- C. Meningoencephalitis
  1. Herpes simplex
  2. Toxoplasmosis
  3. Coxsackie B
  4. Rubella
  5. Cytomegalovirus

III. Intracranial hemorrhage and ischemia
- A. Subarachnoid hemorrhage
- B. Subdural hemorrhage
- C. Intraventricular hemorrhage
- D. Stroke

IV. Congenital anomalies
- A. Cerebrocortical dysgeneses
  1. Agyria
  2. Pachygyria
  3. Polymicrogyria
- B. Hydranencephaly
- C. Holoprosencephaly
- D. Trisomies

Table 2.2 continues on p. 30

Table 2.2 (*continued*)

V. Acute metabolic problems
  A. Hyponatremia and hypernatremia
    1. Inappropriate fluid therapy
    2. Sodium bicarbonate therapy in prematures
    3. Inappropriate antidiuretic hormone
  B. Hypoglycemia
    1. Transient
      a) Small for gestational age
      b) Prematurity
      c) Hyperinsulinemia, infant of diabetic mother
      d) Perinatal asphyxia or trauma (hemorrhage)
      e) Meningitis
      f) Postexchange transfusion
    2. Persistent
      a) Galactosemia
      b) Fructosemia
      c) Leucine sensitivity
      d) Glycogen storage disease (glucose-6-phosphatase deficiency)
      e) Infantile gigantism (3.8–5.3 kg)
      f) Macroglossia (Beckwith)
      g) Pancreatic islet tumor
      h) Anterior pituitary hypoplasia
  C. Hypocalcemia
    1. Early (secondary)
      a) Perinatal asphyxia trauma (hemorrhage)
      b) Small for gestational age
      c) Infant of diabetic mother
      d) Postexchange transfusion
      e) DiGeorge syndrome
      f) Septicemia
      g) Maternal hyper- or hypoparathyroidism
    2. Late (primary)
      Diet—low calcium/phosphorus ratio
    3. Hypomagnesemia
      a) Associated with hypocalcemia
      b) Magnesium malabsorption syndrome

VI. Unknown

VII. Rare causes
  A. Inborn errors of metabolism
    1. Aminoaciduria
      a) Phenylketonuria
      b) Maple sugar urine disease
      c) Hyperglycinemia
      d) Congenital lysinuria
    2. Urea cycle defects
      a) Carbamyl phosphate synthetase deficiency
      b) Ornithine carbamyl transferase deficiency
      c) Citrullinemia
      d) Argininosuccinic aciduria
      e) Transient hyperammonemia of preterm and associated with perinatal asphyxia
    3. Organic acidurias
      a) Propionic acidemia
      b) Methylmalonic acidemia
      c) Methylmalonyl-CoA mutase deficiency

Table 2.2 (*continued*)

- 4. Pyridoxine
  - a) Deficiency
  - b) Dependency (autosomal recessive)
- B. Neurodermatoses
  - 1. Incontinentia pigmenti
  - 2. Neurofibromatosis
  - 3. Sturge-Weber disease
  - 4. Tuberous sclerosis
- C. Toxins
  - 1. Endogenous
    - a) Bilirubin encephalopathy
  - 2. Exogenous
    - a) Mercury
    - b) Hexachlorophene
    - c) Injected penicillin or anesthetics (for labor)
- D. Maternal drug dependency
  - 1. Narcotics
  - 2. Barbiturates
- E. Familial
  - 1. Benign neonatal seizures

The relative incidence of specific etiological factors has varied over the last 25 years as a reflection of new developments in diagnostic techniques, increased recognition of different etiological agents and disorders, and, primarily, an increasing sophistication of neonatal care. Figure 2.10 and Table 2.3 summarize these changes and help to explain why the literature concerning this subject appears to be conflicting and often confusing. Distinction of a single etiological agent as responsible for the seizures is often difficult and may, indeed, be futile. For example, the prime factor in early neonatal hypocalcemia may be hypoxia or hypoglycemia, but the focal motor clonic seizures are a direct result of the hypocalcemia. If tonic seizures are also present, they will not be due to hypocalcemia but to the primary insult—hypoxia or hypoglycemia. Distinctions are even more difficult when hemorrhage coexists with asphyxia and focal infarction coexists with ischemic hypoxia.

The earliest studies of etiology and prognosis dealt primarily with autopsy material (Burke 1954; Craig 1960). Other diagnostic techniques were either not available or not utilized. Some investigators, e.g., Craig (1960), were hesitant to perform lumbar punctures on infants in whom the diagnosis was uncertain. By the mid 1960s, biochemical assays became more routinely available. The 1970s were marked by the development of techniques for the characterization of viral infections and the application of computerized axial tomography and cranial B scan ultrasound to neonates. As a result of these developments, the percentage of cases in which the etiology is unknown should have declined significantly; but the etiology still cannot be established in a significant percentage (Watanabe 1981; Ment et al. 1982; Bergman et al. 1983). In one series there was little difference in the percentage of unknown etiologies between a group collected between 1962 and 1971 and one studied between 1972 and 1977 (Kellaway and Hrachovy 1983).

It is difficult to ascertain from the literature the true relative incidence of asphyxia as a cause of neonatal seizures because criteria and terminology have varied widely among investigators. For example, these infants have been included in groups having "perinatal complications" (McInerny and Schubert 1969),

Table 2.3. Percent occurrence of various etiologic factors in neonatal seizures reported since 1954

Investigator	Year	Patient number	Asphyxia	Hemorrhage[e]	CNS infection	Anomaly	Infarction	Hypoglycemia	Hypocalcemia	Unknown
Burke	1954	48	66			2				32
Ribstein and Walter	1958	75	63		4					
Craig[a]	1960	374		21	7	5				48
Harris and Tizard	1960	41	44	7		10		5		20
Schulte	1966	57	54		7	7				23
Massa and Neidermeyer	1968	82	10	2		7		1	6	30
McInerny and Schubert	1969	95	32		9	4		6	30	12
Keen	1969	100	7	2	2	1		6	34	37
Rose and Lombroso	1970	137	21		10	8		5	20	
Kellaway[b]	1971	240	36		4	6		5	31	23
Hopkins[c]	1972	75	22	13					39	36
Brown	1973	45							55	
Keen and Lee	1973	13			1	1		3	41	33
Rossier et al.	1973	53				6		22	21	4
Combes et al.	1975	129	77					11	10	9
Kellaway[b]	1977	80	36		12	5		4	12	30
Volpe	1977	70	60	15	12			9	13	
Boros and Nystrom	1977	38	45		8			10	42	21
Watanabe et al.	1977	215	52		8	8		2	13	12
Dennis	1978	50	44		12	4				10
Ericksson and Zetterstrom	1979	77	48		12			6	3	29
Watanabe	1981	319	51		9	8		3	14	12
Ment et al.	1982	116	32	33	11	5				
Bergman et al.	1983	131	56		9	4		5	2	12
Lombroso	1983	210	25	17	12	9		9	7	23
Levy et al.	1985	50	52	6	14	6	14			14
Mizrahi and Kellaway[d]	1986	33	48	18	15	3	9	3		

[a] Asphyxia not a diagnostic category; unknowns include 152 patients with "presumptive diagnosis of intracranial disturbance."
[b] See Kellaway and Hrachovy (1983).
[c] Multiple diagnoses reported for each patient.
[d] See Table 2.4.
[e] Includes intracerebral, intraventricular, and subarachnoid hemorrhage.

"fundamental perinatal factors" (Dennis 1978), "intracranial disturbances" (Craig 1960), and, more accurately, "hypoxic–ischemic encephalopathy" (Volpe 1981). Taking these variables into account, it appears that the *relative* incidence of asphyxia as a cause of neonatal seizures diminished from more than 60% in early studies (Burke 1954; Craig 1960; Harris and Tizard 1960) to 20%–30% in the late 1960s (Rose and Lombroso 1970; Hopkins 1972; Kellaway and Hrachovy 1983), with an eventual rise to the current level of about 50% (Watanabe 1981; Bergman et al. 1983).

The fluctuation in the relative role of asphyxia (see Fig. 2.10) in neonatal seizures is related to the high incidence of early and late neonatal hypocalcemia that

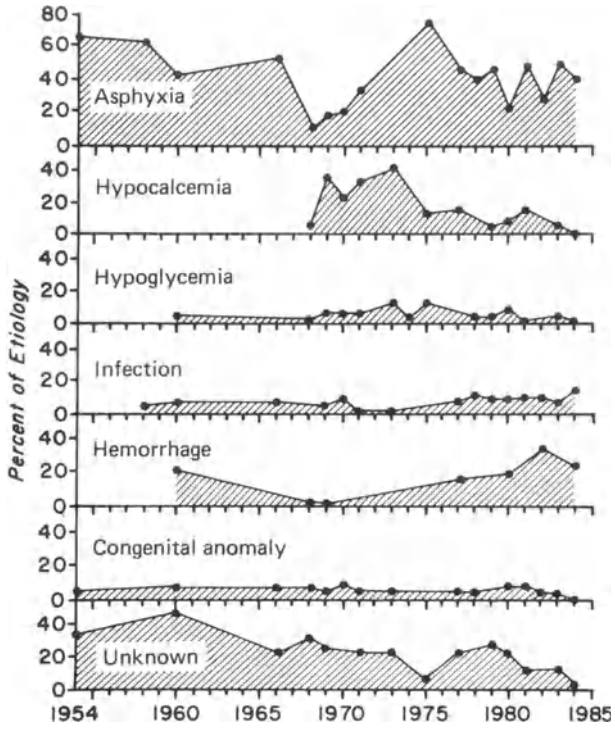

Fig. 2.10. Trends in relative occurrence of etiologic factors of neonatal seizures compiled from studies noted in Table 2.3. The current rise in infarction as an etiologic factor is not shown since this cause of neonatal seizures has been documented only recently.

occurred in the 1960s, which resulted in a relative decrease in the percentage of seizures secondary to asphyxia. The more recent increase in the percentage of seizures ascribed to asphyxia may be related to the drastic reduction in metabolic derangements resulting from more sophisticated neonatal care and to the increased survival of asphyxiated pre- and full-term newborns.

By the late 1960s, it was recognized that metabolic derangements, particularly hypocalcemia (Keen 1969), hypoglycemia (Griffiths 1968), and hypomagnesemia (Freidman et al. 1967; Wong and Teh 1968), were significant factors in the genesis of some neonatal seizures and, with increasing awareness of the metabolic requirements of newborns, hypocalcemia has been virtually eliminated as a common cause of neonatal seizures.

On the other hand, the reported incidence of intracranial hemorrhage gradually increased during the 1970s (Volpe 1981). This was largely a consequence of increased survival of those infants subject to intracranial hemorrhage (the asphyxiated full-term and the premature) and of improved techniques of detection (Dubowitz et al. 1981; Ment et al. 1982).

The relative incidence of congenital CNS anomalies has remained constant at less than about 5% of cases (Kellaway and Hrachovy 1983). Until recently, the incidence of CNS infection had also remained constant, but it now appears to be

Table 2.4. Seizure type, etiology, immediate outcome, and duration of short-term follow-up in 33 neonates studied by EEG/polygraphic/video monitoring

Seizure type	No. of patients	Patient identification	Conceptional age (weeks)	Etiology									Outcome			Age at death or discharge (weeks)
				Hypoxia-ischemia	CNS infection	Infarction	Intracerebral hemorrhage	Subarachnoid hemorrhage	Intraventricular hemorrhage	Hypoglycemia	Inborn errors of metabolism	CNS malformation	Died	Abnormal	Normal	
Focal motor		1	42					×							×	1
		2	40			×									×	1
		3	40				×								×	1
		4	40							× [a]					×	3
		5	39			×									×	1
		6	40					×							×	2
		7	42	× [b]											×	2
		8	40				×								×	2
		9	40			× [c]								×		2
(Total)	(9)			(1)	(0)	(3)	(2)	(2)	(0)	(1)	(0)	(0)	(0)	(1)	(8)	
Automatisms		10	43		x [d]									×		7
		11	37	×											×	2
		12	41	× [e]											×	2
		13	40	×										×		2
		14	40		× [f]									×		3
		15	43		× [f]										×	3
		16	36	× [b]										×		8
(Total)	(7)			(4)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(4)	(3)	

Table 2.4 (*continued*)

Tonic		17	31	×[e]									×		23
		18	38	×[e]										×	2
		19	40	×[g]										×	2
		20	40	×										×	2
		21	40	×										×	2
		22	34	×									×		5
(Total)	(6)			(6)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)	(3)	(1)	
Automatisms + tonic		23	38		×[f]									×		7
		24	41	×										×		4
		25	38		×[f]										×	4
		26	40						×						×	5
		27	39	×										×		4
(Total)	(5)			(2)	(2)	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(3)	(2)	
Myoclonic		28	33	×[e]									×			10
		29	38				×							×		1
		30	42	×									×			2
		31	36	×											×	1
		32	34									×[h]		×		2
		33	37								×[i]				×	2
(Total)	(6)			(3)	(0)	(0)	(1)	(0)	(0)	(0)	(1)	(1)	(2)	(2)	(2)	
Grand totals	(33)			16	5	3	3	2	1	1	1	1	4	13	16	
Percentage				48%	15%	9%	9%	6%	3%	3%	3%	3%	12%	39%	49%	

[a] Secondary to hyperinsulinism.
[b] Hypotension + acidosis.
[c] In association with skull fracture, left parietal contusion, and subarachnoid hemorrhage.
[d] Herpes simplex virus.
[e] With intracerebral or intraventricular hemorrhage.
[f] Group B streptococcus.
[g] With hypoglycemia.
[h] Congenital hydrocephalus.
[i] Citrullinemia.
[j] Disseminated intravascular coagulation and shock.

rising (Kellaway and Hrachovy 1983), possibly as a result of improved techniques of detection and an increased awareness of the role of viral infection in CNS diseases of the newborn.

Recently, there has been interest in the role of stroke as an etiological factor in seizures of the newborn. Earlier studies rarely mentioned stroke as a possible cause; however, cerebral infarction may be a more common cause of neonatal seizures than was previously appreciated. Mannino and Trauner (1983) reported five neonates with cerebral infarctions of arterial origin, four of whom had focal clonic seizures on the first day of life. Clancy et al. (1985) described their findings in 11 full-term infants with localized cerebral infarction confirmed by CT scan. Of special interest is their finding that the major presenting feature in all of these cases was repeated, persistently unifocal, clonic seizures without lateralizing features on neurological examination. Levy et al. (1985), in a study of 50 full-term infants admitted to the nursery or neonatal intensive care unit over a period of 12 months, found that in seven (14%), infarction was the cause of the seizures. Our own recent monitoring studies indicate that cerebral infarction may account for as many as 9% of neonatal seizures (see Table 2.4). Again, this growing awareness of infarction may be related to improved diagnostic techniques but may also be related, in some studies, to a lack of differentiation between hemorrhage and infarction.

Obviously, seizure recognition is important for institution of therapy and for evaluating the cause of neurological dysfunction, but is the type of clinical seizure also important as a clue to etiology? Some investigators think not. For example, Freeman (1982) indicated that "classification [of seizures] is of little importance because it is not related to cause. . . ." Others, however, have indicated that some seizure types are closely associated with certain etiological categories. Brown et al. (1972) reported that tonic convulsions were seen almost exclusively in "brain-damaged" convulsing infants, whereas all metabolically caused convulsions were clonic, with a tonic element occurring in only 3%. Lombroso (1974) indicated that "minimal" seizures [later equated with subtle seizures (Lombroso 1983)], myoclonic seizures, and generalized tonic seizures were frequently seen in neonates with the "common denominator of widespread neuronal loss or disorganization." On the other hand, "strongly focal seizures" were commonly seen in association with metabolic encephalopathies (e.g., hypocalcemia, hypomagnesemia, and transient hypoglycemia), with mild intracranial birth injuries (e.g., subarachnoid hemorrhage), or with mild perinatal anoxia. Lombroso (1983) concluded that "strongly focal, well organized clonic seizures . . . raise certain etiological possibilities." Volpe (1981) indicated that some seizure types are more frequently associated with certain etiological factors. Generalized tonic seizures were frequently seen with intraventricular hemorrhage, particularly in the group with birth weights of less than 2500 g. In the group of infants with hypoxic–ischemic encephalopathy, Volpe found that virtually all neonates with asphyxia exhibited subtle seizures and that, in addition, some prematures had tonic seizures while some full-term infants had clonic seizures.

In this regard, it is also important to note that the relative incidence of various seizure types has changed over the years, paralleling the fluctuation in etiology. Thus, the relative incidence of tonic seizures and subtle seizures has increased with the increase in hypoxia and ischemia and the decrease in hypocalcemia, whereas the incidence of clonic seizures has decreased coincident with the decline in primary metabolic disorders (Kellaway and Hrachovy 1983).

Prognosis

Until recently, it was believed that the prognosis for neonates who have seizures depended primarily on the severity of the underlying neurological disorder rather than on adverse effects of the seizures themselves (Cadilhac et al. 1959; Schulte 1966; McInerny and Schubert 1969; Brown 1973; Volpe 1973; Lombroso 1974; Hill and Volpe 1981; Bergman et al. 1983; Kellaway and Hrachovy 1983). However, in the last few years there has been increasing emphasis on putative deleterious effects of the seizures themselves, leading to zealous efforts to "stop the seizures" the instant they appear, often without real proof that the signs and symptoms are truly epileptic. This concern has been engendered by recent animal studies that have shown that *prolonged* seizures result in an "... increased utilization and decreased supply [which] depletes energy stores and, perhaps by raising the GDP/GTP [guanosine diphosphate/guanosine triphosphate] ratio, inhibits the initiation of protein synthesis, which in turn dissociates polysomes, slows growth, and profoundly inhibits DNA synthesis" (Wasterlain and Dwyer 1983). There is a question, however, as to whether isolated or *less prolonged* seizures may also result in an inhibition of cell multiplication that is not quickly compensated for by the developing brain.

Early studies viewed neonatal seizures as a homogeneous group when considering outcome (Burke 1954; Craig 1960). Mortality ranged from 20% to 42% in studies up to 1960, and morbidity ranged from 3% to 27% (Burke 1954; Cadilhac et al. 1959; Craig 1960; Harris and Tizard 1960). However, as outcome began to be analyzed in relation to etiology, it became clear that seizures associated with certain diagnoses had a worse prognosis than others. McInerny and Schubert (1969) and Rose and Lombroso (1970) found that the highest percentage of abnormal outcomes occurred in neonates with congenital malformations. Normal outcomes occurred with increasing frequency in association with each of the following etiologies: (a) asphyxia, (b) infection, (c) hemorrhage, (d) hypoglycemia, (e) unknown, (f) hypocalcemia (Table 2.5).

More recent investigations reflect advances in neonatal care and the effect of an increasing population of low-birth-weight infants with seizures (Hill and Volpe 1981; Bergman et al. 1983). Bergman and colleagues (1983) noted that the incidence of seizures and of neonatal mortality associated with seizures was very high in infants with a gestational age of 31 weeks or less. However, the outcome for the premature infants with seizures who survived was not significantly different from that of term babies with seizures who survived. Table 2.6 lists the prognoses reported in various studies.

One series of reports requires special mention because of the scope of the original undertaking and the attention these reports have received since publication (Holden et al. 1982; Mellits et al. 1982). These studies reported the findings of the National Collaborative Perinatal Project (NCPP), a prospective investigation of 54 000 pregnant women whose infants were followed up to the age of 7 years. Seizures occurred during the neonatal period in 277 infants. Although published in 1982, these investigations were based on criteria for diagnosis of seizures in the period of the study (1959–1966) and reflect the known etiological factors and the level of clinical recognition of neonatal seizures of that era—a period, incidentally, when hypocalcemic seizures were at a peak. The authors concluded that *most children with neonatal seizures do well.* However, without the specification of

Table 2.5. Morbidity and mortality recorded by various investigators according to etiology

	Year	No. of patients	Dead		Neurological deficits		Normal	
			%	No.	%	No.	%	No.
Asphyxia								
Harris and Tizard	1960	17	12	2	29	5	59	10
Schulte	1966	57	9	2	41	9	36	8
McInerny and Schubert	1969	31	19	6	42	13	19	6
Rose and Lombroso	1970	10	20	2	70	7	10	1
Bergman et al.	1983	28	–	–	57	16	39	11
Lombroso	1983	51	22	11	57	29	22	11
Mizrahi and Kellaway[a]	1986	16	25	4	44	7	31	5
Infection								
Schulte	1966	4	75	3	25	1	0	0
McInerny and Schubert	1969	9	56	5	33	3	11	1
Rose and Lombroso	1970	15	40	6	33	5	27	4
Bergman et al.	1983	16	–	–	44	7[c]	56	9
Lombroso	1983	20	25	5	40	8	35	7
Mizrahi and Kellaway[a]	1986	5	0	0	60	3	40	2
Hemorrhage								
Harris and Tizard	1960	3	33	1	33	1	33	1
Rose and Lombroso	1970	14	21	3	21	3	57	8
Lombroso	1983	30	20	6	50	15	30	9
Mizrahi and Kellaway[a]	1986	6	0	0	17	1	83	5
Congenital anomalies								
Harris and Tizard	1960	4	75	3	25	1	0	0
McInerny and Schubert	1969	4	100	4	0	0	0	0
Rose and Lombroso	1970	11	64	7	36	4	0	0
Bergman et al.	1983	5	0	0	100	5[c]	0	0
Lombroso	1983	19	32	6	63	12	5	1
Mizrahi and Kellaway[a]	1986	1	0	0	100	1	0	0
Hypocalcemia								
McInerny and Schubert	1969	29	0	0	3	1	48	14
Keen	1969	34	0	0	9	3	35	12
Rose and Lombroso	1970	28	11	3	7	2	82	23
Bergman et al.	1983	2	–	–	0	0	100	2
Lombroso	1983	42	19	8	31	13	50	21
Hypoglycemia								
Harris and Tizard	1960	1	0	0	0	0	100	1
McInerny and Schubert	1969	6	17	1	33	2	50	3
Rose and Lombroso	1970	7	0	0	43	3	57	4
Bergman et al.	1983	7	–	–	29	2[c]	71	5
Lombroso	1983	19	5	1	21	4	74	14
Mizrahi and Kellaway[a]	1986	1	0	0	0	0	100	1
Unknown								
Harris and Tizard	1960	5	0	0	0	0	100	5
Schulte	1966	7	9	1	18	2	36	4
McInerny and Schubert	1969	12	8	1	33	4	33	4
Rose and Lombroso	1970	38	11	4	29	11	61	23
Bergman et al.	1983	16	–	–	25	4[c]	75	12
Lombroso	1983	54	6	3	26	14	69	37
Infarction								
Mannino and Trauner	1983	4[b]	0	0	50	2	50	2
Clancy et al.	1985	7[b]	0	0	27	2	73	5
Levy et al.	1985	7	0	0	86	6	14	1
Mizrahi and Kellaway[a]	1986	3	0	0	33	1	66	2

[a] See Table 2.4. [b] One year or more follow-up.
[c] Mortality and significant neurological deficits reported together by Bergman et al.

Table 2.6. Outcome of neonatal seizures reported by various investigators

Investigator	Year	Patient number	Percent mortality	Percent morbidity	Percent normal
Burke	1954	46	38	17	
Cadilhac et al.	1959	90	20	20	
Craig	1960	374	42	3	35
Harris and Tizard	1960	41	20	27	44
Prichard	1964	278	23	27	50
Keith	1964	56	32	36	33
Schulte	1966	57	26	45	29
Massa and Niedermeyer	1968	82	10	28	59
McInerny and Schubert	1969	95	19	25	30
Rose and Lombroso	1970	137	20	29	52
Kuromori et al.	1976	130	33	24	43
Dennis	1978	50	22	36	44
Holden et al.	1982	277	35[b]	30	
Lombroso	1983	117	16	35	48
Bergman et al.	1983	131	–[c]	42	39
Mizrahi and Kellaway[a]	1986	33	12	39	48

[a] See Table 2.4.
[b] Reflects 1959–1966 data.
[c] Reported death and significant morbidity together.

etiology (hypoxic–ischemic encephalopathy with poor outcome) and with the exclusion of subtle seizures (probably not recognized as seizures at that time but now the most common type), the conclusions of these studies may not be relevant to current neonatology.

Other factors in determining prognosis require some consideration: *the relationship of seizure type to prognosis*, and *the relationship of the EEG to outcome*. The latter will be discussed later, but seizure type in relation to outcome will be discussed here. We have seen that prognosis is related to etiology, and we have also seen that seizure type is related, in part, to etiology. Can the clinical manifestations of seizures provide some clue as to prognosis? Various investigators have suggested that certain seizure types indicate prognosis. Brown (1973) suggested that the outcome for an infant with recurrent tonic seizures is poor, whereas "the infant with a good prognosis has only a convulsion which is focal rather than tonic." The investigations of Holden et al. (1982) and Mellits et al. (1982), which reflect the period from 1959 through 1966, also indicate that the outcome for infants with tonic seizures is worse than that for infants with seizures of other types. Bergman et al. (1983), investigating a group of infants from 1976 through 1979, also indicated that a factor contributing to a poor outcome was the occurrence of tonic seizures. The association between diffuse CNS pathology and subtle seizures suggests that this seizure type also is associated with a poor prognosis (Volpe 1981). The relationship of seizure type to prognosis has not been fully investigated. There has not been sufficient time for long-term follow-up in recent studies that explored this issue (Mizrahi and Kellaway 1985a,b), and earlier studies were limited by the techniques used to characterize the clinical manifestations of the neonatal seizures (Bergman et al. 1983).

Pathophysiology

The results of our intensive video/EEG monitoring studies demonstrate that electrocortical seizure activity is *not* essential for the elaboration of subtle clinical seizures. Indeed, such seizures may occur when there is no electrocortical activity recorded at the scalp. There are two possible explanations for this observation. (a) Subtle seizures are generated in subcortical nuclei, and concomitant cortical electrical seizure activity is absent either because there is no projection of the epileptiform discharges from the depth to the cortex or because the presence of profound cortical depression prevents the expression of such activity at the cortex. (b) Subtle seizures are not epileptic in character but are primitive brain stem and spinal motor patterns that have somehow been released from normal tonic inhibition.

Certainly there are basic *physiological* mechanisms that can explain these clinical phenomena without recourse to an epileptic explanation. The assumption that these phenomena are epileptic (and that is all it is—an assumption; there is no proof) requires that the mechanism be exempt from certain physiological constraints, which makes the epileptic hypothesis difficult to justify. Subcortical gray matter is remarkably nonepileptogenic compared with the cortex and hippocampus, and for many years there was doubt that a convulsive seizure could be generated by stimulation of the brain stem (Moruzzi 1950). Kreindler et al. (1958) showed, however, that relatively low levels of stimulation of the brain stem in the rat and cat could produce a clinical response "characterized by a strong emprosthotonoid contraction, hyperextension of the limbs, powerful flexion of the head, and trismus." In the cat, the tonic seizure outlasted the stimulus by 15–50 s. This effect was preserved in animals decerebrated by precollicular section. The important aspect of these observations for this discussion is that the electrical activity of the reticular neurons "activated" by the stimulus was not "hypersynchronous activity of the convulsive type." Recordings from both the cortex and the reticular substance showed "desynchronized activity comparable to what is seen in arousal." Such an activation of a neuronal system, even if it outlasts the stimulus, cannot be equated with the induction of an epileptic seizure.

The points in the brain stem from which these investigators elicited the tonic motor responses were in the "bulbopontomesencephalic reticular substance." The caudal projections of this system have a wide distribution in the spinal cord and a predominant action on axial and proximal motor pools (Peterson et al. 1979). They constitute an important system for the initiation and control of postural and alerting movements of the body (Kuypers 1964). This same region is confluent with the area of the brain stem from which Lindsley et al. (1949) produced facilitation of spinal myotatic reflexes and showed that this facilitory effect was normally subject to tonic inhibition by cortical and other forebrain structures. With this in mind, we have suggested that tonic posturing in the neonate may not be epileptic but "brain stem release" phenomena (Kellaway and Hrachovy 1983). This term has been used appropriately to characterize the hypertonic state produced by decortication in animals. Our conception is that the tonic seizures of the newborn are the motor expression of *disinhibition* of normal brain stem facilitory mechanisms consequent upon depression or absence of forebrain inhibitory influences.

Tonic seizures are not seen in alert, normotonic infants, but are peculiar to infants who are obtunded, hypertonic, or hypotonic and who show a paucity of

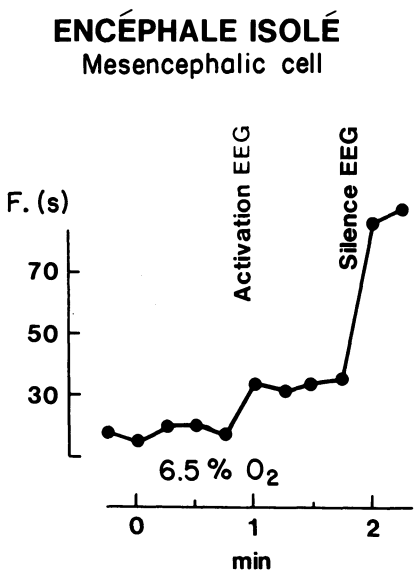

Fig. 2.11. This graph shows the progressive increase in the firing of a single reticular neuron in a curarized cat breathing 6.5% O_2. After about 2 min, the rate of firing abruptly increases, coincident with the time the electroencephalogram became flat (Bonvallet and Hugelin 1961).

spontaneous movements. These infants also have depressed and undifferentiated EEGs, and all these findings are consistent with depressed forebrain function. Bonvallet and Hugelin (1961), using microelectrode recording in the experimental animal, demonstrated that when electrocortical activity is depressed and eventually abolished by hypoxia, the firing of reticular neurons is, on the contrary, markedly enhanced (Fig. 2.11). Some parallel observations have been made in humans. Transient asystole produced by activation of the trigeminal–vagus reflex, if it lasts more than 10 s, causes syncope in which the subject is first limp and then has a transient episode of hyperextension of the trunk, flexion of the arms, and hyperextension of the legs. The simultaneously recorded EEG shows an episode of hypersynchronous slow activity, followed by a brief episode in which the EEG is "flat," followed by another period of generalized slow waves. The tonic seizure occurs and persists during the episode of electrocortical inactivity (Maulsby and Kellaway 1964).

We have made another observation relevant to the question of the nature of neonatal tonic seizures and motor automatisms. These motor phenomena can usually be elicited by sensory stimulation, and the intensity and extent of the muscular response are related to the intensity of the stimulus. Stimuli repeated in quick succession, or with greater intensity, or given to more than one place on the body may produce a stronger tonic movement and involvement of more muscle groups. It is, of course, well established that certain epileptic seizures in certain patients may be elicited by sensory stimuli, usually of a specific type. However, in such cases, the stimulus appears to act only as a trigger, and the intensity of the stimulus, once threshold is reached, does not bear a relationship to the intensity or spread of the clinical seizure. Neonatal tonic seizures, however, appear to conform to Sherrington's basic principles of reflex action. Temporal and spatial summation, recruitment, and irradiation are phenomena characteristic of reflex responses but are not typically aspects of epileptic seizures.

The episodic occurrence of tonic seizures (and of motor automatisms that gives them the appearance of seizures) may be explained by fluctuations in the level of interoceptive and proprioceptive sensory input to the brain stem reticular facilitory system. The facilitory center extends into the subthalamus and intralaminar area of the hypothalamus; it receives a rich input of collaterals from the ascending fibers of the spinothalamic tract and the trigeminal system. The lateral area of the reticular formation is the major area for this afferent collateral input (the extralemniscal system) (Starzl et al. 1951). Stimulation of cutaneous sensory endings over the entire body surface (Peterson et al. 1975) and of muscle afferents (Casey 1969) evokes responses in medial pontoreticular neurons. The most pronounced responses, however, are elicited by noxious stimuli (Casey 1969; Eccles et al. 1975). The receptive fields of the individual reticular neurons are characteristically extensive and range from a single limb to virtually the entire body surface (Peterson et al. 1975). Finally, the asymmetry and crossed flexor extension that often characterize neonatal tonic seizures can be understood in terms of the observation in animals that simulation of the reticular substance at intensities just above the threshold for evoking movement may produce motor patterns consisting of flexion of ipsilateral limbs, extension of contralateral limbs, and turning of the head toward the side of the stimulus (Sprague and Chambers 1954).

Invoking an epileptic mechanism to explain motor automatisms also appears to be gratuitous in view of the physiological constraints that exist for such a hypothesis and because of the presence of autochthonous mechanisms for the elaboration of such movements in the spinal cord and brain stem.

At all levels of the vertebrate phylogenetic scale there are central pattern generators within the spinal cord that can generate a basic motor output for locomotion [see reviews by Grillner (1981) and Grillner and Wallén (1985)]. Rhythmic locomotor output in the spinal animal is elaborated only during some type of tonic excitation arising either from sensory stimulation or from high-frequency stimulation of descending pathways. It also may be produced by the application of certain excitatory neurotransmitters directly to the isolated spinal cord (Viala and Buser 1971; Poon 1980). The level of activity of the central pattern generators is controlled by higher brain structures located particularly in the brain stem (Mori et al. 1977, 1980), but locomotor movements may be elicited from subthalamic, mesencephalic, and pontine regions by local stimulation (Grillner 1981).

Humans are born with locomotor reflexes. The normal full-term infant manifests walking reflexes when lowered to the ground (Forssberg and Wallberg 1979). Similarly, when the newborn infant is submerged in a prone position, the position is maintained, and definite rhythmic flexor–extensor movements of upper and lower extremities usually occur. "The movements are ordinarily sufficiently forceful to propel the baby a short distance through the water" (McGraw 1939). These reflex swimming movements are gradually replaced over the next few months by struggling movements and by the infant's bringing his hands to his mouth (protective reflex) (McGraw 1939, 1963). It would appear that with maturation of the forebrain (encephalization), the primitive reflex response to immersion is suppressed by higher level inhibitory influences. It is our hypothesis that neonatal motor automatisms are, like tonic seizures, brain stem release phenomena.

In concluding this section on the pathophysiology of neonatal seizures, we wish

to emphasize our awareness that in suggesting that phasic disinhibition of primitive spinal reflex mechanisms constitutes the pathophysical basis of neonatal tonic seizures and motor automatisms, we have merely substituted one hypothesis for another. In extenuation, we submit that despite the significant amount of data that provide a rational basis for our suggestion, the idea that these seizures are engendered by subcortical epileptiform activity is based only on the clinical fact that this behavior occurs paroxysmally and on reports that such phenomena have been observed in temporal association with electrical seizure activity recorded in the EEG.

Therapy

Whether the motor automatisms and tonic seizures are epileptic or not, they constitute important signs of brain damage or serious brain dysfunction. Obviously, the primary therapeutic concern must be remediation, insofar as possible, of the underlying dysfunction and its causal mechanism. However, current experimental evidence indicates that epileptic seizures are bad for the brain and that status epilepticus may be devastating, particularly to a brain still in the process of development (Wasterlain and Plum 1973; Plum et al. 1974). It is generally believed that stopping the seizures requires immediate and, if necessary, vigorous treatment with anticonvulsant drugs. But there is also evidence from cell culture studies that sustained treatment with phenobarbital, the drug most commonly employed in neonates (Aicardi 1983; Painter 1983a,b), may also have a deleterious effect on neuronal maturational processes (Bergey et al. 1981; Neale et al. 1985). Clearly, there is a therapeutic trade-off involved, and the problem is further complicated by the possibility that some neonatal seizures may not be epileptic. There is no doubt that tonic posturing, motor automatisms, and other types of subtle seizure may be stopped by anticonvulsant drugs. The serum drug levels required are often high and, as Lockman (1983a,b) has pointed out, the general depressive effects on the CNS and cardiovascular system must be considered in pushing the drug levels beyond the normal therapeutic range. It would seem that this consideration is of critical importance in neonates with subtle seizures, since these infants are invariably already depressed and obtunded.

Another problem confronting the neonatologist who believes that the advent of a seizure demands immediate and possibly vigorous anticonvulsant drug treatment is the evidence that cerebral protein synthesis (Wasterlain 1974) and ischemic cell damage (Meldrum 1983) are directly related to the *enhanced neuronal firing* that occurs during seizures. Thus, if electrical seizure activity continues to be present in the brain even though the clinical seizures have stopped, the deleterious processes presumably continue. Our own prolonged monitoring studies have shown that drug treatment (phenobarbital, phenytoin, or diazepam) may (a) initially stop both the clinical and electrical seizure activity, with a subsequent return to the latter; (b) stop the clinical seizures, but not the electrical seizure activity, which continues with only some modification of waveform amplitude and duration; (c) stop both the clinical and electrical seizure activity (less common). In clinical practice, however, in all but exceptional instances, control of the overt clinical manifestations is the end point of therapy. If, as the experimental evidence suggests, it is

necessary for the electrical seizure activity to be abolished, some sort of simple monitoring system will be required in order to avoid inadequate or unnecessarily protracted treatment.

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Chapter 3

Infantile Spasms (West Syndrome)

Barbara F. Westmoreland and Manuel R. Gomez

Introduction and History

Infantile spasms were first described by Dr. W. J. West in 1841 in a letter to *Lancet* in which he described "a peculiar form of infantile convulsions" occurring in his own son.

> Sir:—I beg, through your valuable and extensively circulating Journal, to call the attention of the medical profession to a very rare and singular species of convulsion peculiar to young children.
>
> As the only case I have witnessed is in my own child, I shall be very grateful to any member of the profession who can give me any information on the subject, either privately or through your excellent Publication.
>
> The child is now near a year old; was a remarkably fine, healthy child when born, and continued to thrive till he was four months old. It was at this time that I first observed slight *bobbings* of the head forward, which I then regarded as a trick, but were, in fact, the first indications of disease; for these *bobbings* increased in frequency, and at length became so frequent and powerful, as to cause a complete heaving of the head forward towards his knees, and then immediately relaxing into the upright position, something similar to the attacks of emprosthotonos: these bowings and relaxings would be repeated alternately at intervals of a few seconds, and repeated from ten to twenty or more times at each attack, which attack would not continue more than two or three minutes; he sometimes has two, three, or more attacks in a day; they come on whether sitting or lying; just before they come on he is all alive and in good motion, making a strange noise, and then all of a sudden down goes his head and upwards his knees; he then appears frightened and screams out; at one time he lost flesh, looked pale and exhausted, but latterly he has regained his good looks, and, independent of this affection, is a fine grown child, but he neither possesses the intellectual vivacity or the power of moving his limbs, of a child of his age; he never cries at the time of the attacks, or smiles or takes any notice, but looks placid and pitiful, yet his hearing and vision are good; he has no power of holding himself upright or using his limbs, and his head falls without support. . . . In my own child's case, the bowing convulsions continued every day, without intermission, for seven months; he had then an interval of three days free; but, on the fourth day, the convulsions returned, with this difference, instead of bowing, he stretched out his arms, looked wild, seem to lose all animation, and appeared quite exhausted.

Little additional mention of infantile spasms appeared in the literature until 1883, when Féré published his article on "tic de salaam" and first suggested a subdivision of symptomatic and idiopathic forms (cited by Jeavons and Bower 1964). In 1924, Asal and Moro used the term "*Blitz-Nick und Salaam Krämpfe*" for

the entity. In 1946, Buchanan described the main features of the attacks, which he referred to as "lightning major seizures." Subsequently various aspects of the syndrome were described by other authors, including Zellweger (1948), Lennox and Davis (1950), Vazquez and Turner (1951), and Kellaway (1952). Among the terms used for these seizures are the following: salaam, flexion, massive, nodding, salutation, greeting, or cheerleader spasms; jackknife convulsions; infantile myoclonic seizures; propulsive petit mal; *spasms en flexion du nourrison, nictatio capitis, spasmus nictitans*, and *eclampsia nutans* (Druckman and Chao 1955; Jeavons and Bower 1964; Lacy and Penry 1976; Niedermeyer and Lopes da Silva 1982). "Minor motor seizures" is another term used for infantile spasms. However, this is an imprecise term that has also been used to refer to other short-lasting generalized seizures such as bilateral massive myoclonic, akinetic, atonic, tonic, and atypical absence seizures, and this term is now becoming obsolete. In 1952, Gibbs and Gibbs used the term "infantile spasms" to designate the seizures, and this has become the most commonly used term for the condition in the English medical literature. At the same time, Gibbs and Gibbs also described the electroencephalographic (EEG) pattern associated with infantile spasms and called it "hypsarrhythmia." The term "West syndrome" is used to refer to the triad of infantile spasms, psychomotor retardation, and hypsarrhythmia (Gastaut 1973).

Clinical Aspects

Incidence and Natural History

The prevalence of infantile spasms has been reported to be 1.3% of all patients with epilepsy and 2.8% of patients with epilepsy who are younger than 15 years of age (Gastaut et al. 1975). In the infant age group, in which infantile spasms are most prevalent, the incidence of the disorder is 1 per 4000–6000 (Dreifuss 1983). More boys tend to be affected than girls, the ratio ranging from 1.5:1 to 2:1 (Bamberger and Matthes 1959; Jeavons et al. 1973; Lombroso 1983). The familial incidence of infantile spasms is 3%–6% (Jeavons and Bower 1964; Watanabe et al. 1973; Lacy and Penry 1976), and the incidence of other types of seizure in family members is 7%–17% (Lacy and Penry 1976).

The onset of infantile spasms occurs between 3 and 12 months of age in most patients, and the peak age at onset is between 4 and 6 months (Low 1960; Jeavons and Bower 1961; Jeavons et al. 1973; Charlton 1975; Kellaway et al. 1979; Lombroso 1983). The earliest reported onset has been during the newborn period (Druckman and Chao 1955; Lombroso 1983) and the latest at 6 years of age (Kurokawa et al. 1980). In most cases, however, the onset of infantile spasms occurs before 2 years of age (Bower and Jeavons 1959; Jeavons and Bower 1961).

The mean duration of infantile spasms is 3–8 months (Jeavons et al. 1973; Lacy and Penry 1976), although they may persist for up to 32 months (Jeavons et al. 1973; Lacy and Penry 1976) with periods of exacerbation and remission (Lacy and Penry 1976). Infantile spasms usually cease spontaneously by 3–4 years of age (Jeavons and Bower 1964; Jeavons et al. 1973), but with treatment most cases

resolve by 1–2 years of age (Druckman and Chao 1955; Jeavons et al. 1973; Lacy and Penry 1976). A patient very rarely has infantile spasms beyond 7 years of age (Jeavons and Bower 1964; Jeavons et al. 1973; Lacy and Penry 1976).

Description

Kellaway et al. (1979), using extensive monitoring techniques, showed that the typical infantile spasm consists of a brief initial phase in which the muscles of the neck, trunk, and limbs contract abruptly followed by a more prolonged tonic phase of sustained muscle contraction that lasts 2–10 s. On the basis of the predominant type of movement, infantile spasms have been subdivided into three main types: flexor, extensor, and mixed.

The typical flexor spasm consists of an abrupt flexion of the neck and trunk with bilateral flexion and abduction or adduction of the arms and legs (Jeavons and Bower 1964; Lacy and Penry 1976; Kellaway et al. 1979). The terms "salaam" or "jackknife" seizures refer to the type of spasm in which the arms are flung outward and forward and the contraction of the abdominal muscles causes the body to flex or jackknife at the waist (Lacy and Penry 1976; Kellaway et al. 1979). More fragmentary or partial spasms can occur with abduction or adduction movements of the upper extremities or flexion movements of the arms over and around the body as if the child were hugging him- or herself (Ladwig et al. 1962; Jeavons and Bower 1964; Kellaway et al. 1979). At times, the child may have only a brief flexion movement of the head and neck—the "nodding spasm"—or only a brief contraction of the abdominal muscles (Kellaway et al. 1979).

The extensor spasm consists predominantly of a contraction of groups of extensor muscles that results in a sudden extension of the neck, arching of the back, and extensor abduction or adduction movements of the extremities (the "spread-eagle posturing" or the "cheerleader type of spasm") (Druckman and Chao 1955; Kellaway et al. 1979).

The mixed spasm consists of flexor movements of one part of the body and extensor movements of another part of the body (Kellaway et al. 1979).

The mixed and flexor types of spasm are the most common types, and the pure extensor form is the least common. Kellaway et al. (1979) noted that 42% of their patients had the mixed type, 34% the flexor type, and 22% the extensor type. Lombroso (1983) observed the mixed type in 50% of his patients, the flexor type in 42%, and the extensor type in 19%. Druckman and Chao (1955) noted that 55% of their patients had flexor spasms, 50% mixed spasms, and 21% extensor spasms. In the series of Jeavons and Bower (1964), 68% of the patients had flexor spasms, 22% mixed, and 6% extensor. A mixture of the various types of spasm can occur in the same patient, and the predominant type of spasm can change over time (Druckman and Chao 1955; Lacy and Penry 1976).

Although the spasms are usually bilateral and symmetrical, they can be unilateral or asymmetrical, with a greater jerk on one side than the other or deviation of the head and eyes to one side (Jeavons and Bower 1964; Lacy and Penry 1976).

Various other accompaniments that have been observed during infantile spasms include fluttering of the eyelids, nystagmus, lacrimation, grimacing, a smile-like

expression, laughing, hiccuping, crying, cyanosis, incontinence, and autonomic phenomena such as sweating, flushing, pupillary dilatation, or a change in respirations or heart rate (Lacy and Penry 1976; Kellaway et al. 1979; Lombroso 1983). At times, the child may look startled or begin to cry before an attack; at other times, the child may cry at the end of an attack (Dreifuss 1983). Whether a significant impairment of consciousness occurs during the spasms is uncertain since this factor is difficult to assess because of the age of the patients and the presence of mental retardation (Jeavons and Bower 1964; Kellaway et al. 1979).

A spasm usually lasts 2–5 s but may last up to 90 s (Chao et al. 1957; Jeavons and Bower 1964; Lacy and Penry 1976; Kellaway et al. 1979; Lombroso 1983). One of the characteristics of infantile spasms is their tendency to occur in clusters. The number of spasms occurring in a cluster is usually 5–10, but up to 125 have been reported (Jeavons and Bower 1964; Lacy and Penry 1976; Kellaway et al. 1979; Lombroso 1983). One to 60 clusters may occur per day (Kellaway et al. 1979). The duration of a cluster of spasms ranges from several seconds up to 20 min (Jeavons and Bower 1964; Lacy and Penry 1976; Kellaway et al. 1979; Lombroso 1983). In some instances, the spasms may be severe and prolonged at the onset of the cluster and then gradually slow down and decrease in severity at the end of the cluster. In other instances, the intensity and frequency of the spasms increase to a peak and then progressively decline until the spasms cease (Druckman and Chao 1955; Kellaway et al. 1979). After a cluster of spasms, the patient may be drowsy, listless, lethargic, or show an attenuated responsiveness (Druckman and Chao 1955; Ladwig et al. 1962; Kellaway et al. 1979); on other occasions, however, the patient may transiently appear to be more alert or responsive than before the spasms (Jeavons and Bower 1974; Lombroso 1983).

Infantile spasms tend to occur during the awake and drowsy states and much less frequently during sleep (Kellaway et al. 1979; Gomez and Klass 1983). In Kellaway's (1979) series of patients, only 2.5% of the spasms occurred during the sleep state. The spasms are most likely to occur prior to going to sleep or after arousal from sleep (Fig. 3.1) (Druckman and Chao 1955; Jeavons and Bower 1964; Lacy and Penry 1976; Gomez and Klass 1983). Other precipitants that can induce,

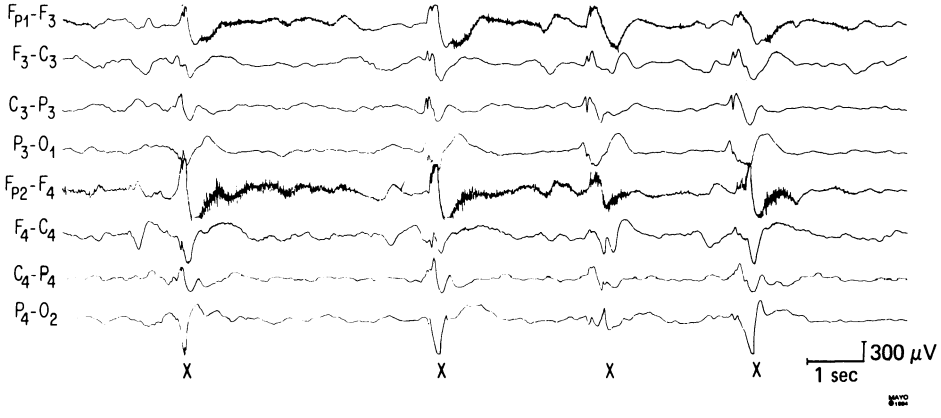

Fig. 3.1. EEG showing a series of flexor spasms (*X*) after arousal from sleep in a 15-month-old girl with infantile spasms.

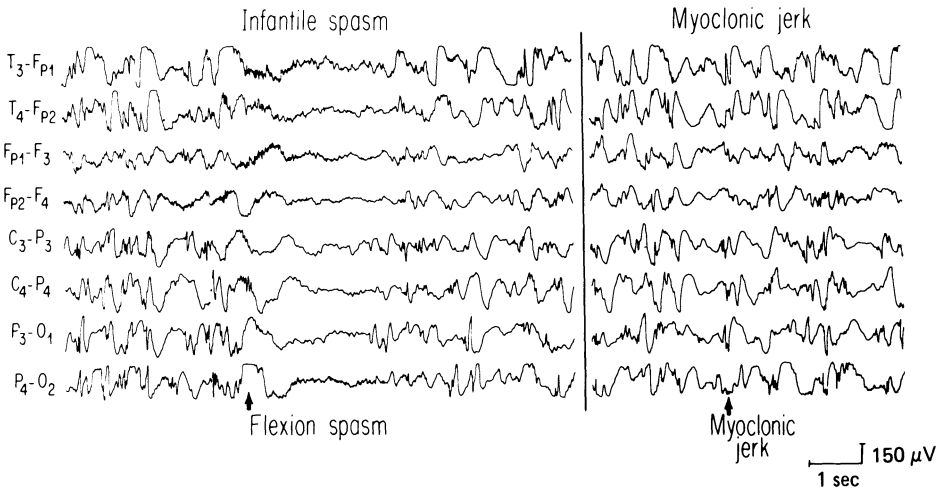

Fig. 3.2. EEG showing an infantile spasm (*left*) and myoclonic jerk (*right*) in a 6-month-old girl.

aggravate, or increase the frequency of the spasms are handling, feeding, and startling the patient, teething, fever, infections, viral illness, vaccination, hunger, excitement, fright, anger, and exercise (Druckman and Chao 1955; Jeavons and Bower 1964; Lacy and Penry 1976; Lombroso 1983).

Some patients may also have true myoclonic jerks. Although the term "myoclonic jerk" at times has been used as a synonym for infantile spasms, a true myoclonic jerk is a lightning-quick contraction or movement of the body or part of the body that lasts less than a second whereas a spasm lasts several seconds. The coexistence of both seizure types (Fig. 3.2) and the similarities in their clinical manifestations have contributed to the existing confusion.

Etiology

Patients with infantile spasms can be classified into two main etiological groups, the *idiopathic* or *cryptogenic* group and the *symptomatic* group. The idiopathic classification is based on ignorance of the cause of the seizures in many instances. For the most part, the idiopathic group consists of patients who were normal prior to the onset of infantile spasms and in whom the cause is unknown. This group constitutes 25%–56% of the various reported patient groups (Lacy and Penry 1976). The symptomatic group are those patients in whom a recognizable predisposing factor or pathological process can be identified. This group constitutes 44%–75% of the patient groups (Lacy and Penry 1976). On the basis of when the insult occurs, the factors can be subdivided into prenatal, perinatal, and postnatal causes (Table 3.1). Hypoxic or ischemic encephalopathy, occurring at or after birth, is the most common cause (Gomez and Klass 1983; Lombroso 1983). Other common causes include congenital defects, dysgenetic conditions such as tuberous sclerosis, and metabolic encephalopathies.

Table 3.1. Etiological classification of infantile spasms

Prenatal
Hypoxic or ischemic encepatholopathy
Congenital anomalies
Lissencephaly
Schizencephaly
Pachygyria
Holoprosencephaly
Porencephaly
Ulegyria
Microcephaly
Macrocephaly
Cerebral atrophy or dysplasia
Vascular malformation
Cornelia de Lange syndrome
Aicardi syndrome
Infections
Rubella encephalopathy
Cytomegalic inclusion body disease
Toxoplasmosis
Syphilis
Maternal toxemia or diabetes
Placental abnormalities
Chromosomal abnormalities
Down syndrome
Trisomy 13 or 18
Dysgenetic conditions
Tuberous sclerosis
Sturge-Weber disease
Incontinentia pigmenti
Linear nevus sebaceus
Biochemical or metabolic conditions
Phenylketonuria
Leigh's disease
Maple syrup urine disease
Isovaleric acidemia
Hyperornithinemia
Homocitrullinuria
Nonketotic hyperglycinemia
Pyridoxine dependency
Leucine-sensitive hypoglycemia
Tay-Sachs disease
Sandhoff disease
Alpers' cerebral poliodystrophy
Perinatal
Hypoxic or ischemic encephalopathy
Trauma
Intracranial hemorrhage
Abruptio placentae
Infections
Encephalitis
Meningitis
Neonatal icterus
Postnatal
Hypoxic or ischemic encephalopathy
Infections
Meningitis
Encephalitis
Trauma
Subdural hematoma
Intracranial hemorrhage
Postimmunization encephalopathy
Postexanthematous disease
Intracranial tumor
Reye's syndrome
Metabolic derangements
Hypoglycemia
Hyperinsulinism
Carnitine deficiency
Endocrine diseases
Hypopituitarism
Hypothyroidism
Adrenal insufficiency
Pancreatic adenoma

Pathophysiology

Pathologic studies have shown various lesions in patients with infantile spasms. These lesions have included various congenital defects of the central nervous system (porencephaly, microcephaly, macrocephaly, and lissencephaly), dysgenetic conditions (tuberous sclerosis), metabolic disease (leukodystrophy and lipidosis), inflammatory processes (toxoplasmosis and cytomegalovirus disease), and hydrocephalus. Among the congenital syndromes of the central nervous system,

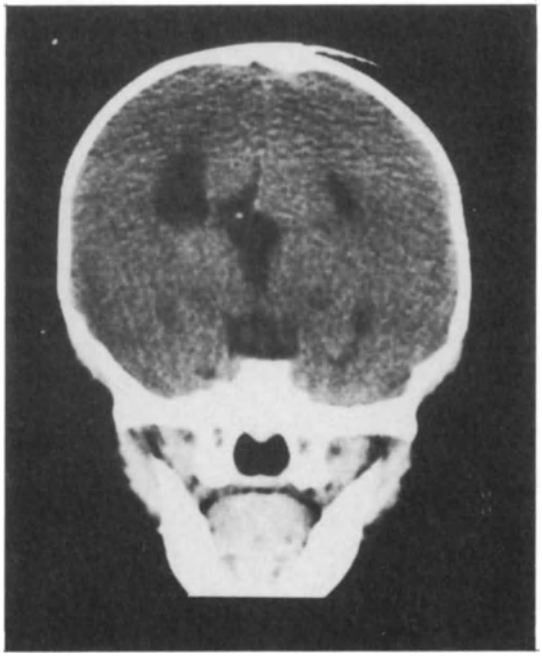

Fig. 3.3. Computed tomographic scan (coronal cut) of a patient with Aicardi syndrome, demonstrating agenesis of the corpus callosum.

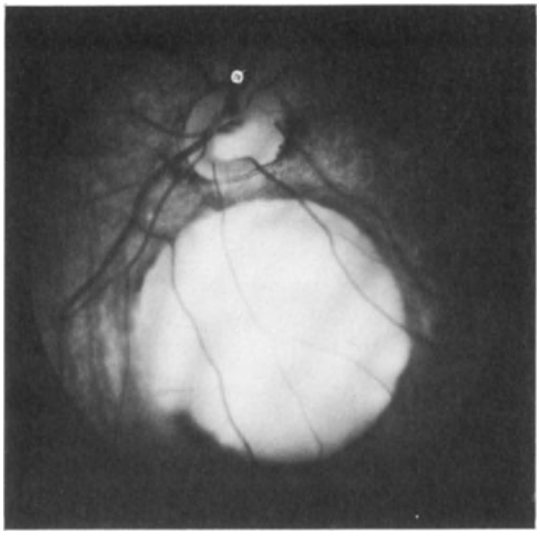

Fig. 3.4. Photograph of fundus of a patient with Aicardi syndrome, showing retinal coloboma and lacunae of absent retinal pigment epithelium throughout the posterior pole (same patient as in Fig. 3.3).

one described by Aicardi et al. (1969) occurs exclusively in female infants. These patients have agenesis of the corpus callosum, cortical heterotopia, a lacunar type of defect of the retinal epithelium, infantile spasms, and mental retardation (Figs. 3.3, 3.4).

Microscopic studies, for the most part, have shown rather nonspecific findings such as gliosis, spongy degeneration, and edema. Huttenlocher (1974), using Golgi-Cox staining methods, found a paucity of dendritic spines in several patients with infantile spasms. Whether there is a cause-and-effect relationship between the infantile spasms and the dendritic changes is unknown; if there is such a relationship, which factor is the cause and which is the effect and whether the symptoms and the pathological findings are epiphenomena are also unknown. Most of the cases studied with the classic histological methods have been unrevealing.

Neurotransmitters have been suggested to be involved in the pathophysiology of infantile spasms (Lacy and Penry 1976). Several studies have indicated a disturbance of tryptophan–serotonin metabolism in some patients with infantile spasms (Coleman 1971; Coleman et al. 1971; Klawans et al. 1973; Lacy and Penry 1976; Ito et al. 1980). A recent study reported low cerebrospinal fluid levels of 5-hydroxyindoleacetic acid, a serotonin metabolite, in patients with infantile spasms, a finding that suggests that altered serotonin metabolism may play some role in the pathophysiology of infantile spasms (Silverstein and Johnston 1984).

In brief, no one single factor has been identified as the cause of infantile spasms (Riikonen 1983); instead, the main critical feature is the occurrence of an insult to the brain in an early stage of development (Chao et al. 1957; Lacy and Penry 1976). Infantile spasms are, therefore, the symptom of a "malady of the immature or developing central nervous system" whose pathophysiology is not yet understood (Lacy and Penry 1976).

Associated Clinical Findings

Other Types of Seizure

Additional types of seizure have been reported in 33%–55% of patients with infantile spasms (Druckman and Chao 1955; Jeavons and Bower 1964; Jeavons et al. 1970; Jeavons et al. 1973; Lombroso 1983). Generalized tonic–clonic and partial seizures are the most common types of seizure. Clonic, tonic, myoclonic, atonic, akinetic, and atypical absence seizures and hemiconvulsions are less frequent (Druckman and Chao 1955; Jeavons and Bower 1964; Lacy and Penry 1976; Lombroso 1983). These seizures may occur prior to or concurrent with the infantile spasms or persist or develop after the infantile spasms have resolved. The additional seizure types are more likely to occur in the symptomatic group of patients than in the idiopathic group (Jeavons and Bower 1964; Lacy and Penry 1976). Patients who have had additional seizure types generally have a poorer prognosis than those with only infantile spasms (Jeavons and Bower 1964; Lacy and Penry 1976; Lombroso 1983).

Skin Lesions

Of particular importance is a careful examination of the skin in patients with infantile spasms. Easily recognizable is the nevus flammeus that is distributed over the skin supplied by the ophthalmic division of the trigeminal nerve and often neighboring skin areas; this defect forms part of the Sturge-Weber malformation. Rarely, a patient with tuberous sclerosis has the lesions known as facial angiofibroma (adenoma sebaceum), periungual fibroma, or shagreen patches at the onset of the infantile spasms. In some patients, however, such lesions develop later in life—this finding makes diagnosis of tuberous sclerosis certain. A more frequent finding often associated with infantile spasms that makes the diagnosis of tuberous sclerosis tenable is the hypomelanotic skin macule. In young infants with little skin pigmentation, this lesion may not be visible with the artificial light of fluorescent or incandescent lamps. The use of ultraviolet light produced by a Wood lamp will demonstrate hypomelanotic macules on light-coloured skin, especially if the examination is done in a darkroom. Thus, examination of the skin with ultraviolet light provides the physician with an inexpensive, safe, and quick method of establishing the cause of infantile spasms.

Incontinentia pigmenti and linear nevus sebaceus syndrome are also recognized by examination of the skin.

Eye Findings

Examination of the fundi for retinal phakoma is also a simple method to diagnose tuberous sclerosis. In infants, the phakoma is usually as yet uncalcified and therefore difficult to find. The lesion appears only as a rounded opacity of the fundus. When it overlies a vessel it is easy to find it by following the vessel from the disk to the periphery and noticing that it is interrupted by the semitransparent phakoma.

In the Aicardi syndrome, the lacunar retinal epithelium defect is so characteristic that the condition can be diagnosed by looking at only the fundi. Computed tomography of the head confirms the diagnosis by demonstrating agenesis of the corpus callosum.

Neurological Abnormalities

Neurological abnormalities have been reported in 33%–89% of patients with infantile spasms (Lacy and Penry 1976). As expected, neurological abnormalities occur more frequently in the symptomatic group (80%–90%) than in the idiopathic group (10%–20%) (Jeavons and Bower 1964; Lacy and Penry 1976; Lombroso 1983). Almost any type of neurological abnormality may be present; the most frequent finding is mental retardation. Other types of abnormality include motor deficits, visual impairment, auditory problems, congenital defects (such as

microcephaly, macrocephaly, and agenesis of the corpus callosum), and various dysgenetic conditions (Lacy and Penry 1976).

Although some infants have retarded psychomotor development prior to the onset of infantile spasms, some who have had a normal development slow or stop progressing after the onset of infantile spasms. Still others show signs of regression or increased mental and motor retardation.

Mental Retardation

Mental retardation is the most frequent neurological abnormality that occurs in association with infantile spasms; it is present in 75%–90% of the patients (Jeavons and Bower 1964; Lacy and Penry 1976). As expected, mental retardation occurs in the symptomatic group of patients more often than in the idiopathic group (Jeavons and Bower 1964; Lacy and Penry 1976). Prognostic factors that influence the outcome of intelligence include the level of intelligence prior to the onset of infantile spasms, age at onset, time course of infantile spasms, the presence of other neurological abnormalities, the occurrence of other types of seizure, idiopathic versus symptomatic causes, and the presence of an underlying organic or dysgenetic condition (Jeavons et al. 1973; Lacy and Penry 1976). Patients who have evidence of cerebral disease, abnormal development and mental retardation prior to the onset of infantile spasms, early onset of infantile spasms, and a prolonged course of infantile spasms have a poor prognosis. Patients who are normal prior to the onset of infantile spasms and have no underlying organic disturbance or associated neurological signs have a better prognosis (Jeavons et al. 1973; Lacy and Penry 1976).

EEG Findings

Interictal Patterns

The most common type of EEG finding in patients with infantile spasms is hypsarrhythmia (Fig. 3.5). This pattern was first described in detail by Gibbs and Gibbs in 1952 as

> an exceedingly abnormal type of interseizure electroencephalogram ... commonly encountered in infants with a clinical history of spasms. It consists of random high voltage slow waves and spikes. These spikes vary from moment to moment, both in duration and location. At times they appear to be focal, and a few seconds later they seem to originate from multiple foci. Occasionally the spike discharge becomes generalized, but it never appears as a rhythmically repetitive and highly organized pattern that could be confused with a discharge of the petit mal or petit mal variant type. The abnormality is almost continuous, and in most cases it shows as clearly in the waking as in the sleeping record. It is referred to as *hypsarhythmia* (the prefix *hypsi*, meaning high or lofty, elided with *arhythmia*).

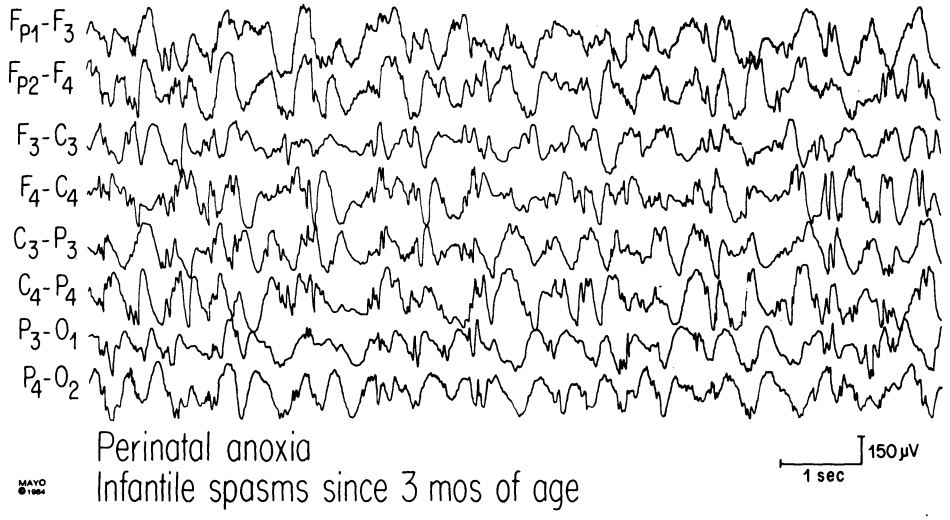

Fig. 3.5. EEG showing hypsarrhythmia in a 7-month-old girl.

The hypsarrhythmic pattern, like infantile spasms, is an age-specific abnormality that occurs as a response of the immature brain to various multifocal or diffuse insults or disease processes affecting the central nervous system (Jeavons and Bower 1974; Lacy and Penry 1976; Lombroso 1983).

The hypsarrhythmic pattern is found in 66%–89% of patients with infantile spasms (Jeavons and Bower 1974; Lacy and Penry 1976; Kurokawa et al. 1980; Lombroso 1983) (Fig. 3.5). The onset of the hypsarrhythmic pattern usually coincides with the onset of the infantile spasms; the peak age at onset is 3–6 months (Lacy and Penry 1976). The pattern usually resolves by 4–5 years of age in untreated patients (Jeavons and Bower 1964; Lacy and Penry 1976; Gomez and Klass 1983) but has been noted in patients up to 8 years of age in a few rare cases (Jeavons and Bower 1964). After treatment, the pattern may resolve within several days to several weeks. The hypsarrhythmic pattern has also been found in infants and children with other types of seizure, but almost all of these patients had evidence of cerebral damage and mental retardation (Jeavons and Bower 1964).

Although the typical hypsarrhythmic pattern consists of continuous, irregular, high-voltage, multifocal spikes and slow waves, it may become more regular and organized with greater interhemispheric synchrony and the occurrence of bilaterally synchronous spike and wave discharges with some intervening normal background activity (Fig. 3.6). This has been called the "modified hypsarrhythmic pattern" and is usually seen as the hypsarrhythmic pattern begins to resolve, either after treatment or spontaneously as the child grows older (Druckman and Chao 1955).

Other variations of the hypsarrhythmic pattern have also been reported (Hrachovy et al. 1984). An asymmetrical hypsarrhythmic pattern can occur with a persistent difference in the amplitude of activity over the two hemispheres. Occasionally, the hypsarrhythmic pattern is present over just one hemisphere, a finding which has been termed "unilateral hypsarrhythmia" or "hemihypsarrhythmia" (Hrachovy et al. 1984). This pattern has usually been seen in association with

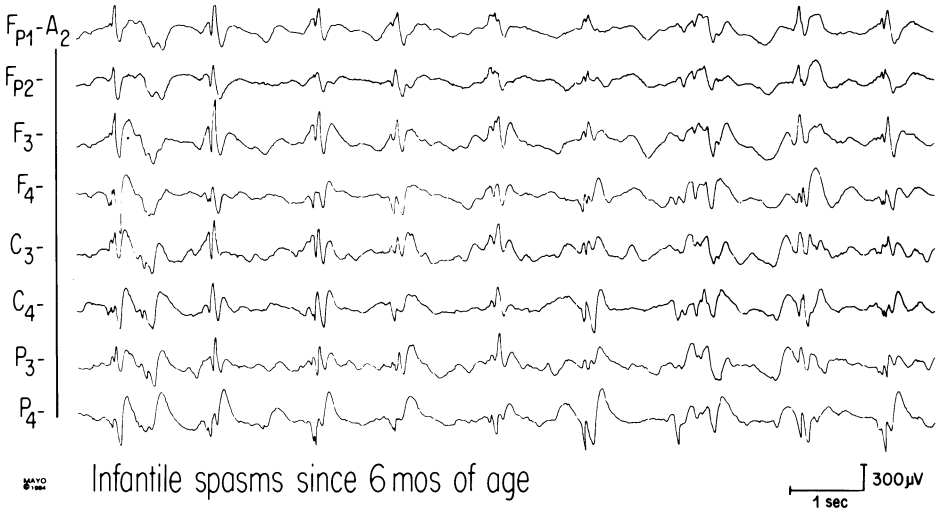

Fig. 3.6. EEG showing modified hypsarrhythmia in a 15-month-old girl.

a large cystic lesion or porencephaly involving one hemisphere (Hrachovy et al. 1984). In the Aicardi syndrome, the EEG pattern consists of asymmetrical and asynchronous ictal and interictal activity occurring independently over the two hemispheres (Aicardi et al. 1969; Gastaut and Tassinari 1975) (Fig. 3.7). At times the EEG may show a persistent ictal and interictal focus that is distinguishable from the multifocal discharges and in which a focal seizure discharge can occur without an alteration in the ongoing hypsarrhythmic pattern (Hrachovy et al. 1984). On occasion, the EEG may consist predominantly of high-voltage, asynchronous slow waves with little evidence of spikes or sharp waves (Gibbs and Gibbs 1952; Hrachovy et al. 1984). Another variation is periodic episodes of attenuation that occur every few seconds and last 2–10 s. These episodes of

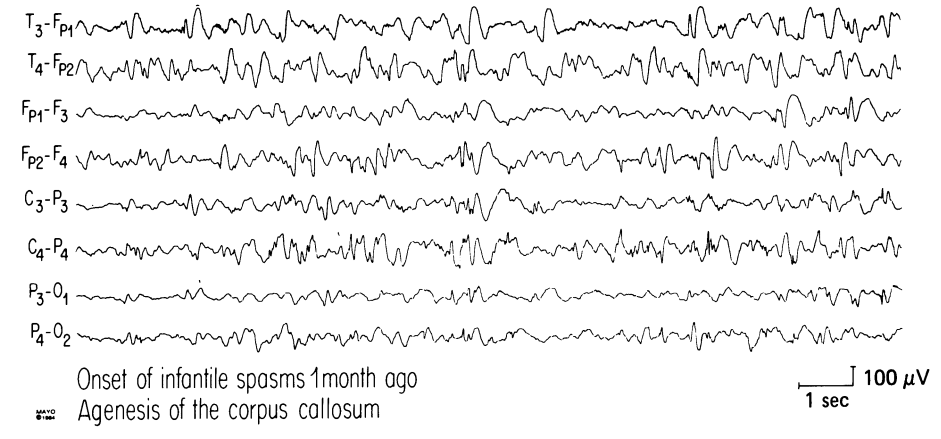

Fig. 3.7. EEG of a 4-month-old boy with Aicardi syndrome, showing asymmetrical and asynchronous activity over the two hemispheres.

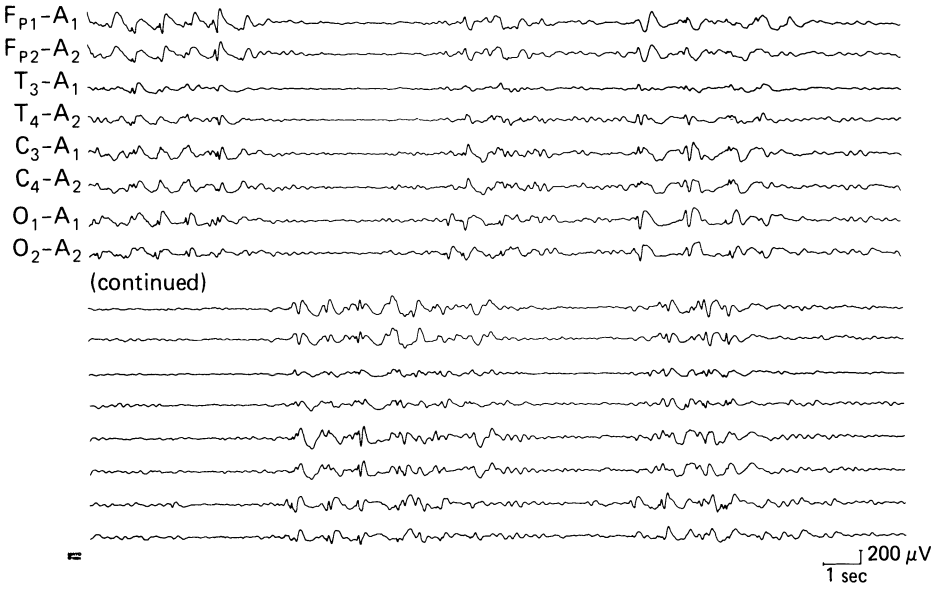

Fig. 3.8. Sleep tracing showing intermittent occurrence of hypsarrhythmic pattern alternating with episodes of attenuation.

attenuation can be focal, unilateral, or generalized and mainly occur during non-rapid eye movement (non-REM) sleep (Hrachovy et al. 1984).

There are modifications of the EEG pattern during sleep. The EEG abnormalities are often increased during sleep, and the hypsarrhythmic pattern may become more apparent (Niedermeyer and Lopes da Silva 1982). On occasion hypsarrhythmia may be evident only during sleep, even when the awake EEG is normal (Jeavons and Bower 1974; Niedermeyer and Lopes da Silva 1982). During non-REM sleep, the amplitude of the activity is increased and the hypsarrhythmic pattern is accentuated (Hrachovy et al. 1981; Niedermeyer and Lopes da Silva 1982; Hrachovy et al. 1984). At times, the discharges may occur more synchronously during sleep. Another characteristic of non-REM sleep is a tendency toward fragmentation of the EEG pattern—bursts of spikes and slow waves alternate with periods of generalized flattening in a quasiperiodic fashion and at times almost simulate a "burst-suppression" pattern (Jeavons and Bower 1964; Hrachovy et al. 1981; Lombroso 1983; Hrachovy et al. 1984) (Fig. 3.8). On the other hand, the hypsarrhythmic pattern is significantly reduced or disappears during REM sleep (Hrachovy et al. 1981; Neidermeyer and Lopes da Silva 1982; Hrachovy et al. 1984). Also, a transient "relative normalization" of the EEG may occur immediately after arousal from sleep: the hypsarrhythmic pattern temporarily disappears for a few seconds or minutes immediately after arousal (Hrachovy et al 1984).

Although hypsarrhythmia is the most frequent EEG pattern associated with infantile spasms, other types of EEG abnormality may be found, including generalized slow spike and wave or atypical spike and wave discharges, focal or multifocal spikes, and focal or generalized slow-wave abnormalities. Between 1% and 2% of patients with infantile spasms have been described as initially having a normal or near-normal EEG (Jeavons and Bower 1964; Lacy and Penry 1976).

Ictal Patterns

Several different types of ictal pattern may be associated with infantile spasms (Kellaway et al. 1979). The most common type is the "electrodecremental pattern" (Bickford and Klass 1960), which consists of an initial high-voltage spike- or slow-wave complex that is followed by an abrupt generalized decrement or attenuation of the ongoing electrical activity. A train of low-voltage fast activity in the range of 12–20 Hz may occur at the onset of the decremental pattern. The decremental pattern lasts several seconds and is followed by an abrupt or gradual return of the original activity (Fig. 3.9).

When a patient is having a flurry of spasms, the electrodecremental pattern may occur quasiperiodically. Sometimes the electrodecremental pattern may occur repetitively without a return of the intervening hypsarrhythmic pattern and only a prolonged period of generalized attenuation of the EEG with periodic bursts of low-amplitude fast activity is seen (Fig. 3.10). This pattern is particularly likely to occur when a patient is having frequent spasms without a recovery period between them.

The second most common ictal pattern is a generalized spike or spike and wave complex in association with myoclonic jerks (Fig. 3.2). Other variations of the ictal pattern include attenuation only, attenuation with superimposed fast activity, attenuation and rhythmic slow activity, a generalized slow-wave complex, or a generalized slow-wave complex followed by attenuation with or without superimposed fast activity (Kellaway et al. 1979). There is not a close correlation between

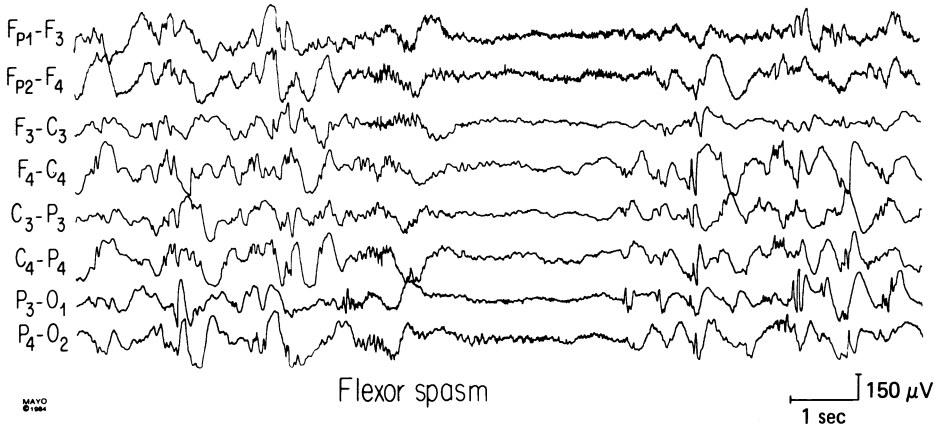

Fig. 3.9. Electrodecremental pattern in a 7-month-old girl.

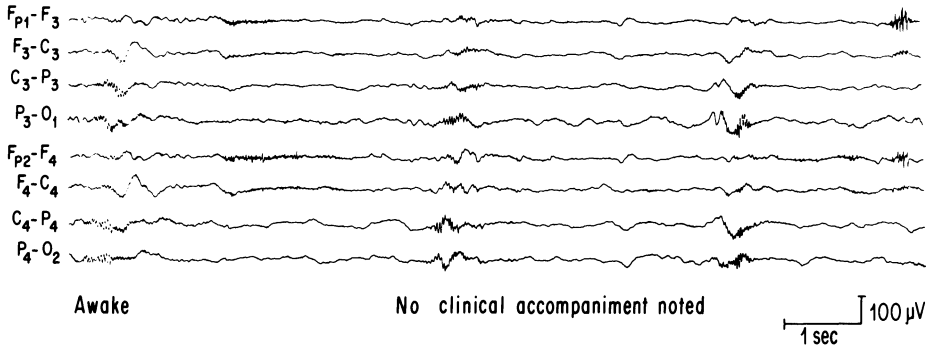

Fig. 3.10. Serial electrodecremental episodes manifested by intermittent episodes of low-amplitude fast activity in a 4-month-old boy.

the type of ictal EEG pattern and the type of infantile spasm (Kellaway et al. 1979). The ictal patterns can occur without a clinical accompaniment being apparent; conversely, at times there may be little or no change in the EEG in association with infantile spasms (Pampiglione 1964). After a seizure episode, the EEG may show a transient improvement with a decrease in abnormal activity and a tendency toward a more normal background (Kellaway et al. 1979).

Evolution of Hypsarrhythmia

The hypsarrhythmic pattern can evolve from other types of abnormal EEG pattern or it can emerge from a normal background. Watanabe et al. (1973) prospectively studied a series of patients in whom recordings were obtained prior to the onset of the hypsarrhythmic pattern. The patients were subdivided into prenatal, perinatal, and postnatal groups, depending on when the insult to the brain occurred. The prenatal group initially had various types of focal abnormality and in some cases normal EEGs. They then developed multifocal abnormalities that evolved into hypsarrhythmia. The perinatal group initially had severely abnormal EEGs that were consistent with a severe insult to the brain. The recordings then transiently improved and in some cases became normal. The patients subsequently developed focal or multifocal abnormalities that then progressed to hypsarrhythmia (Fig. 3.11). The postnatal group had abnormal EEG patterns, usually consisting of slow-wave abnormalities, at the time of the insult. This pattern was followed by a transient improvement or a normal EEG that then evolved into a hypsarrhythmic pattern.

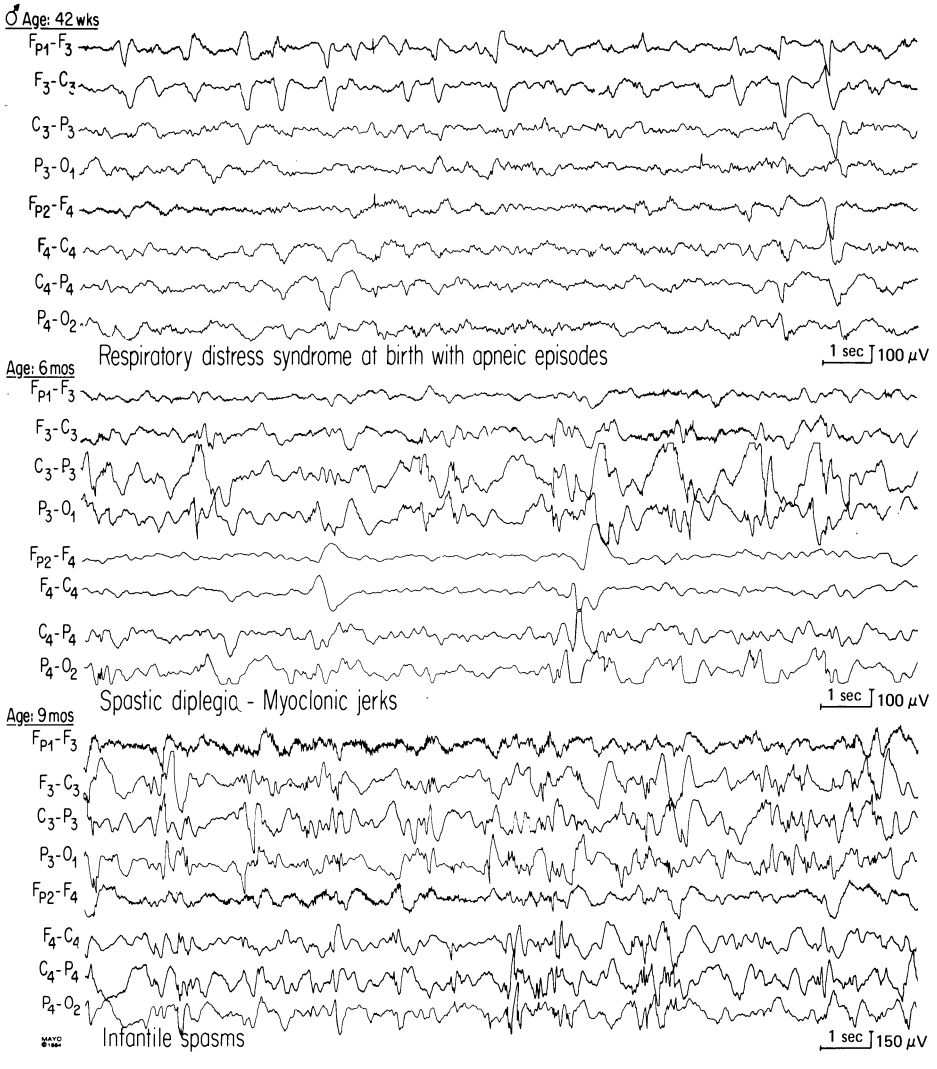

Fig. 3.11. Abnormal EEGs showing multifocal sharp waves in a 42-week-old boy (*top*), multifocal spikes and sharp waves at 6 months (*middle*), and development of hypsarrhythmic pattern at 9 months (*bottom*).

Resolution of Hypsarrhythmia

There is a progressive resolution of the hypsarrhythmic pattern after treatment or with increasing age. With treatment, the improvement can occur within 1–2 weeks (Jeavons and Bower 1974). The initial changes are a decrease in the amplitude of the high-voltage discharges and in the chaotic nature of the EEG. These changes are followed by the appearance of more rhythmic and synchronized activity and

the emergence of some more normal background activity (that is, a modified hypsarrhythmic pattern). After these changes, the hypsarrhythmic pattern may completely resolve or be replaced by focal or generalized slow-wave abnormalities or other types of epileptiform activity, such as the slow spike and wave pattern (Fig. 3.12), generalized atypical spike and wave discharges, or focal or multifocal spikes or sharp waves. The subsequent development of other EEG abnormalities is more likely to be found in the symptomatic group than in the idiopathic group (Jeavons and Bower 1964). The resolution of the hypsarrhythmic pattern usually coincides with the resolution of infantile spasms, although at times one may persist after the other has resolved (Lacy and Penry 1976). If there is a clinical relapse, the EEG abnormality returns but is usually not as severe as before (Jeavons and Bower 1964). About 25%–50% of patients will ultimately have normal EEGs after resolution of infantile spasms (Jeavons and Bower 1964; Lacy and Penry 1976) (Fig. 3.13).

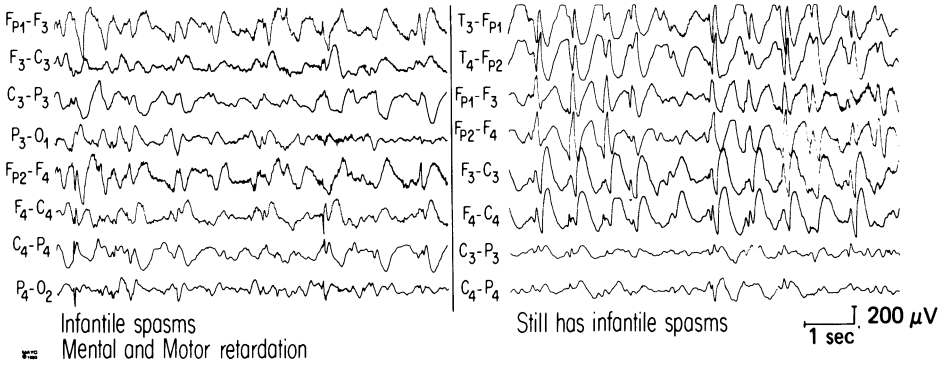

Fig. 3.12. EEG showing hypsarrhythmia in a 2-year-old boy (*left*), which was replaced by slow spike and wave pattern at 4 years of age (*right*).

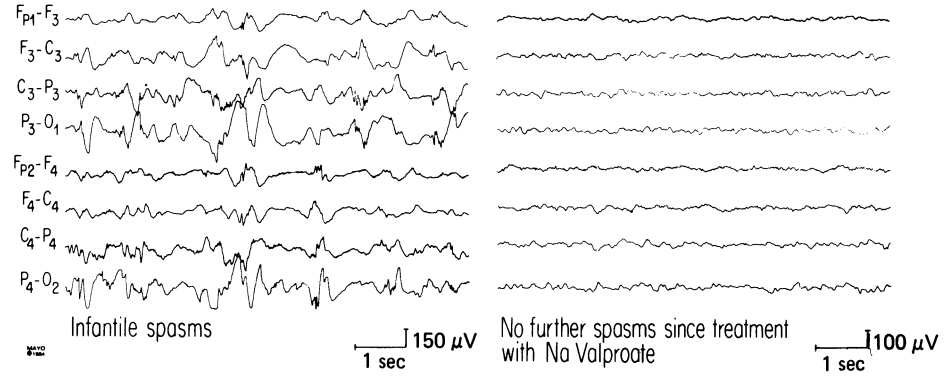

Fig. 3.13. EEG showing hypsarrhythmia in a 6-month-old boy (*left*), which became normal 1 month later after treatment with valproate sodium (*right*).

Other Laboratory Studies

Other laboratory studies used in the evaluation of patients with infantile spasms include head radiography, computed tomography, arteriography, cerebrospinal fluid analysis, and chemical examination of the blood and urine to search for the effects of metabolic diseases. Of these tests, computed tomography has been the most useful in demonstrating intracranial pathological changes (Gastaut et al. 1978) (Fig. 3.14). Magnetic resonance imaging also has the potential of being a valuable tool in this regard (Fig. 3.15). Other tests have been less useful, although on occasion plain skull roentgenograms may show the presence of intracranial calcification or increased intracranial pressure. Cerebrospinal fluid studies have been of little value other than to indicate the presence of an infectious process of the central nervous system. Pneumoencephalography and ventriculography have largely been replaced by computed tomography of the head.

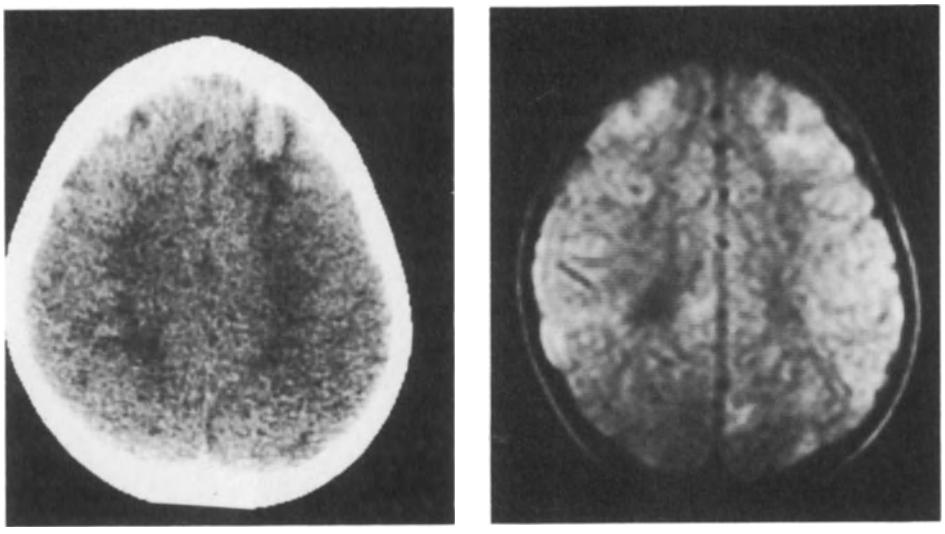

Fig. 3.14. Computed tomographic scan (*left*) and magnetic resonance image (*right*) at approximately the same horizontal level in a patient with tuberous sclerosis, showing a large cortical tuber in the left frontal pole and a smaller one in the right frontal cortex.

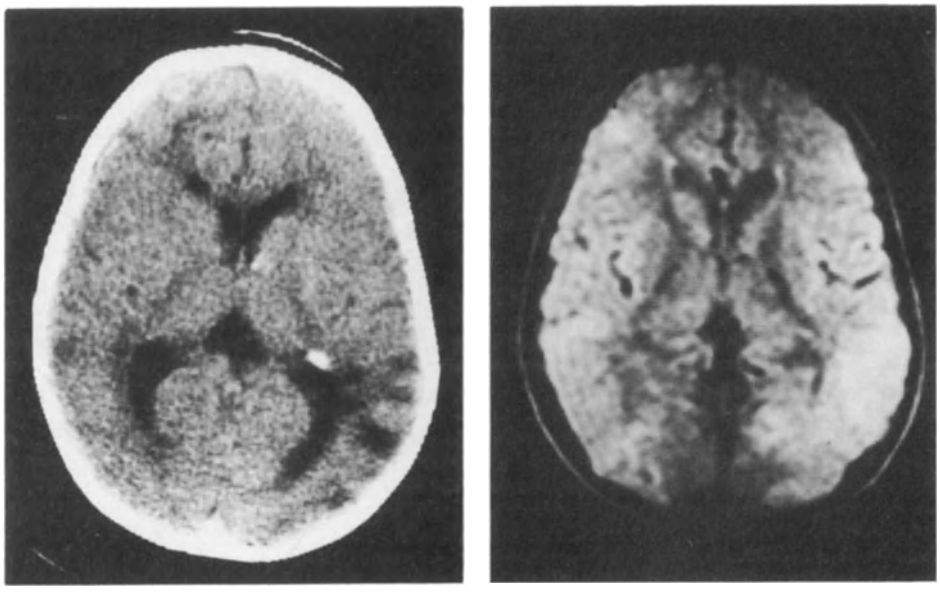

Fig. 3.15. Computed tomographic scan (*left*) and magnetic resonance image (*right*) of same patient as in Fig. 3.14 at approximately the same level, showing subependymal nodular increased attenuation and an area of hypomyelination in the computed tomographic scan and increased signal in the occipital–parietal region in the magnetic resonance image.

Treatment

Etiological

Patients with infantile spasms of known cause should receive the appropriate therapy directed to the underlying cause of the spasms. Among these causes are metabolic disorders, infections, and craniocerebral trauma with hematoma. Hypoglycemia is one of the most common types of metabolic disorder. It may be secondary to various enzymatic defects, endocrine disorders (such as hypopituitarism, hypothyroidism, adrenal insufficiency, or insulin-secreting pancreatic adenoma), or liver disease. It may also be induced by leucine ingestion or be secondary to ketosis from inanition and dehydration. Inborn errors of metabolism such as phenylketonuria, maple syrup urine disease, isovaleric acidemia, and pyridoxine dependency are treatable causes of infantile spasms. Hexosaminidase A deficiency (Tay-Sachs disease), hexosaminidase A and B deficiency (Sandhoff disease), hyperornithinemia, and nonketotic hyperglycinemia are also metabolic disorders but unfortunately can be treated only symptomatically. The prenatal infections include cytomegalovirus, syphilis, and toxoplasmosis and are treatable with antibiotics. The lesions acquired during intrauterine life in cytomegalovirus

disease, however, preclude resolution. Craniocerebral trauma may be the cause of infantile spasms, which may occur in association with cerebral contusion, unilateral or bilateral subdural hematomas, or increased intracranial pressure. Surgical evacuation of a subdural hematoma may not only relieve the danger of a progressive increase in intracranial pressure but also abolish infantile spasms.

Symptomatic

Symptomatic treatment with adrenocorticotropic hormone or adrenocorticosteroids is the ultimate choice of therapy for all idiopathic and many symptomatic types of infantile spasm. A 1-week trial of an anticonvulsant drug such as valproate sodium or nitrazepam is reasonable; however, if the trial is unsuccessful after 1 week of treatment with each of these two anticonvulsants, the patient should be given intramuscular injections of ACTH. The recommended dosage is 150 U/m^2 per day in two divided doses for 1 week followed by 75 U/m^2 per day in a single dose for another week and then this same dose only on alternate days for 2 weeks. Four weeks after the treatment is begun, the alternate-day dose of ACTH is gradually reduced over 8 or 9 weeks until it is discontinued. The patient should be given an anticonvulsant, preferably valproic acid (30–60 mg/kg per day), before discontinuation of the ACTH.

ACTH is more often and more rapidly effective than corticosteroids for the treatment of infantile spasms (Kurokawa et al. 1980; Snead et al. 1982). In the study by Snead et al., 100% of the patients treated with ACTH stopped having seizures after an average of 5 days whereas only 60% of patients treated with prednisone were controlled in 14 days. Proponents of the use of valproic acid (Bachman 1982) have claimed that 40% of patients with infantile spasms have a beneficial response to this anticonvulsant and that the side effects are less than with hormonal therapy.

Although there is a great dissension about the results of hormonal therapy (Lacy and Penry 1976), the prevailing view is that the earlier the treatment is instituted, the better the chance of a complete remission. Patients with cryptogenic or idiopathic infantile spasms have remission more often and relapse less often than patients with a demonstrable cause of the seizures (Jeavons and Bower 1964). The relapse rate for ACTH-treated patients is about 50%. Although a second course of ACTH is reasonable when relapse occurs, the probabilities of a good response are less after the second attempt (Lacy and Penry 1976).

Although many untoward reactions are associated with ACTH, perhaps the most annoying to the infant's parents are irritability, sleeplessness, and prolonged episodes of crying. Other side effects include obesity with a cushingoid appearance, an acneiform skin eruption on the face and trunk, arterial hypertension, congestive heart failure, peptic ulcer, and arrest of growth during therapy. The subarachnoid and ventricular spaces may enlarge, as demonstrated by computed tomography, and give the false impression of cerebral atrophy. This condition resolves after discontinuation of the ACTH (Hara et al. 1981) and is probably due to decreased reabsorption of cerebrospinal fluid.

Prednisone and other corticosteroids have been used for the treatment of infantile spasms, but they are less effective than ACTH (Snead et al. 1982).

Prognosis

The long-term prognosis for patients with the syndrome of infantile spasms is related to (a) the cause, (b) the state of psychomotor development prior to the onset of seizures, and (c) whether there is a prompt cessation or persistence of the infantile spasms.

Seizures

In one study, patients with idiopathic (cryptogenic) infantile spasms and those with infantile spasms after immunization for pertussis had the highest rate (37%) of seizure control (Jeavons et al. 1973). In the same study, only 16% of the total group recovered completely, 34% had subnormal intelligence, 47% had other neurological deficits, and 22% died. In another study (Matsumoto et al. 1981), 44% of the treated patients with cryptogenic infantile spasms had normal mental and physical development.

Psychomotor Development

A common observation is that as the seizures stop, the patients become more alert and psychomotor development resumes. This important effect is noticed even in patients with structural lesions of the brain (Gomez et al. 1982).

Mortality

Patients with infantile spasms have a significant death rate. Before adequate therapy was available, the death rate was approximately 30% (Lacy and Penry 1976; Dreifuss 1983); recently, however, it has been reported to be 11%–20% (Jeavons et al. 1973; Lacy and Penry 1976; Dreifuss 1983). The mortality is usually related to the underlying cause and to the state of the patient rather than to the spasms themselves (Lacy and Penry 1976). It is highest in the symptomatic group of patients who are severely retarded and have severe neurological deficits (Lacy and Penry 1976). Most of the deaths occur as a result of the debilitated state of the patient, which predisposes the infant or child to pneumonia or other infectious processes (Lacy and Penry 1976).

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Chapter 4

Lennox-Gastaut Syndrome

Warren T. Blume

Introduction

The eponym "Lennox-Gastaut syndrome" refers to patients with intractable generalized, usually motor, seizures and bilaterally synchronous slow spike–waves on the electroencephalogram (EEG). Most patients are, or become, mentally subnormal; the seizures usually start in childhood. In one population of patients with epilepsy the syndrome was identified in 10% of those less than 15 years of age (Gastaut et al. 1975).

History

Gibbs et al. (1939) first described the "slow wave and spike" as distinct from the "fast wave and spike". The former repeated at 2 Hz, the latter at 3 Hz. These authors also recognized that impairment of consciousness with the 2-Hz form was less complete and called the seizure "petit mal variant." Lennox and Davis (1950) reemphasized that patients with 2-Hz spike–waves (slow spike–waves) were clinically very different from those with 3-Hz spike–waves in that the former had a high incidence of mental subnormality and intractable seizures of multiple types with an early age of seizure onset.

This clinical aggregate remained relatively unrecognized until Sorel (1964) and Gastaut et al. (1966a,b) revived interest in the syndrome. Sorel described tonic seizures, atonic drop attacks, bilateral clonic seizures, and atypical absences with slow spike–waves, while Gastaut et al. termed the condition a "childhood epileptic encephalopathy with diffuse slow spike–waves." Its common property was the "reaction of a child's brain to some chronic cerebral aggression . . ." (Gastaut et al. 1966b). They felt that the title, although descriptive, was cumbersome; and

preferred to honour the clinician who first described it in detail—thus "Lennox syndrome." Niedermeyer (1968) recognized Gastaut's substantial contribution to our concept of this affliction and introduced the now commonly used eponym "Lennox-Gastaut syndrome."

The Syndrome

A syndrome is not, however, a disease. Thus, the borders of a syndrome may be imprecise and its components variable. Elements of the constellation may be shared by entities not considered part of it. As will be discussed, the age of patients and the method of clinical investigation play major roles in authors' descriptions of the component seizure types.

The literature urges us to distinguish West syndrome from Lennox-Gastaut syndrome, yet infantile spasms and tonic seizures share common properties, as do hypsarrhythmia and slow spike–waves. We are further enjoined not to confuse myoclonic–atonic epilepsy with Lennox-Gastaut syndrome, but their epileptic and EEG phenomena overlap. Defining a syndrome, whose fundamental pathogenesis is undetermined, on the basis of whether causative factors can or cannot be identified is also arbitrary and presumptive. Instead, our focus should be on the common properties which link the several elements of the syndrome. These include: (a) an intractable generalized seizure disorder which almost always includes motor events whose tonic, atonic, or myoclonic properties cause the patient to fall; (b) onset of the seizure disorder in early childhood, i.e., 1–6 years; (c) slow spike–waves on EEG; and (d) a high prevalence of mental subnormality. These components occur together sufficiently often to constitute a syndrome. As Gastaut et al. (1966a,b) suggested, these features represent the reaction of an immature central nervous system to a chronic diffuse insult of some type [see discussion by Aicardi (1982)].

Seizure Disorders

Tonic Seizures

The first clinical sign of neurological illness in the majority of patients with Lennox-Gastaut syndrome is recurrent seizures (Gastaut et al. 1966a,b; Chevrie and Aicardi 1972; Blume et al. 1973). In a study of 100 patients with slow spike–waves, Gastaut et al. (1966a,b) found tonic seizures to be the most common, occurring in 70.

From polygraph recordings, Gastaut et al. (1963; 1966a,b) and Gastaut and Broughton (1972) were able to divide tonic seizures into axial, axorhizomelic, and global types. Chatrian et al. (1982) also scrutinized tonic seizures by polygraph. The following description is derived from these studies. In the axial type, neck, facial, and masticatory muscles contract to flex, extend, or fix the neck in position.

Contraction of respiratory musculature causes respiration to become shallow and then to cease in expiration; air forced through a spasmodic glottis produces vocalization. Added participation of proximal muscles of the arms and legs in the axorhizomelic type may cause the shoulders to shrug and the arms to elevate in extension or semiflexion. Less often, the legs may flex and abduct. In the global tonic seizure, the aforementioned features are associated with contraction extending to the distal portions of the limbs, giving clenched fists and triply flexed legs. Consciousness is impaired or lost during these attacks; autonomic changes such as facial flushing, tachycardia, and pupillary dilatation may occur (Chatrian et al. 1982).

Chatrian et al. (1982) noted several ocular and periocular phenomena: conjugate deviation upward or horizontally, blinking, opening, or closure of eyes, and elevation of the eyebrows. These occur in any one of the three types of tonic seizure mentioned above.

Several studies have shown a dramatic increase in tonic seizures during non-REM sleep (Gastaut et al. 1966a,b; Gastaut and Broughton 1972; Tassinari et al. 1977; Chatrian et al. 1982) but not in REM sleep (Chatrian et al. 1982).

Atypical Absence Seizures

Atypical absence attacks occurred in 32 of Gastaut et al's (1966a,b) patients. As Gibbs et al. (1939) had first recognized, these differ from typical absences in that the onset and termination are gradual and consciousness is incompletely lost. They share some components of tonic seizures as contraction of ocular and periocular muscles may open the eyes, which may deviate upward. Slight rigidity of the jaw and neck may occur with elevation of the arms. Conversely, atonic features may be seen. As with tonic seizures, autonomic changes such as color alteration and salivation may occur. Gastaut et al. commonly observed automatisms during these attacks. Atypical absences are not precipitated by hyperventilation or photic stimulation.

Myoclonic Attacks

"Clonic" or myoclonic attacks occurred in 14 of the 100 patients studied by Gastaut's group. The common feature of these attacks is falling, either through loss of tone or a sudden diffuse clonic or brief tonic spasm which may be followed by several synchronous myocloni. These attacks were appropriately included under "epileptic falls" by Chevrie and Aicardi (1972) and termed "myoclonic–astatic" by Doose et al. (1970). Doose et al. described symmetrical jerking of the proximal arms with nodding of the head and twitching of the facial muscles—particularly the eyes and mouth. Clinically, it may be impossible to see whether falling results from a simple loss of tone or a brief contraction followed by hypotonia.

Grand Mal Attacks

Grand mal attacks occurred in 15 of Gastaut et al.'s patients, usually among the older patients.

Factors Affecting Reported Incidence of Seizure Type

Chevrie and Aicardi (1972) studied 80 patients presenting with any type of epileptic seizure and whose interictal waking EEG contained diffuse slow spike–waves. Their results closely resembled those of the Gastaut group: tonic seizures occurred most commonly (in 56%), atypical absences being the next most usual (44%). They included epileptic drop attacks or falls in a single category as their clinical study did not permit distinction between atonic and myoclonic events. Such drop attacks occurred in 27%.

The particular value of the Chevrie and Aicardi study lies in their attention to age of seizure onset, as this factor largely explains interstudy differences in the incidence of seizure types. Thus, mean age of seizure onset was less among patients presenting with tonic seizures than among those who presented with other types. Conversely, clonic and tonic–clonic seizures appeared significantly later. Atypical absences appeared at a midpoint along this continuum. In other words, their findings indicated that the ictal symptomatology of the Lennox-Gastaut syndrome depends somewhat upon the maturation of the brain when the attacks begin.

Although Gastaut et al. (1966a,b) were unable to provide data about age of onset, the median age of onset for Chevrie and Aicardi's (1972) patients was 11 months, compared with 28 months for Blume et al. (1973) and 24 months for Markand (1977). Blume et al. found tonic seizures to be the third most common after atonic and tonic–clonic, and Markand found "minor motor" attacks, including tonic, in only 13%.

These studies (Chevrie and Aicardi 1972; Blume et al. 1973; Markand 1977) lack the scrutiny provided by polygraph recordings and may have misclassified some tonic attacks. Chatrian et al. (1982) detected visually inapparent tonic events during electrographic seizures by multiple EMG monitors.

Doose et al. (1970) reported a group of patients with atonic and myoclonic attacks who had some features of the Lennox-Gastaut syndrome. Their spike–wave repetition rate, 2–3 Hz, overlapped on the high side with those of previously discussed works. In these children, who also had absence and grand mal attacks, the seizure disorders began between 24 and 36 months of age, which is older than the mean age (17 months) that Chevrie and Aicardi found for tonic seizure onset.

Severity of the Seizure Disorders

Several data reflect the severity of the seizure disorders. Between 50% and 75% of Lennox-Gastaut patients have more than one type of seizure (Gastaut et al.

1966a,b; Chevrie and Aicardi 1972; Blume et al. 1973). Moreover, the attacks occur daily in at least half of these patients. As will be shown below, the attacks are usually therapy resistant. Moreover, status epilepticus is not an uncommon feature (Niedermeyer 1984). Thus, absence status with varying degrees of unconsciousness may last up to several weeks. Tonic status epilepticus may occur: tonic seizures following each other in rapid succession, lasting about 5–40 s and occurring 15–100 times in an hour. This situation may persist for several days. Myoclonic status, in contrast, appears less commonly.

Electroencephalography

The slow spike–wave complex forms one of the bases of the Lennox-Gastaut syndrome. The complex classically consists of single or multiple 100- to 200-ms biphasic or triphasic, predominantly electronegative, sharp wave(s) followed by a 350- to 400-ms rhythmic wave whose downslope may be steepened as the next sharp wave begins (Figs. 4.1, 4.2). Occasionally, the epileptiform component of the slow spike–wave is a spike; typical 3-Hz spike–waves may be mixed with slow spike–waves. The quantity of slow spike–waves varies from single complexes to almost continuous sequences; they occupy much greater quantities of an awake recording than 3-Hz spike–waves usually do. Their abundance usually decreases with increased age at recording, but quantity has no prognostic value for future

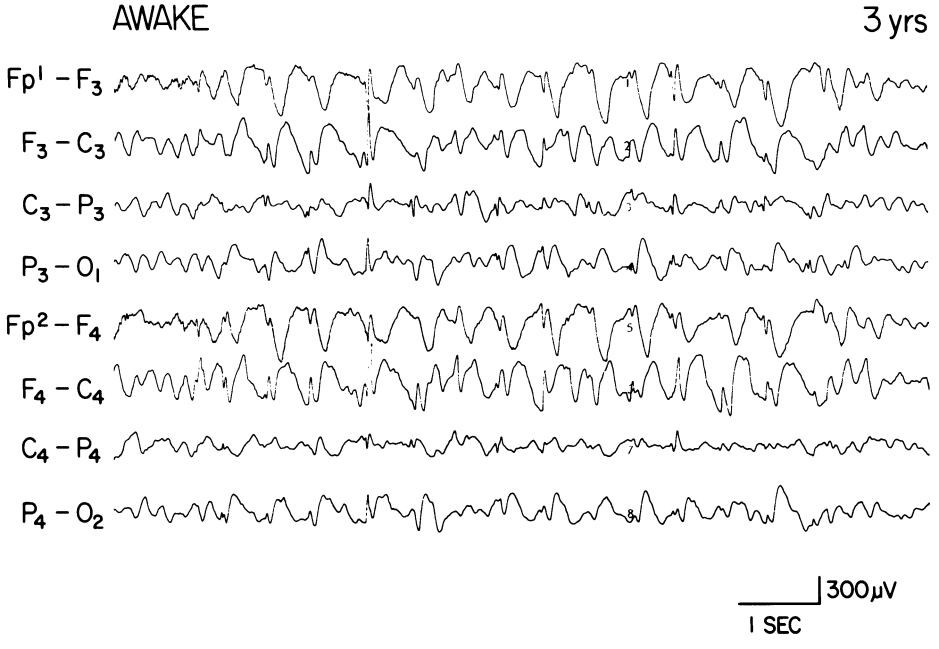

Fig. 4.1. Bilaterally synchronous slow spike–waves appearing diffusely but maximally expressed at F_3 and F_4. At the onset of slow spike–waves, the child stopped crying and stared ahead.

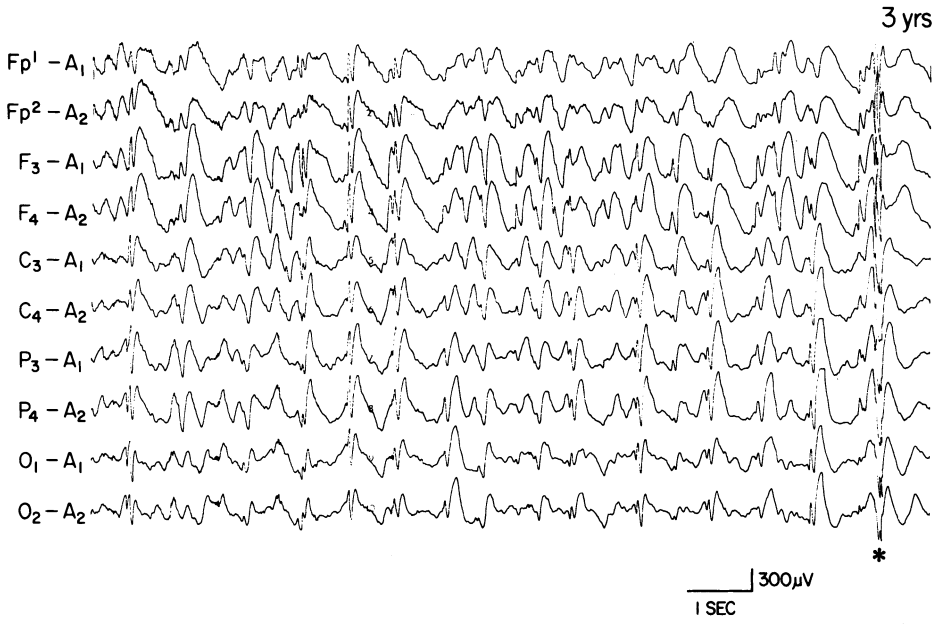

Fig. 4.2. Ear reference recording may best illustrate slow spike–wave morphology and distribution, and their variability. During slow spike–waves, the child stopped crying, stared, and blinked: but many similar sequences of discharges were not accompanied by clinical change. Myoclonus of the trunk and proximal portions of the arms accompanied the highest voltage discharge (*).

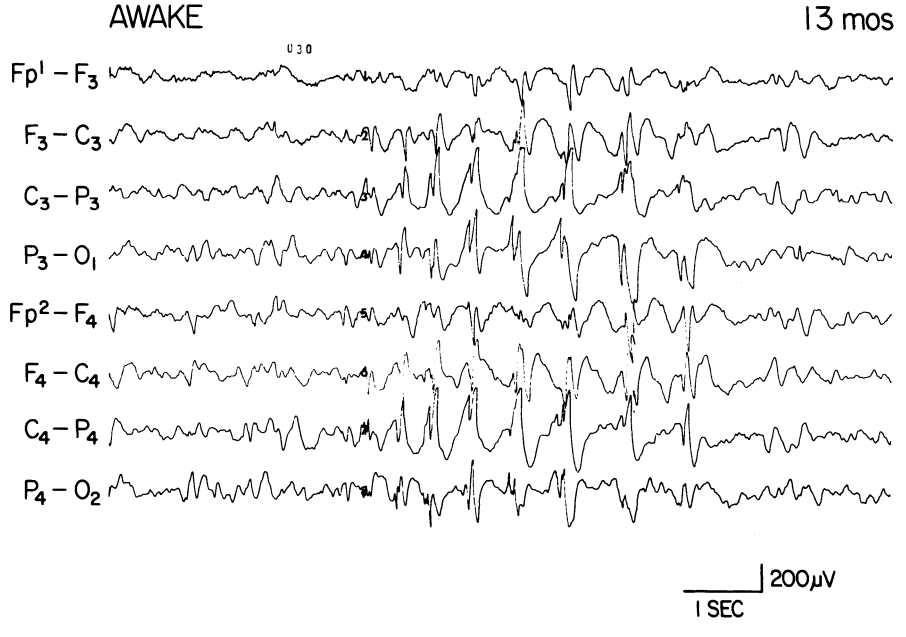

Fig. 4.3. Although diffusely distributed, these slow spike–waves appear principally in the occipital–parietal regions with propagation anteriorly. Note again the variability of morphology and field distribution. Compare with Fig. 4.1. Eyes open.

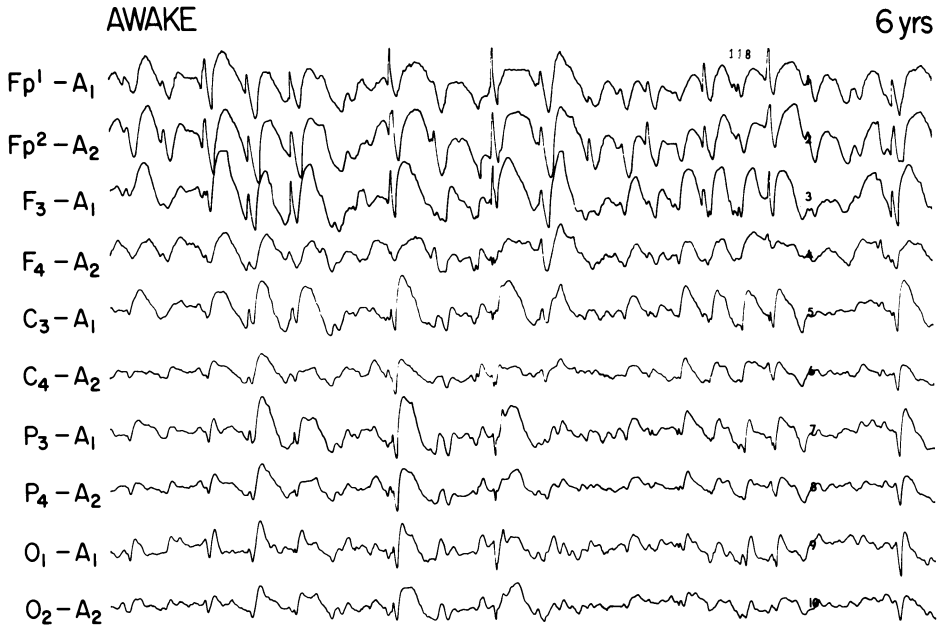

Fig. 4.4. Slow spike–waves are lower in amplitude over F_4, C_4 and P_4, the site of a large intracerebral cyst. Note that this asymmetry extends to the occipital region as well. Left hemiplegia from birth.

seizure control or mental development (Blume et al. 1973). The morphology, amplitude, and repetition rate of slow spike–waves may vary moderately within bursts and between bursts.

Although commonly diffusely distributed, they may be principally expressed in, or confined to, the anterior (Fig. 4.1) or more posterior head regions (Fig. 4.3). Complexes are usually symmetrical but shifting asymmetries appear commonly; hemispheric or even regional (e.g., temporal) slow spike–waves can be seen. Slow spike–waves more often have an asymmetrical distribution when antecedent neurological disease has occurred (Fig. 4.4) (Sorel 1964; Ohtahara et al. 1976). Hyperventilation rarely augments the abundance of slow spike–waves, but photic stimulation has no effect.

The interparoxysmal portions of the awake recording commonly exhibit greater-than-normal quantities of slow activity; the background frequency is usually lower than normal. Excessive delta or theta may appear focally, multifocally, or diffusely.

While mental alerting may attenuate slow spike–waves, drowsiness and non-REM sleep typically augment their quantity. In fact, they may appear only during drowsiness or sleep. This property contrasts with 3-Hz spike–waves, which may fragment even in light sleep. Sleep may alter the morphology of complexes as

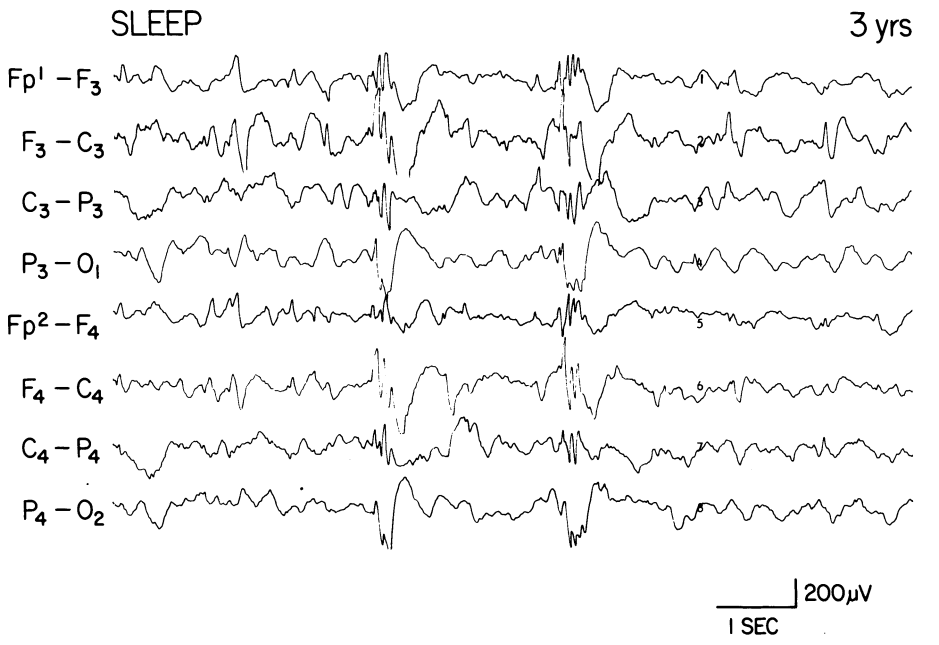

Fig. 4.5. Burst of bilaterally synchronous polyspikes in light non-REM sleep of patient with slow spike–waves during wakefulness. Note lack of well-formed V-waves and of spindles, features normally present in light to moderate levels of sleep.

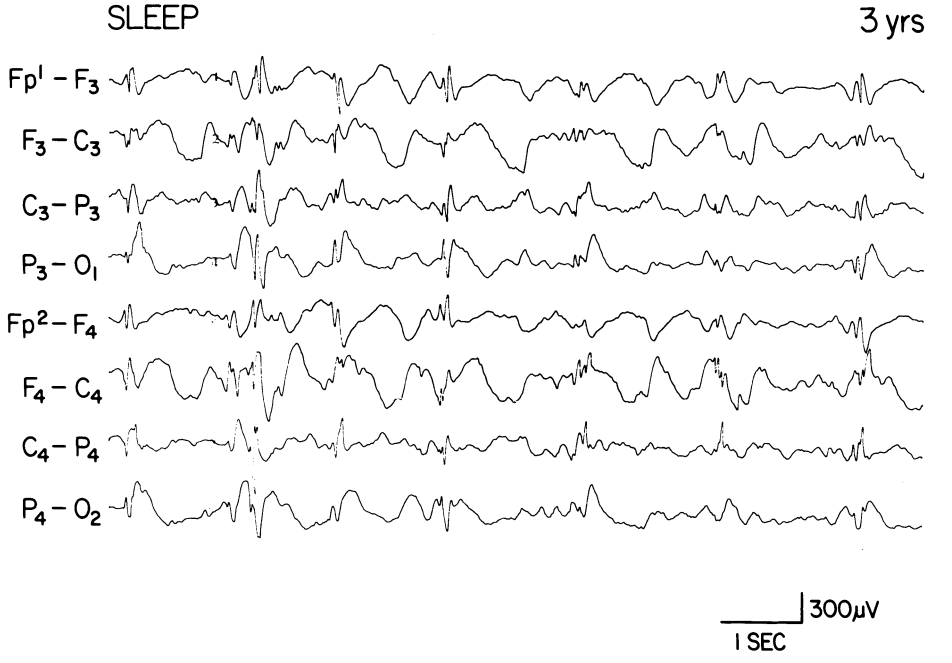

Fig. 4.6. Many bursts of bilaterally synchronous and diffuse polyspikes accompanied by irregular slow waves in deeper non-REM sleep of the same patient. High voltage (note sensitivity) reflects widespread synchrony of discharges on this and the preceding figure.

polyspikes become more prominent (Figs. 4.5, 4.6). Runs of generalized polyspikes and rhythmic 10- to 20-Hz waves may appear. Electrodecremental events may interrupt ongoing activity. If alternating with bursts of polyspikes, a burst–suppression pattern is constituted—a sporadically appearing event in moderately deep sleep. Reflecting the diffuse encephalopathy, normal sleep potentials such as spindles, V-waves, and posteriorly accentuated delta activity may be diminished or absent.

The maximum incidence of slow spike–waves is 1–5 years of age, but their presence extends well into adulthood in some patients. Slow spike–waves also occur in the first year of life, when they may be intermixed with a hypsarrhythmic pattern.

Unlike 3-Hz spike–waves, long series of slow spike–waves may be unaccompanied by any discernible clinical alteration, although testing for subtle changes is often impeded by mental subnormality. Tonic seizures are most often accompanied by diffuse electrodecremental events (Fig. 4.7), fast (10- to 25-Hz) rhythmic

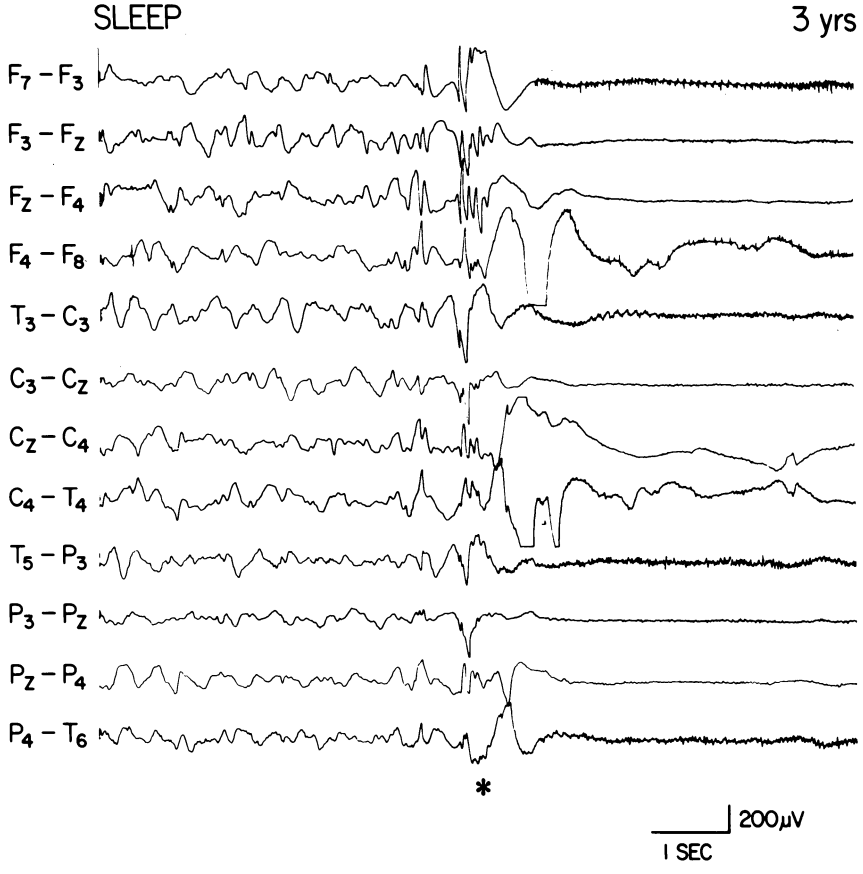

Fig. 4.7. Following a frontally predominant diffuse polyspike–wave discharge (*), a sudden, diffuse decrease in amplitude of EEG potentials occurs [electrodecremental event (EDE)], with an increase in potentials of muscular origin. During this EDE the patient's trunk stiffened and both arms flexed at the elbows. High-voltage slow potentials during EDE are an artifact.

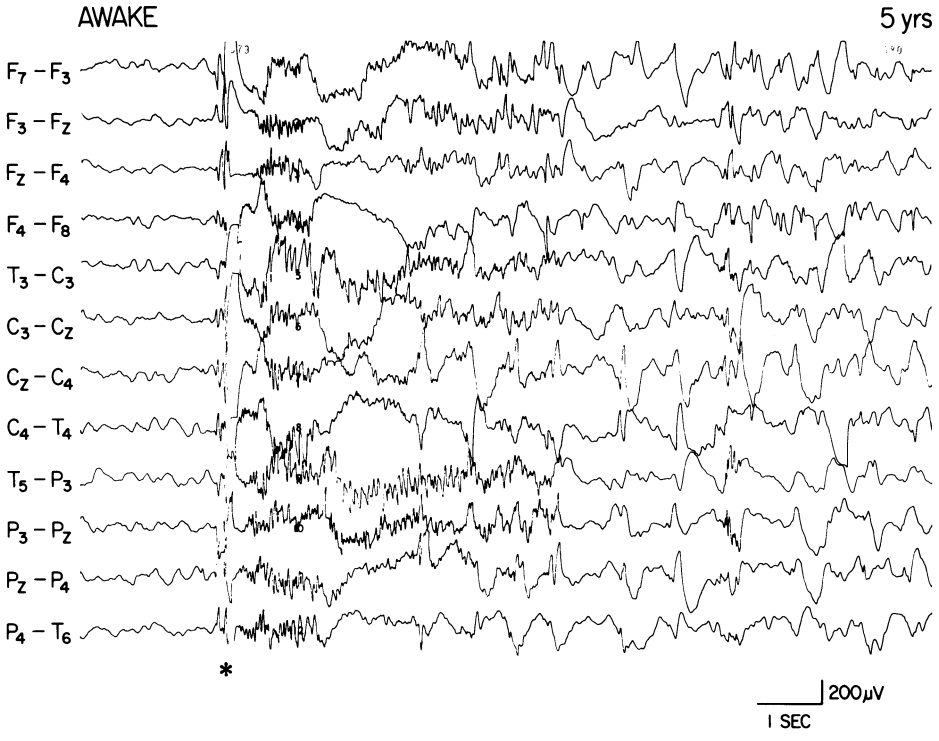

Fig. 4.8. Following a diffuse polyspike–wave discharge (*), high frequency polyspikes appeared lasting about 5 s. At (*) both arms abducted at the shoulders and elbows flexed while the head was thrust forward; this position was maintained during polyspike discharge. Following ictus, slow spike–waves appeared.

waves, and/or polyspikes (Figs. 4.8, 4.9). These phenomena may be preceded by a diffuse polyspike–wave discharge. Electrodecremental events may precede rhythmic waves or polyspikes, whose frequency may slow during the tonic attack. The EEG at termination of a tonic seizure may revert immediately to the preictal pattern or may be followed by transient 1- to 2-Hz waves. Atypical absence may be detected at the onset or during generalized slow spike–waves (Figs. 4.1, 4.2) or may accompany any of the patterns of tonic seizures. Myoclonic attacks occur in association with high voltage bisynchronous spikes superimposed upon slow spike–waves (Fig. 4.2), with very brief decremental events or rhythmic waves, or without any EEG change. Atonic seizures electrographically resemble myoclonic events.

Terminology for the slow spike–wave phenomenon has varied over the years. Gibbs et al. (1939) first named it the "slow wave and spike formation." Subsequent terminology for the discharge has been either cumbersome (sharp and slow wave complexes) or clinical (petit mal variant discharge). As the duration of the epileptiform component varies from complex to complex and is not, therefore, the defining feature of the phenomenon, reversion to the simpler "spike" is justified. Moreover, it is well known that the wave component of any such complex, "fast" or "slow", is that of a delta wave. Therefore, "slow wave" can be shortened to

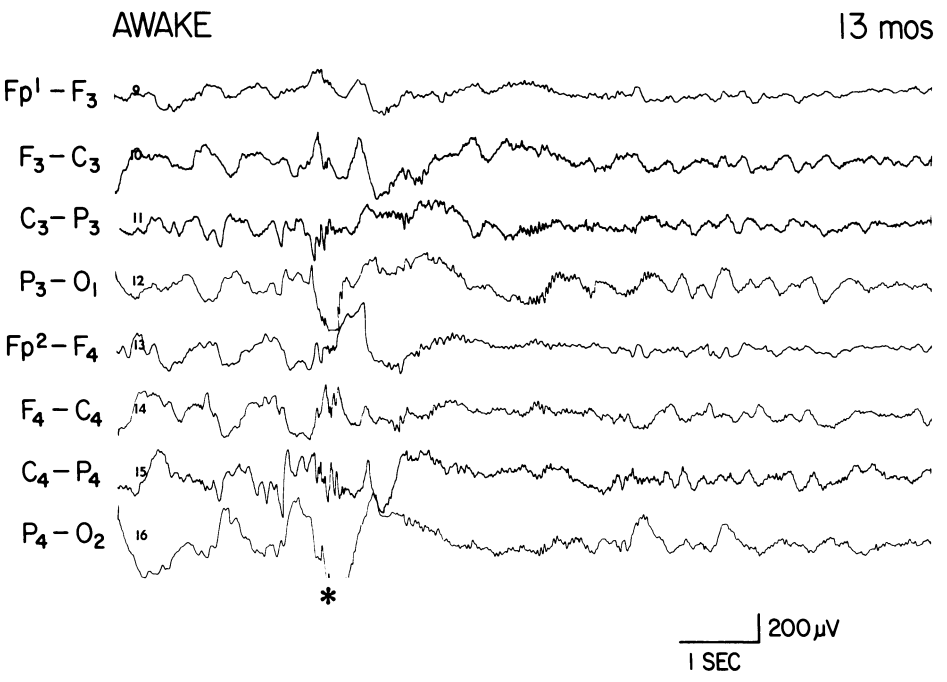

Fig. 4.9. A brief burst of polyspikes, maximum right hemisphere (*), is followed by diffuse 20-Hz rhythmic waves lasting 4–5 s. At (*) all limbs jerked once and the eyes opened and deviated upward for the duration of the rhythmic waves.

"wave." Finally, "complex" is redundant. My only disagreement with the appellation of the original authors is the sequence: since the spike usually precedes the wave, the terminology should be in the same order. Hence, "slow spike–wave" is used here [as did Lennox and Davis (1950)], the adjective referring to the repetition rate of the complex and not to the morphology of the epileptiform component.

Mental Status and Neurological Examination

Lennox and Davis (1950) first noted that about half of their patients with slow spike–waves were mentally subnormal as compared with only 5% with 3-Hz spike–waves. Gastaut et al. (1966a,b) and Markand (1977) each reported subnormal mental development in 80% of their patients. Blume et al. (1973) found that mental subnormality became progessively evident with time. Seventy-nine percent of their patients had normal motor milestones whereas only 34% had normal intellect at initial evaluation, at age 4 years.

Chevrie and Aicardi (1972) found microcephaly in 18 of 58 cases (31%). Deficits of the motor system at initial evaluation appear in about one-third of patients overall (Chevrie and Aicardi 1972; Blume et al. 1973; Markand 1977). Blume et al.

found ophthalmological changes suggesting lipidosis and early infection such as toxoplasmosis in 4 of 84 patients. All of these cognitive, neurological, and ophthalmological abnormalities suggest antecedent neurological insults in a substantial proportion of patients with Lennox-Gastaut syndrome. This factor affects prognosis (see below).

Etiology

The syndrome may appear in a previously healthy child, or it may supervene in a patient who is already neurologically and mentally handicapped.

Lennox and Davis (1950) listed possible etiological factors in 41% of their 200 patients with slow spike–waves. As would be expected, birth injury and encephalitis formed the majority of such cases. About half the patients in subsequent studies (Gastaut et al. 1966a,b; Chevrie and Aicardi 1972; Blume et al. 1973, Ohtahara et al. 1976; Markand 1977) had either historical or examination evidence of antecedent central nervous system illness which presumably accounted for the syndrome. These included diseases which affect the cerebrum in early life: e.g., prematurity, birth injury, encephalitis, and the hemiconvulsions–hemiplegia–epilepsy (HHE) syndrome. Less often, progressive conditions such as tuberous sclerosis, neuronal ceroid lipofuscinosis, lipidosis, and metabolic encephalopathies (e.g., aminoacidopathies) produce the symptom complex.

In about 20%–25% of some series (Chevrie and Aicardi 1972; Markand 1977) the Lennox-Gastaut syndrome follows infantile spasms with hypsarrhythmia. Gastaut et al. (1966b) describe a quiescent interval in some of these patients in whom the spasms disappear and the EEG improves. Soon the clinical and EEG manifestations of Lennox-Gastaut syndrome follow.

Chevrie and Aicardi (1972) noted that seizures of the Lennox-Gastaut syndrome began earlier among patients in whom a presumed etiology was present than among idiopathic or "primary" cases. As discussed above, tonic seizures are less common in this slightly older group of primary cases, in whom myoclonic, atonic, and atypical absences predominate. These associations may explain the low (6%) incidence of definite antecedent neurological insult among Doose et al.'s (1970) slightly older group with myoclonic, atonic, and absence attacks.

Even antecedent neurological disease may not entirely account for the pathogenesis of the syndrome: not all patients with such presumed CNS insults develop the Lennox-Gastaut syndrome. There are likely appropriate spectra of severity and distribution of damage, as well as timing, which are requisite for its occurrence.

No etiology, even presumptive, can be discerned in 30%–50% of cases (Lennox and Davis 1950; Gastaut et al. 1966a,b; Chevrie and Aicardi 1972; Blume et al. 1973; Markand 1977). Gastaut et al. (1966b) found normal histology in many biopsy specimens.

These concerns raise the question of genetic predisposition for the syndrome. Our knowledge in this area is meager. Incidence of family history of seizures varies from 2.5% (Chevrie and Aicardi 1972) to about 25% (Lennox and Davis 1950; Blume et al. 1973) among different studies. Unfortunately, the definition of "family" and of epilepsy type is rarely given. Doose et al. (1970), however, gave more detailed data about families in their 51 patients with myoclonic–atonic

seizures. Twenty patients had at least one sibling, parent, or grandparent with a history of seizures. Thirteen percent of all siblings, 7% of parents, and 2% of grandparents had a seizure history; there was no sex predilection. Spike–waves were found in the resting record or with hyperventilation in 8% of siblings as compared with 1.4% of controls; a photoconvulsive response occurred in 28% of siblings and only 2.8% of controls. (Their category of other "abnormal rhythms" is non-specific and difficult to interpret.) These data suggest that genetic factors may play a role in the etiology of the slightly older group of Lennox-Gastaut syndrome patients without antecedent neurological disease and without tonic seizures. Even in this group, the magnitude of this role needs to be verified; moreover, the exact mode of inheritance awaits further study. Whether a genetic factor is involved among those patients with antecedent neurological disease is unknown.

Histocompatibility antigens may be helpful in identifying individuals at risk for epilepsy. Smeraldi et al. (1976) reported an increased incidence of HLA-A7 antigen among 21 children with Lennox-Gastaut syndrome as compared with 443 healthy control subjects.

Differential Diagnosis

Having identified the presence of two or more components of the Lennox-Gastaut syndrome, the clinician must realize that a diagnosis in the strict sense has yet to be made. Faced with a previously well child with brief diffuse motor seizures, the main worry is whether a specific progressive disorder is present. Aicardi (1982) gives a useful classification of myoclonic epilepsies and encephalopathies of childhood, dividing them into progressive and nonprogressive entities. The former include lipidoses and neuronal ceroid lipofuscinosis. Distinction between an identifiable incrementing disorder and a so-called nonprogressive condition such as "idiopathic" Lennox-Gastaut syndrome may be difficult as both the mental impairment and the seizure disorder become increasingly obvious as the disorders continue. Clinical features suggesting a specific progressive illness would include: (a) downhill course (mental and/or epileptic) over months or a few years, (b) presence of specific neuro-ophthalmological signs of one of the progressive disorders such as a cherry-red spot, (c) emergence of new neurological signs, especially relating to the pyramidal system or to the cerebellum, and (d) dermal lesions suggesting tuberous sclerosis or other phakomatosis.

Distinction between the Lennox-Gastaut syndrome and infantile spasms (West syndrome) may be difficult as there is some overlap in age, features of infantile spasms and tonic seizures, and EEG patterns. As West syndrome may evolve gradually to Lennox-Gastaut syndrome, the distinction may be arbitrary in some instances.

Rarely, patients with uncontrolled primary generalized epilepsy may share some features of the Lennox-Gastaut syndrome. Thus, a child with reiterative absence seizures or in absence status may appear mentally subnormal; the usual 3-Hz spike–waves may slow to 2-Hz in this situation. Aggressive therapy with an intravenous benzodiazepine may clarify the situation.

Tassinari et al. (1977) described a rare condition characterized by status epilepticus with continuous spike–wave discharges at 2–2.5 Hz every time the child falls into non-REM sleep. Electrographic status epilepticus during sleep may persist for years. Such substitution of spike–wave status for usual sleep may produce behavioral disturbances in wakefulness, such as apathy and school failure. During wakefulness spike–waves may appear but slow spike–waves are not a feature.

Bilateral or diffuse spike–wave discharges with temporal or central–parietal accentuation occur in the syndrome of acquired aphasia of childhood. Their repetition rate may be 2 Hz, but the regional accentuation differentiates them from slow spike–waves. In this syndrome, an expressive and receptive dysphasia becomes established over days to months in previously healthy children 3 to 8 years old. Sporadic generalized or focal seizures may occur. Nonverbal intellect remains normal.

Secondarily generalized epileptiform discharges may resemble slow spike–waves. Therefore, the electroencephalographer should scrutinize slow spike–wave recordings for persistent focal or focally accentuated abnormalities, particularly frontal. The latter may rarely relate to a tumor or other focally progressive condition.

Finally, episodes of decorticate or decerebrate posturing associated with syncope or breath-holding spells can be distinguished from tonic or clonic seizures by their invariable association with precipitating factors and by a normal EEG.

Prognosis

Seizure Control

As noted above, the seizure disorder of the Lennox-Gastaut syndrome is usually severe: many have daily seizures and have more than one type. Thus, it is not surprising that Blume et al. (1973) found that 63% of patients were still having seizures after a 12-year follow-up, with an average duration of seizure disorder of almost 15 years. Patients whose seizures were controlled had a later average age of seizure onset than those whose seizures were uncontrolled. In a 3- to 14-year follow-up, Ohtahara et al. (1976) found persisting seizures in 61%. Sixteen of the 18 patients (89%) with normal intellect were seizure-free, as compared with 29 of 98 (30%) with subnormal mentality. Blume et al. (1973) found that the longer the seizure disorder lasted, the less likely that it would be controlled at follow-up.

Mental Evolution

The studies by Chevrie and Aicardi (1972) and Blume et al. (1973) both documented that the percentage of patients with Lennox-Gastaut syndrome who are manifestly retarded increases with age. In the 1973 study, 79% had normal

motor milestones, 34% were mentally normal at 4 years, and only 26% were normal at 16 years. In the 1972 study, 30% were considered retarded at the time of the first seizure, 69% at first EEG showing slow spike–waves, and 93% at last examination. This confirms the observation of Gastaut et al. (1966a,b) that an arrest of mental development appears to occur in most patients with this syndrome.

Chevrie and Aicardi (1972) were the first to demonstrate convincingly that early age of seizure onset was the factor which correlated best with ultimate mental subnormality. Blume et al. (1973) and Ohtahara et al. (1976) subsequently confirmed that patients whose seizures began before age 2 years fared less well than those with older ages of onset. The differentiating age for Komai (1977) was 3 years, while Bauer et al. (1983) found more favorable mental outcomes in those whose Lennox-Gastaut syndrome began after age 6 years. In a penetrating analysis of their material, Chevrie and Aicardi were able to demonstrate that type of seizure, including infantile spasms (West syndrome), had no prognostic value for mental development when age of seizure onset was controlled. As would be expected, patients with evidence of central nervous system disease prior to developing Lennox-Gastaut syndrome had a higher prevalence of retardation at follow-up than those who had been normal; this difference was still significant after correction for age of seizure onset. However, even in this secondary group, early age of seizure onset further impeded mental attainment.

Possibly consequent upon frequent generalized motor seizures, there is evidence that additional temporal lobe dysfunction may be grafted upon the diffuse encephalopathy. Gastaut et al. (1966a,b) described temporal lobe spikes in association with diffuse slow spike–waves. Using positron emission tomography, Gur et al. (1982) found hypometabolism in a temporal lobe in two patients with Lennox-Gastaut syndrome. Margerison and Corsellis (1966) found sclerosis and neuronal loss principally in the temporal lobes in patients with chronic generalized seizure disorders. This secondary insult could add a memory impairment to the already compromised mental activity.

In parallel with the mental evolution, the long-term social outlook for most patients is bleak. Forty-six percent of the patients who Blume et al. (1973) followed for 12 years had either died or resided in institutions. Only 21% were in regular school classes or nonsheltered jobs.

Pathophysiology

The mechanisms underlying clinical phenomena of the Lennox-Gastaut syndrome remain incompletely determined, but astute clinical and experimental observations over the years have begun to sketch in the picture.

Gloor et al. (1968) correlated the EEGs of patients with diffuse encephalopathies with their histopathological diagnoses. The most striking consistent finding in patients with diffuse cortical and subcortical gray matter disease was bilaterally synchronous discharges either as slow spike–waves, sharp waves, or bursts of delta. White matter lesions and those limited to cortical gray matter rarely exhibited this feature.

Subsequent experimental studies by Gloor's group (see Gloor 1979 for review) and by Fisher and Prince (1977a) indicated that synchronous spike–wave discharges produced by systemic penicillin represent an abnormal cortical response to afferent thalamocortical volleys. This abnormal cortical response in turn induces spike–wave activity in the thalamus which helps to sustain the cortical bursts (Avoli and Gloor 1982; Avoli et al. 1983). Pellegrini et al. (1979) severed thalamic input to the cortex and converted penicillin-induced spike–wave discharges to paroxysms resembling slow spike–waves. McLachlan et al. (1982) produced a similar effect in the systemic penicillin model by rendering the cats hypoxic.

These clinical and experimental data suggest that slow spike–waves are produced by abnormal interaction involving at least the cortex and thalamus. The clinical homologue of experimental penicillin epilepsy is unclear. However, penicillin acts primarily by antagonizing the effects of GABA, i.e., by decreasing inhibition (Prince and Connors 1984). There is some evidence that inhibitory interneurons are more vulnerable to hypoxia and other injury than other neurons. Moreover, it appears that following injury, sprouting of axons results in a new functional connectivity: in some instances excitatory terminals can be shifted from dendrites to soma. This would produce a marked increase in neuron excitability, especially if such excitatory synapses took the place of inhibitory ones that normally end on cell somata (Prince and Connors 1984). If such structural alterations occurred diffusely over the cortex and in the thalamus in humans from early hypoxia or other insult, they would have the same physiological effect as systemic penicillin in producing an epileptic encephalopathy.

Inhibition in this situation is not abolished, however. Fisher and Prince (1977b), Pollen (1964), and others have shown that the spike of the experimental spike–wave complex, whether produced by systemic penicillin or by electrical stimulation of thalamic nuclei, at least in part represents EPSPs generated in apical dendrites, whereas the subsequent surface negative slow wave is likely produced by IPSPs at the soma (see also Kostopoulos et al. 1982). The long duration wave of the slow spike–wave complex probably indicates that cortical inhibition remains but that it is triggered by excessive and synchronous excitation.

The foregoing therefore provides some insight into the mechanism of slow spike–waves and of those atypical absence attacks accompanying such discharges, as the slow spike–waves may have similar cellular correlates as spike–waves.

Less attention has been given to the mechanism of the motor seizures. In their scrutiny of tonic seizures in children, Gastaut et al. (1963) observed tachycardia, increased blood pressure, and EEG desynchronization during some attacks. These features, together with those of the tonic seizures, suggested to them an origin in mesencephalo-ponto-bulbar structures. Gastaut et al. further speculated that those tonic attacks accompanied by high-voltage, high-frequency discharges originated in the thalamus. The EEG desynchronization was supposedly mediated from the brain stem by the ascending reticular activating system while diffuse thalamocortical projections would have effected the high-voltage EEG waves. Because low- and high-voltage, high-frequency discharges are commonly intermixed in the clinical situation, Chatrian et al. (1982) believe that only a single mechanism needs to be postulated for these phenomena.

Evidence supporting a brain stem reticular formation origin of tonic seizures had been provided by Kreindler et al. (1958), who produced tonic seizures with EEG desynchronization by electrically stimulating the brain stem reticular formation and periaqueductal region of rats and cats. Moreover, Rodin et al. (1971,

1975) found that high-frequency activity originated in the brain stem reticular formation when myoclonic and tonic-clonic seizures were induced in cats by intravenous pentylenetetrazol, bemegride, or bicuculline. Myoclonus was associated with bursts of high-frequency activity, while the tonic phase of tonic–clonic seizures correlated with the same discharge but sustained. These findings would therefore support the hypothesis of Gastaut et al. that the brain stem reticular system is the origin of the motor seizures of Lennox-Gastaut syndrome.

If such experimental data reflect the clinical situation, the question of what triggers such reticular formation discharge and how it is related to diffuse cortical-thalamic dysfunction remain undetermined. As spike–waves are replaced by high-frequency cortical discharges (as represented by EEG desynchronization and/or high-frequency activity) during such attacks, cortical inhibition is apparently overwhelmed by excitation at that point. Clues to genesis may be the increased tonic seizures effected by sleep and occasionally by benzodiazepines—both of which affect reticular formation function. Finally, whether myoclonic and atonic seizures are simply very brief tonic events which are aborted by rapidly developing inhibition or whether they are a different physiological entity needs clarification. On EEG some myoclonic attacks are accompanied by brief high-frequency bursts similar in kind to those of tonic seizures, while others appear with high-voltage single spikes. This suggests two different mechanisms for clinically similar attacks, although Rodin's data suggest otherwise.

The arrest or reverse of mental development among Lennox-Gastaut patients and others with repetitive seizures in early life has prompted inquiry into the effect of seizures on protein synthesis. Giuditta et al. (1983) and Dwyer and Wasterlain (1983) have shown decreased brain protein and DNA synthesis following electroshock seizures and status epilepticus in rabbits and rats. This factor would particularly affect the immature brain, whose rate of protein synthesis is high. Reduced protein synthesis might affect cell viability by inhibiting synthesis of enzymes or other proteins. By prolonging cell cycle time in actively dividing cell populations, growth and differentiation would be reduced. This could lower cell populations and create aberrant synaptic organization. This is critical in the developing brain as once the strictly defined periods of cell division and differentiation have been bypassed, reparation is impossible and the dysmorphogenesis will be permanent (Dwyer and Wasterlain 1983).

Although Margerison and Corsellis (1966) described areas of neuronal loss and gliosis in patients with chronic generalized seizure disorders, and rare pathological specimens have revealed a specific etiology, most pathological specimens have not disclosed a precise pathogenesis (Gastaut et al. 1966b). Newer pathological techniques, concentrating on synapses, may shed light on the problem.

Treatment

Seizures of the Lennox-Gastaut syndrome are often resistant to many standard anticonvulsants. In an attempt to avert the complications of excessive polypharmacy, it is wise to set the goal of treatment early in management, i.e., as soon as the magnitude of the problem is realized. The goal may include less-than-complete

seizure control. Wherever possible, this compromise between better seizure control and drug toxicity should be discussed frankly with the parents. Devising an overall plan of therapy early in management helps. This includes the sequence of drugs to be tried, their possible combinations, and the maximum dosages or blood levels that should be achieved. Performance of each drug should be completely documented as it may be necessary to return to a somewhat helpful medication later. Thus, uselessness and moderate usefulness should be distinguished.

Valproic acid is regarded as the drug of first choice by some authors (Eeg-Olofsson 1980; Vasella, cited by Gram and Bentsen 1984), although Dulac and Arthuis (1984) doubt its usefulness. Vasella et al. (1973) found clonazepam to be effective in 6 of their 13 patients with Lennox-Gastaut syndrome. Tassinari et al. (1972) and Bittencourt and Richens (1981) caution that intravenous benzodiazepines may produce tonic status epilepticus in Lennox-Gastaut patients.

Classical anticonvulsants such as phenytoin, primidone, carbamazepine, and phenobarbital should be tried. If any clinical or EEG overlap with West syndrome exists, therapy appropriate for it could be instituted, i.e., pyridoxine, ACTH, or steroids. It is doubtful whether regimes such as the ketogenic diet or medium chain triglycerides will be useful in a chronic illness such as this.

Therapy for the related symptom complex of myoclonic–atonic seizures (Doose et al. 1970) is generally more effective. Valproic acid appears to be the drug of choice (Jeavons et al. 1977; Delgado-Escueta et al. 1983a,b). Benzodiazepines can also be effective.

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Chapter 5

Febrile Seizures

Gerald Erenberg and Harold H. Morris III

Introduction

The term "febrile seizures" refers to a clinical syndrome based on the tendency of young children to experience seizures during a febrile illness. In ancient times, Hippocrates had already noted that "convulsions occur to children if acute fever be present . . . most readily up to their seventh year. Older children and adults are not equally liable to be seized with convulsions in fevers, unless some of the strongest and worst symptoms precede . . ." (Adams 1929, p. 212). Hippocrates also described a relationship between convulsions and fever due to teething, stating that "at the approach of dentition, pruritis of the gums, fevers, convulsions, diarrhoea . . ." occur in susceptible children (Adams 1929, p. 217).

Despite the fact that febrile seizures have been described since antiquity, debate continues over their definition and their relationship to epilepsy. Some authors have concluded that febrile seizures are a form of epilepsy (Faerber 1929; Bridge 1949; Peterman 1952), while others have believed that they represent an entity which is distinct from the other forms of epilepsy (Livingston 1972). Much of the controversy over the relationship to epilepsy undoubtedly is related to the source of patient material studied by various investigators. Markedly different outcomes have been reported between studies performed on clinic-based populations and studies performed on defined populations followed prospectively (Ellenberg and Nelson 1980). A current definition of febrile seizures was put forth by a National Institutes of Health Consensus Development Conference on Febrile Seizures in 1980. A febrile seizure was defined as "an event in infancy or childhood, usually occurring between 3 months and 5 years of age, associated with fever but without evidence of intracranial infection or defined cause." Seizures with fever in children who had suffered a previous nonfebrile seizure were excluded. Febrile seizures were to be distinguished from epilepsy, characterized by recurrent nonfebrile seizures.

Incidence

The reported incidence of febrile seizures clearly indicates that such seizures are among the most common neurological problems in childhood. Much information about febrile seizures has been learned from the analysis of 54 000 children born to mothers registered in the Collaborative Perinatal Study between 1959 and 1966 (Nelson and Ellenberg 1976). These children underwent a regular schedule of examinations until they were 7 years old. In this study, febrile seizures occurred in 3.5% of white children and 4.2% of black children. Other studies from the Western Hemisphere have shown that between 2.2% and 5% of all children will experience convulsions during a febrile illness before they are 5 years old (Hauser 1981). Tsuboi (1984) found an even higher prevalence in children studied in Japan. In his study, 8.3% of children studied at 3 years of age had experienced a febrile seizure. It is not known whether the wide variation reported in epidemiological studies represents true differences in prevalence or differences in sampling methods. Febrile seizures occur slightly more frequently in males than in females, but the reason for this is unknown (Nelson and Ellenberg 1978).

Genetics

An increased frequency of febrile seizures has been found among parents and siblings of children with febrile seizures. Although it is generally agreed that a genetic predisposition exists (Frantzen et al. 1970; Metrakos and Metrakos 1970; Tsuboi 1977; van den Berg 1974), the estimates of how frequently first-degree family members experience febrile seizures have varied. The proportion of siblings who also experience febrile seizures has ranged from 9% to 17% (Hauser 1981). The exact pattern of heredity is also unclear. Possibilities include inheritance patterns consistent with a single gene-dominant trait (Frantzen et al. 1970), a recessive trait (Rutter and Smales 1977), or polygenic inheritance (Tsuboi 1977).

Siblings of children with epilepsy are also at increased risk for experiencing febrile seizures (Annegers et al. 1980), but the prevalence of epilepsy in relatives of probands with febrile seizures is less clear. Some studies have shown an increase in the frequency of nonfebrile seizures among siblings (Metrakos and Metrakos 1970; van den Berg 1974) while others have not (Frantzen et al. 1970; Annegers et al. 1979).

Clinical Characteristics

The majority of febrile seizures begin by the age of 3 years, and it is unusual for the first febrile seizure to occur after that age. The most common age of onset is between 1 and 2 years (Lennox-Buchthal 1973). The usual child is of good health and normal development, and the seizure occurs while the child has a recognizable infection. Most infections are of viral origin, and common examples include upper

respiratory infections, otitis media, and gastroenteritis. Some illnesses have been associated with an unusually high incidence of febrile seizures. These include shigella gastroenteritis (Kowlesser and Forbes 1958) and roseola infantum (Lennox-Buchthal 1973).

By definition, fever of extracranial source is always present and is usually above 39°C rectally. The relative importance of the height of the temperature elevation as compared with the rate of rise remains uncertain (Ouellette 1974). The duration of fever prior to the seizure is virtually always less than 24 h (Livingston 1972), and most seizures will occur in the first few hours after the fever has begun. Many times, the parents will be unaware of the presence of the fever until the child begins to have a seizure.

The vast majority of febrile seizures are generalized. The number of children reported to have focal seizures is small, although the incidence is high in series which have included children with intracranial abnormalities. These generalized seizures, usually tonic–clonic in form, are of brief duration. However, since the seizures have occurred at home and are being reported by distraught parents, it has been difficult to obtain answers to questions such as the exact body temperature at the onset of the seizure or the exact duration of the seizure.

Evaluation

Most children with a febrile seizure will be seen by a physician after the seizure has already ended. If the child is actively convulsing when seen, immediate treatment is required. The treatment is no different than the treatment of any other seizure. Support of vital functions is required while a rapid clinical and laboratory assessment is made. The fever must be lowered and intravenous anticonvulsants used to end the seizure.

After the seizure has ended spontaneously or has been stopped with medications, an assessment of the cause of the seizure must be undertaken. As recently as 1974, an extensive battery of laboratory tests was routinely suggested (Ouellette 1974). These included blood urea nitrogen, sugar, and calcium; electrolytes; complete blood count; urinalysis; spinal tap; cultures of blood, urine, and nasopharynx; skull X-rays; and electroencephalogram. While many of these tests may be appropriate in individual children (depending on the clinical circumstances), several studies have concluded that most children with febrile seizures do not require such extensive testing (Nealis et al. 1977; Wolf 1978; Gerber and Berliner 1981; Jaffe et al. 1981). The only possible exception to this is the spinal tap. Since the classic signs of meningitis are often absent in children less than 18 months of age, a spinal tap is recommended for this age group as well as when meningitis is suspected (Rutter and Smales 1977).

A final decision to be made is whether or not the child with a febrile seizure should be admitted to the hospital. This decision must be made on the basis of the child's clinical condition as well as the state of mind of the parents. If the child has recovered completely by the time the evaluation has ended, there is no reason for hospitalization. If the child's neurological examination is abnormal or the neurological condition is unstable, hospital admission would be best. Some physicians admit all children with a febrile seizure to the hospital so that distraught parents

can be reassured. This is generally not necessary if the family is given a full explanation of the situation. Attention to the parents' feelings and needs is of the utmost importance since one study found that 30% of parents who witnessed their child's febrile seizure thought their child was dying or dead (Rutter and Metcalfe 1978).

Electroencephalography

By and large the electroencephalographic findings in patients with febrile seizures have been of interest to investigators but of little practical help to the clinician treating the individual child with the seizure (Jaffe and Sanderson 1972; Gerber and Berliner 1981).

In the first week following a febrile seizure, approximately one-third of the patients are said to demonstrate marked delta activity, most prominent posteriorly and frequently asymmetrical (Frantzen et al. 1968). The slow activity tended to resolve after the 1st week. The finding of pronounced focal slow activity did not predict future occurrence of seizures, although a small percentage of children subsequently did develop a spike focus which tended to be in the region of the slow activity. Frantzen's study, while well done, did not separate children into groups with simple febrile seizures or complicated febrile seizures. The study also did not exclude patients with neurological deficits.

Finding specific epileptiform activity in the first EEG after a febrile convulsion is unusual. In Frantzen's study only 3 of 218 children (1.4%) demonstrated such abnormalities. Kajitani et al. (1976) found only 3% of 154 children had epileptiform activity after their first simple febrile seizure. Jaffe and Sanderson (1972) found only a 1% incidence of epileptiform activity in 100 patients with simple febrile seizures. These figures are not significantly different from the 1.9% incidence of focal sharp wave activity in normal children as reported by Eeg-Olofsson et al. (1971).

If serial EEG studies are done over several years, up to 29% of children with febrile seizures have been reported to show some form of epileptiform activity (Frantzen et al. 1968) in their EEG. These authors found 30 children (13.8%) with generalized spike–wave complexes. Twelve children (5.5%) had a photoparoxysmal response, an incidence similar to the 8.9% of normal children (Eeg-Olofsson et al. 1971). Nineteen children (8.7%) developed a sharp-wave focus. Two children (1%), both having "gross organic defect," had a slow spike–wave pattern. Spike–wave complexes were detected at an average time of 16 months after the febrile convulsion and usually were seen in children 4 years of age or older. Spike–wave complexes had no prognostic value as to the occurrence of future epilepsy. Only 5 of 218 children (2.3%) eventually developed epilepsy. Of these five children, three developed recurrent seizures before epileptiform activity was present in the EEG, and one child did not exhibit epileptiform activity. The 19 children who developed a sharp-wave focus form an interesting group. The illustration in the paper shows a discharge with a morphology of benign focal epileptiform discharges of childhood. There seems to be a definite association of febrile convulsions and benign focal epilepsy of childhood, and this relationship is reviewed in detail elsewhere in this book.

The studies of Nelson and Ellenberg (1978) and of Annegers et al. (1979) looked at many risk factors involved in febrile seizures, but unfortunately neither study specifically addressed the role of EEG.

In summary, the routine acute EEG appears to be of little value in children with simple febrile convulsions. An EEG should be obtained if the patient exhibits focal or prolonged seizures or for other standard neurological indications.

Pathophysiology

The mechanism that leads to febrile seizures remains unknown, and it is also unknown why some children are susceptible to the effects of fever while others are not. The pathogenesis of febrile seizures has been linked at various times to circulating toxins, immune reactions, viral and bacterial invasion, relative lack of myelination, and increased oxygen consumption in the immature febrile brain (Hirtz and Nelson 1983). Early work by Wegman (1939) led to the hypothesis that the occurrence of febrile seizures in young animals was due to a rapid rise in body temperature. Lennox et al. (1954) believed that both the height of the fever and the rapidity of the rise were equally important, while Millichap (1959) believed that the height of the fever alone was important. Other investigators have found immaturity of thermoregulatory mechanisms (McCaughran and Schechter 1982) to be an important factor. In their experiments, Holtzman et al. (1981) found young animals to have a limited capacity to increase cellular energy metabolism at elevated temperatures.

Another line of investigation has been to search for biochemical abnormalities in the cerebrospinal fluid (CSF) of children with febrile seizures. Evidence to date has been inconclusive as to whether abnormalities of neurotransmitters are of importance in the etiology of febrile seizures (Hirtz and Nelson 1983). Decreased CSF levels of γ-aminobutyric acid have been found, but the exact significance of this is unknown (Löscher et al. 1981). 5-Hydroxyindoleacetic acid and homovanillic acid have not been found to be altered.

Vannucci (1981) has recently reviewed the effects that experimental febrile seizures have on the developing brain in animal models. Two studies did show neuronal damage after experimental febrile seizure but could not distinguish the pathological changes from those caused by hyperthermia alone (Wegman 1939; Lennox et al. 1954). Vannucci concluded that extrapolations from experimental models to the clinical situation remain of uncertain validity.

Prognosis

Following a febrile seizure, children generally continue to enjoy good overall health. They are, however, at risk for experiencing a recurrent febrile seizure. The risk of recurrence varies with the age of the child at the time of the initial seizure (Nelson and Ellenberg 1978). The younger the child, the higher the risk of recurrence. Without treatment, febrile seizures recur in approximately 50% of

children whose first seizure occurred before they were 1 year old and in approximately 25% whose first seizure occurred after they were 1 year old. Eighty-eight percent of all recurrences take place within 24 months of the first seizure (Nelson and Ellenberg 1978).

There has been much concern regarding the possible injurious effect of single or recurrent febrile seizures. One concern has been their significance for later intellectual development and behavior (Wallace 1984). Most studies have shown that febrile seizures do not lead to a reduction in intelligence. Ellenberg and Nelson (1978) compared children with febrile seizures with seizure-free siblings and found no difference in the mean full-scale IQ on the Wechsler Intelligence Scale for Children (WISC). Camfield et al. (1979) and Wolf et al. (1981) also found normal IQ scores in the children they tested. Academic performance was normal in children with febrile seizures (Ellenberg and Nelson 1978) when compared to an uninvolved sibling.

The subsequent behavior and social adjustment of children with febrile seizures has seldom been investigated. Schiottz-Christensen and Bruhn (1973) studied 47 twin pairs where one of each twin pair had a history of febrile seizures. No adverse effect on behavior was found, although there was a tendency for better behavior in the nonconvulsing twin in the few pairs where there was a difference. Cull (1975) also found some increased problems in behavior in children with febrile seizures, but this correlated best to items such as socioeconomic status and did not correlate to any aspect of the seizure history.

In addition to the impact on future learning and behavior, there has been much concern regarding the role of febrile seizures in causing future afebrile seizures (epilepsy). Opinions regarding the likelihood of epilepsy following febrile seizures have often varied depending on the population studied. Population-based studies, where attempts have been made to recognize and follow up all affected persons, have generally shown low rates of future epilepsy (Ellenberg and Nelson 1980). Clinic-based studies, which usually report a biased sample of patients with more complicated disease, have generally shown a high frequency of epilepsy in children with febrile seizures. The Collaborative Perinatal Study showed that 3% of children with febrile seizures had one or more seizures without fever by the age of 7 years (Nelson and Ellenberg 1978). A low frequency of subsequent epilepsy was also seen in the British National Child Development Study, in which only 0.5% of febrile seizure patients seen by general practitioners in England later developed afebrile seizures (Ross et al. 1980).

Some population-based studies may underestimate the risk of future epilepsy because the length of follow-up is inadequate. A population-based study with a 15-year follow-up was reported by Annegers et al. (1979). In their review of residents of Rochester, Minnesota, who had experienced febrile seizures as children, 6% had developed epilepsy by age 20. The risk of epilepsy remained significantly increased during each age interval studied. Even this higher figure, however, is considerably less than the figure reported from clinic-based studies, in which up to 77% of patients have been found to have unfavorable outcomes (Ellenberg and Nelson 1980).

The risk of subsequent epilepsy is not influenced by the number of febrile seizures, the age of onset, or race and sex (Nelson and Ellenberg 1978). There are, however, identifiable groups of patients who have high-risk factors which greatly increase the risk of epilepsy. Livingston (1972) found that 97% of patients developed seizures unassociated with fever if they initially had febrile seizures

Table 5.1. High risk factors associated with increased risk of subsequent epilepsy

Abnormal neurological or developmental status prior to febrile convulsion
Complex seizure
Longer than 15 min in duration
More than one seizure in 24 h
Focal seizure
History of afebrile seizures in parent or sibling

which were prolonged or focal. Other investigators have not found as high a rate of epilepsy, but the concept of high-risk factors has been confirmed in other studies. Nelson and Ellenberg (1978) identified three high-risk factors (Table 5.1). Ninety-four percent of their patients with febrile seizures possessed none or one of these risk factors, and epilepsy developed in only 1%–2% of these patients in later life. Of the 6% with two or more risk factors, epilepsy developed in 10% by the time they were 7 years old. In the study by Annegers et al. (1979), persons with a prior neurological disorder or with febrile seizures that were exceptional or prolonged were also much more likely to experience epileptic seizures. By the age of 20 years, the risk of epilepsy was 2.5% for those with neither risk factor and 17% for those with both risk factors (Table 5.2).

Table 5.2. Risk of future epilepsy

	Low-risk group	High-risk group
Collaborative Study (to age 7)	1%–2%	10%
Rochester, Minnesota (to age 20)	2.5%	17%

There has been special concern that febrile seizures, especially when prolonged, may lead to mesial sclerosis and an increased risk of complex partial seizures. This idea has arisen from both surgical (Falconer 1971) and nonsurgical (Ounsted et al. 1966) series in which many patients with complex partial seizures reported having experienced prolonged febrile seizures as children. These series collected their information retrospectively and did not exclude seizures which had been associated with CNS infections. Leviton and Cowan (1981) have proposed three theories that could account for any possible association: febrile seizures do increase the risk of subsequent complex partial seizures; febrile seizures could be the first manifestation of a seizure disorder; or there could be separate but associated risk factors for both disorders. The association between febrile seizures and complex partial seizures has not been apparent when cohort or population studies of febrile seizures have been reviewed (Hauser 1981). In studies done in the United States (Nelson and Ellenberg 1976) and Denmark (Frantzen et al. 1968), the predominant type of afebrile seizure in patients with epilepsy following febrile seizures has been generalized rather than focal.

Treatment

Three modes of therapy are possible: none, intermittent, or continuous. The question regarding whether or not to treat with anticonvulsant therapy has generated considerable controversy. Those who advocate anticonvulsant therapy in the management of children with febrile seizures argue that doing so will prevent neurological sequelae resulting from recurrent seizures. These possible sequelae include death, status epilepticus, future epilepsy, permanent motor deficits, mental retardation, and learning and behavioral disabilities. The need to allay parental anxiety has also been stated as a possible reason for treating with anticonvulsant medication.

Population-based studies have generally shown that few children with febrile seizures suffer significant neurological sequelae (Nelson and Ellenberg 1978). Recurrences definitely occur, but a prolonged febrile seizure occurring after a brief initial febrile seizure is rare (Nelson and Ellenberg 1978). What is yet unknown is whether treatment started after one or more febrile seizures can prevent the development of epilepsy (Nelson 1981).

Rapid shifts in treatment patterns have occurred through the years. In 1975 (Asnes et al.), a survey of pediatricians in the United States revealed that most physicians used intermittent phenobarbital therapy. Most would now agree that current knowledge of the pharmacokinetics of phenobarbital precludes the use of this agent intermittently. If a standard dose of 5 mg/kg per day is used, more than a week will elapse before a stable therapeutic level is established. On the other hand, starting therapy with 15 mg/kg will provide an adequate therapeutic level in 90 min, but such a dose will produce marked, although transient, symptoms each time a febrile illness occurs (Pearce et al. 1977). Reports on the use of intermittent rectal diazepam have been more encouraging (Knudsen and Vestermark 1978; Thorn 1981). Absorption is good, side effects are mild, and the lowered recurrence rate compares favorably with that obtained by the use of chronic phenobarbital therapy. Unfortunately, no drug used intermittently can prevent seizures in those situations where the convulsion occurs prior to the time the child is noted to be febrile (Porter 1981).

The ability of chronically administered phenobarbital to decrease markedly the frequency of recurrent febrile seizures has now been well established (Wolf et al. 1977; Ngwane and Bower 1980; Wallace and Smith 1981; Bacon et al. 1981; Wolf 1981; Herranz et al. 1984). In prospective studies which utilized control groups and monitored blood levels, the recurrence rate was generally decreased to below 10% as compared with the 19%–34% recurrence rate in the controls. The phenobarbital was given daily, and levels were maintained above 15 μg/ml. Chronically administered phenobarbital has become the standard against which all other forms of therapy are judged. Phenobarbital was also found to be more effective than the use of intermittent antipyretic treatment. The study by Camfield et al. (1980) showed that the use of antipyretic therapy alone did not appear to reduce the recurrence of febrile seizures.

Potential problems with chronic anticonvulsant use must be taken into account when deciding that long-term treatment is indicated. Poor parental compliance is relatively common, especially in conditions where the patient is otherwise normal between seizures. In the study by Wolf et al. (1977), 32% of the children prematurely discontinued treatment with phenobarbital, and this included 10% in

whom medication was stopped because their parents did not wish to continue it even in the absence of side effects. Side effects are seen in up to 40% of children receiving phenobarbital and include hyperactivity, irritability, and sleep disturbances (Wolf and Forsythe 1978; Camfield et al. 1979). Adverse effects are not restricted to children with underlying neurological abnormalities and are rarely associated with toxic levels. In several series, the phenobarbital was discontinued in approximately 20% of treated children because of behavioral abnormalities (Thorn 1975; Wolf and Forsythe 1978).

There has been concern as well that daily phenobarbital taken for several years can adversely affect long-term cognitive function in children who receive the drug for control of febrile seizures. Studies on epileptic subjects receiving phenobarbital have suggested some impairment of either perceptual motor performance or short-term memory (Hirtz 1981), but studies in children with febrile seizures have, at most, shown only subtle findings of cognitive dysfunction (Camfield and Camfield 1981). The study by Wolf et al. (1981) specifically evaluated the impact of medication on a treated group and a control group of children with febrile seizures, and no long-term effect of phenobarbital on cognitive function was found.

Other anticonvulsant medications have been tried in situations where daily therapy is desirable and phenobarbital cannot be tolerated. Clinical trials of phenytoin have shown this to be an ineffective prophylactic agent (Melchior et al. 1971), and therapeutic drug levels were found to be difficult to maintain (Bacon et al. 1981). Phenytoin has also been found unable to prevent seizures induced by hyperthermia in rat pups (Olson et al. 1982). Carbamazepine has not been utilized as extensively but has also failed to show a beneficial effect in preventing recurrent febrile seizures (Monaco et al. 1980; Camfield et al. 1982).

Two other anticonvulsant drugs *have* been found effective in preventing recurrent febrile seizures. Primidone has not been studied extensively but appears to be as effective as phenobarbital. In the study by Herranz et al. (1984), fewer side effects occurred with primidone than with phenobarbital although the phenobarbital level was almost the same. The potential use of valproic acid has been better studied (Ngwane and Bower 1980; Wallace and Smith 1980; Herranz et al. 1984). It was found to be as effective as phenobarbital and to have fewer side effects. Use of valproic acid in febrile seizures has been limited by concern about possible fatal hepatotoxicity, but its use can be considered when an alternative to phenobarbital is definitely required.

Even though effective anticonvulsant medications are available, the trend has been away from treating all children with febrile seizures. Any treatment decision must weigh the risks of a potential adverse outcome of an untreated disease with the efficacy and potential side effects of the available therapies. The suggestions made in the NIH Consensus Statement on Febrile Seizures (NIH consensus development conference summary 1981) are based on the beliefs that the long-term prognosis for most children is excellent and that subgroups of children at high risk for future epilepsy can be identified. Taking these facts into account, the panel recommended considering continuous prophylaxis only in children with known high-risk factors, i.e., abnormal neurological development, complex and atypical seizures, and a history of nonfebrile seizures in a parent or sibling. On this basis, only a small percentage of children require treatment, but most practitioners would add those patients with families that strongly wish to prevent further febrile seizures even after being informed of the advantages and disadvantages of the treatment. Some practitioners have also suggested treatment when more than a

specified number of recurrences have occurred (Addy 1981). Daily therapy usually is continued for at least 2 years or 1 year after the last seizure, whichever is the longer period.

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Chapter 6

Absence Seizures

Manuel R. Gomez and Barbara F. Westmoreland

Introduction

"Absence" is the term now preferred for a type of generalized seizure well recognized by its clinical and electroencephalographic characteristics. Its synonyms, "petit mal" and "minor seizure," have been too often erroneously used to indicate any seizure that is not "grand mal." Absence seizures are characterized by an abrupt loss or impairment of consciousness without warning for a period usually less than 10 s, and rarely as long as 1 min. Responsiveness is decreased or totally lost and sometimes there are associated automatisms, subtle symmetrical clonic movements such as blinking, increased or diminished postural tone, autonomic changes, and version of the head or conjugate deviation of the eyes (or both).

Historical Aspects

According to Lennox (1960), the epileptic seizure now called *absence seizure* was first mentioned in the medical literature in 1772: Tissot, a Swiss neurologist, related that a young girl who had been well until the age of 7 years developed tic-like eyelid movements a few days after a storm had frightened her. Four months later, violent attacks began, and between them, she continued having little attacks consisting only of loss of consciousness. Esquirol was the first to use the term "petit mal," whereas Calmeil used "absence" (Lennox 1960). In 1881, Gowers described "minor attacks." It is difficult to improve Gowers' clinical description of an absence seizure or petit mal attack:

> The most common form is transient loss of consciousness without conspicuous convulsion. A patient suddenly stops for a moment in whatever he or she is doing, very often turns pale, may drop whatever is in the hand, and then is better. There may be no visible spasm, or there may be a slight stoop forward,

or a slight quivering of the eyelids. The patient may or may not fall. Pallor of face is by no means invariable.... The attack usually lasts only a few seconds. The return of consciousness may be sudden, and the patient, after the momentary lapse, may be in just the same state as before the attack, may even continue a sentence or action which was commenced before it came on, and suspended during its occurrence.

Before electroencephalography (EEG), it was not always possible to differentiate absence seizures from partial seizures. Thus, Gowers, in referring to "minor seizures," included both generalized and partial seizures, as indicated by his statement that minor seizures are "often heralded by some sensory warning or aura." With the introduction of EEG, a new era began. In the 1930s and 1940s, Gibbs et al. (1935) at Harvard and Jasper and Droogleever-Fortuyn (1947) and Penfield and Jasper (1947) at the Montreal Neurological Institute provided the basic data on the electrical events that made it possible to differentiate the generalized from the focal seizure. This work culminated in 1964 with the new terminology proposed by the International League Against Epilepsy. The neurophysiologists, particularly Moruzzi and Magoun (1949), also contributed to this end by demonstrating the presence of a specialized region in the mesencephalon and diencephalon which regulates electrical rhythms and the state of consciousness. The stimulation of this system produced a response that resembled an absence seizure and its electrographic accompaniment, the 3-Hz spike and wave discharge. In 1949, Hunter and Jasper showed that stimulation of the intralaminar thalamic nuclei in the cat results in arrest of movement, including fixation of the eyes.

In 1954, Penfield and Jasper emphasized the importance of the subcortical nuclei projecting to the cortex and introduced the term "centrencephalic epilepsy" for a presumed subcortical pacemaker capable of eliciting the bilaterally synchronous 3-Hz spike and wave pattern in patients with "absences" who have no demonstrable cerebral pathological condition. The centrencephalic theory was challenged by many investigators, some of whom found that the fronto-orbital cortex regulates thalamocortical electrical activity (Velasco and Lindsley 1965) while others (Marcus and Watson 1966) showed that extensive bilateral frontal lesions can produce bilaterally synchronous spike and wave activity in isolation from the thalamus.

After Wada's introduction of the intracarotid injection of sodium amobarbital in 1949 (Wada and Rasmussen 1960), Bennett in 1953 and Gloor in 1968 applied this technique, using a unilateral intracarotid injection of pentylenetetrazol in patients with generalized seizures, and produced bilaterally synchronous spike and wave discharges. In 1978, Gloor injected a large intramuscular dose of penicillin into cats and produced generalized seizures with staring, blinking, and myoclonic twitches around the face and proximal muscles of the upper extremities. Simultaneous stimulation of the ascending reticular formation prevented electrographic discharges, and inhibition of this cholinergic neuronal system activated the spike and wave discharges.

Natural History

The onset of absence seizures is rare in children less than 3 years old, is most common in those between 4 and 11 years of age, and is unusual in persons 20 years

old or older (Gomez and Klass 1983). A few adults have had seizures that began in childhood.

There is no known increased prevalence according to sex, race, or geographical location; however, there is a familial aggregation of patients with absence seizures. Lennox (1951) observed that monozygotic twins are 84% concordant for the generalized 3-Hz spike and wave discharges and 75% concordant for absence seizures, whereas dizygotic twins are discordant. In 1961, Metrakos and Metrakos showed that the abnormal electroencephalographic pattern (not the seizures) is inherited as an autosomal dominant trait with an age-dependent penetrance.

Absence seizures are uncommon, even among children with epilepsy. According to Livingston et al. (1965), only 2.3% of 15 102 patients with seizures seen in a pediatric department had "true" petit mal seizures. In 1983, Sherwin estimated that absence seizures account for 5%–10% of all seizures in childhood.

The classification system proposed by Gastaut (1970) divides absence seizures into simple and complex. Complex absence seizures are subdivided into those with (a) mild clonic components, (b) an increase in postural tone, (c) a diminution or abolition of postural tone, (d) automatisms, (e) autonomic phenomena, and (f) mixed types.

In 1975, Penry et al. studied absence seizures in 48 patients whose ages ranged from 4 to 24 years. All patients had simultaneous video and electroencephalographic recordings; a total of 374 seizures were recorded. The authors observed the different types of absence seizure discussed below.

1. *Simple absences* are characterized by a sudden arrest of volitional movement. For instance, there is speech or gait interruption. If the onset occurs during hyperventilation, the patient stops hyperventilating. The eyes are fixed and "vacant," the eyelids are slightly droopy, and there may be slight eye sursumvergence, although the eyes usually remain in primary position. The patient does not answer questions but may respond with a grunt. The seizure ends abruptly, and the patient will then carry on his previous activities as if nothing had happened; and he is unaware of having had an attack. The patient may realize that the conversation was temporarily interrupted. Hyperventilation may resume after a few seconds, apparently the time needed for the patient to respond after regaining consciousness.

2. *Absences with mild clonic components* are also of abrupt onset. During the seizure, there are clonic movements of the eyelids or rhythmic blinking of the eyes. Sometimes the corners of the mouth, the fingers, arms, and shoulders also twitch rhythmically. These movements may be so subtle as to be unnoticed by some observers, although they may be severe enough for the patient to lose the grip of an object or spill the contents of a cup. Myoclonic contractions may affect the neck muscles, and, if standing, the patient may jerk the head forward and fall.

3. *Absences with increase in postural tone* are characterized by a sudden increased tone of extensor or flexor muscles, either symmetrically or asymmetrically. If the patient is standing, the head and trunk may extend in retropulsion ("retropulsive petit mal" of the German literature). If the postural tone change is asymmetrical, the patient's head or trunk may be drawn to one side. The normal erect posture is regained suddenly at the end of the seizure in a voluntary action or before the seizure ends in a less abrupt manner.

4. *Absences with diminished postural tone* may involve the trunk or the trunk and

extremities. The patient's head droops, the trunk slumps, the arms drop, and the grip relaxes. Here also, if the postural tone change is asymmetrical, the patient's head or trunk goes to one side. If the patient is standing, the knees may buckle, but the spell rarely lasts long enough or the loss of tone is rarely pronounced enough to cause a fall.

5. *Absences with automatisms* are characterized by purposeless movements having the appearance of a voluntary act, such as licking the lips, swallowing, or fumbling with clothes or other objects that the patient may be holding before the spell occurs. For instance, if the patient had been asked to pass an object from one hand to the other repeatedly and the seizure supervenes, the object may be held in one hand and moved without changing it to the other hand. Some complex automatisms resemble voluntary acts, such as walking aimlessly, humming, drinking from a cup placed in the hand, or chewing gum placed in the mouth.

6. *Absences with autonomic phenomena* consist of loss of consciousness associated with pallor of the face, mydriasis, piloerection, flushing, tachycardia, salivation, and rarely, emptying of the bladder.

7. *Mixed absences* are those consisting of a combination of the features of two or more complex absence seizures, as described above.

Of the patients studied by Penry et al. (1975), 71% showed some type of clonic component during at least one attack but only 3% showed increased postural tone. Decreased postural tone occurred in 46% of the patients during at least one attack. More significantly, automatisms occurred in 88% of the patients and the six patients who did not exhibit automatisms had only a single seizure recorded on videotape. Twenty-three percent of the patients had automatisms with every seizure, and only the two patients who had many seizures had no automatisms. Simple absences occurred at least once in 40% of the patients. When all seizures were counted, only 9.4% were simple absences, 50% were absences with one single component (myoclonic, increased or decreased postural tone, or automatism), and 40% were absences with multiple components. More than half of the seizures were induced by hyperventilation, more than one-fourth occurred spontaneously, and more than one-fifth were induced by photic stimulation. Most of the seizures lasted 10 s or less, and rarely did they last for more than 45 s.

Associated Symptoms

The absence seizure may be the only clinical manifestation; however, 40%–50% of patients with absence seizures also have tonic–clonic seizures (Gibberd 1966; Lugaresi et al. 1973).

Absence status is a prolonged state of abnormal behavior that may last several minutes, hours, or an entire day without the usual staring, jerking, and blinking phenomena of the typical absence seizure. The patient appears confused, inattentive, and disoriented and moves in a passive or robot-like fashion. The EEG helps to differentiate absence status from other causes of semistupor or psychosis.

Dementia, in association with absence seizures, has been observed more often in patients with onset of absence status between the 2nd and the 7th year of life than in those who at that age did not have absence status (Doose and Völzke 1979).

Differential Diagnosis

Absence seizures often need to be differentiated from partial complex seizures. Other seizure types that may be mistaken for absence seizures are atypical absence, atonic, akinetic, and myoclonic seizures. Daydreaming episodes of normal children may be mistaken for absence seizures, and conversely, absence seizures may be mistaken for daydreaming episodes. Fatigability, excessive somnolence from insufficient sleep or from illness, toxic states, metabolic disorders, and even the brief periodic lapses seen in patients with subacute sclerosing panencephalitis have been mistaken for absence seizures, though such errors are less likely.

Complex partial seizures are less common in children than in adults and are recognized infrequently before sexual maturity. The seizures may originate from the temporal lobe or other regions of the brain. It is important to distinguish them from absence seizures because of the different approach to diagnosis and treatment. Complex partial seizures last longer, often more than 1 min. They may be preceded by an aura and be associated with automatisms. If the patient is not totally unresponsive, he may be able to recall the events that occurred during the attack. Ictally or postictally, there may be speech arrest or the patient may be able to utter only a few incoherent words or just vocalizations. There may be postictal confusion. None of these features are part of absence seizures. The attacks are rarely induced by hyperventilation or by stimulation. Occasionally, the characteristic clinical features are not sufficient to differentiate absence seizures from complex partial seizures, and an interictal or ictal EEG can help distinguish the two types of seizure.

Atypical absence seizures also occur in young persons, usually in those with a long history of generalized seizures of various types (including tonic–clonic, myoclonic, atonic, and tonic), which often are part of the Lennox-Gastaut syndrome. Atypical absence seizures do not have an abrupt beginning and end as absence seizures do; the patient may change his behavior to being less active and less responsive for several seconds without an arrest of movement, staring, myoclonus, automatisms, or muscle tone change. At times, it may be difficult to recognize an atypical absence seizure from the interictal behavior of a child with mental subnormality.

Electroencephalographic Findings

The EEG is the most sensitive test in the diagnosis and confirmation of absence seizures. Gibbs et al. (1935) gave the first description of the electroencephalographic pattern in 1935, when they presented a series of 12 patients with petit mal seizures. In that series, the EEGs showed "... an outburst of waves of great amplitude, amounting to from 100 to 300 microvolts at a frequency of 3 per second. They ... usually include a sharp negative spike near the positive crest so that the record at times forms a perfect "egg and dart" design."

Because of its association with petit mal seizures, the electroencephalographic pattern has been referred to as the "petit mal pattern"; however, the use of a clinical term to describe an electroencephalographic pattern is discouraged (Cha-

trian et al. 1974; Gloor 1976). Other terms that have been used for the 3-Hz spike and wave pattern include "wave and spike complexes," "spike and dome," and "dart and dome complexes"; however, the use of these terms is also discouraged. The preferred terminology is either "3-Hz spike and slow wave" or "3-Hz spike and wave" (Chatrian et al. 1974; Niedermeyer and Lopes da Silva 1982).

Ictal Pattern

The classic electroencephalographic pattern associated with absence seizures consists of generalized, bilaterally synchronous, regular, stereotyped and symmetrical 3-Hz spike and wave complexes that have an abrupt onset and end (Fig. 6.1).

The voltage of the spike and wave complexes ranges from 100 to 1200 μV (Gibbs et al. 1935; Weir 1965; Kiloh et al. 1981). Although the spike and wave discharges are generalized, they often have a maximal amplitude over the superior frontal or midline frontal regions (Gibbs et al. 1935; Gibbs and Gibbs 1952; Gastaut and Broughton 1972). Infrequently, the discharges may be maximal over the posterior head regions (Gastaut et al. 1974; Sato 1983).

Additional studies have shown that the spike and wave discharge is not a simple spike and wave but, instead, consists of four components (Weir 1965). The first is a surface-positive deflection lasting 100–150 ms, which is believed to represent a summation of excitatory postsynaptic potentials (EPSPs) in the depth (Weir 1965).

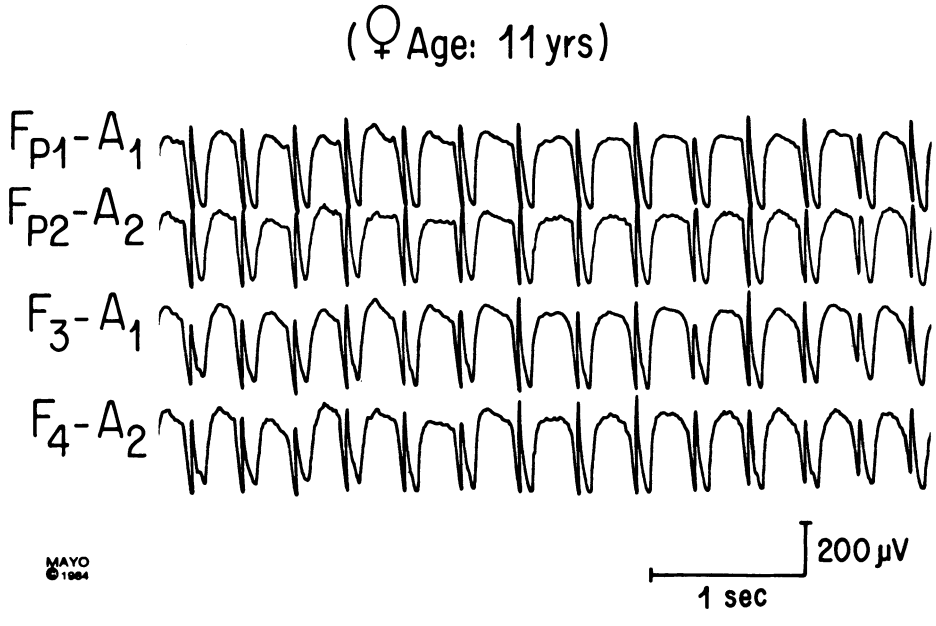

Fig. 6.1. Typical 3-Hz spike and wave pattern.

The second is a low-voltage (25–50 μV) surface-negative spike of short duration (10 ms), which appears 5–10 ms after the beginning of the surface-positive transient and is usually maximal over the centrotemporal region. This is followed by a third component, a second surface-negative spike, which represents the "classic" spike of the spike and wave complex (Weir 1965). This second spike appears approximately 50–60 ms after the first spike, having an amplitude several times that of the first spike and a duration of 30–90 ms, usually with maximal expression over the frontal regions. The spike discharges occur during the trough of the surface-positive transient, which may last 100–150 ms and which then blends into the fourth component, a prominent surface-negative slow wave lasting 150–200 ms (Weir 1965; Gastaut et al. 1974; Daly 1979).

The repetition rate of the complexes is usually 3 Hz; however, at the start of the burst the frequency is faster, about 4 Hz, while at the end of the burst the frequency may slow down to 2 Hz (Gibbs and Gibbs 1952; Gastaut et al. 1974). In adults, the spike and wave bursts may have a faster frequency of 3.5–4 Hz (Kooi et al. 1978).

Single sporadic spikes or spike and wave complexes or brief bursts lasting less than 2 s can occur without an apparent clinical accompaniment (Gibbs and Gibbs 1952; Gastaut and Broughton 1972; Gastaut et al. 1974). Sometimes, more focal or fragmentary spikes can be seen, representing a "forme fruste" of the generalized discharges; these spikes are most likely to occur over the frontal regions, but sometimes they can be seen in other locations (Gastaut and Broughton 1972; Gloor 1976).

At times, preparoxysmal discharges consisting of single or multiple generalized spikes, irregular spike and wave, or focal spikes may occur before the onset of the regular 3-Hz spike and wave complexes (Dalby 1969) (Fig. 6.2). Postparoxysmal

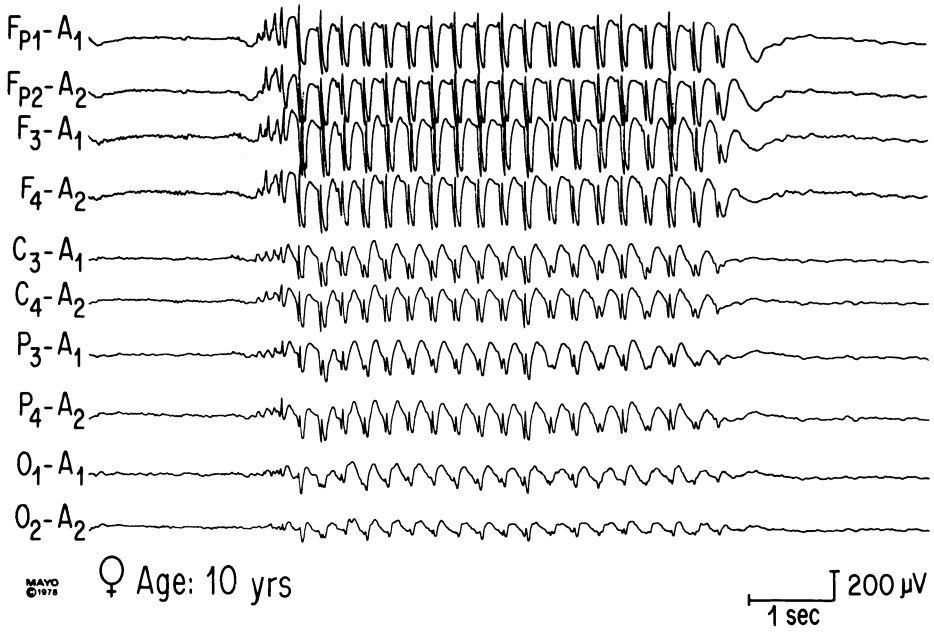

Fig. 6.2. Example of multiple spikes occurring at the onset of a 3-Hz spike and wave burst.

activity, consisting of a brief train of rhythmic or irregular slow wave activity, also can be seen at the end of a spike and wave burst (Dalby 1969).

Occasionally, absence seizures, particularly those that are atypical, may be associated with generalized atypical spike and wave bursts, a slow spike and wave pattern, or paroxysmal rhythmic fast activity (Lee 1983).

The spike and wave discharges are usually symmetrical, but some asymmetry may occur over homologous regions. Dalby found asymmetries in 39% of his patients, in which there was a shift in the maximal amplitude of the bursts from side to side, particularly at the onset of the burst, but without a consistent lateralization (Dalby 1969; Daube and Westmoreland 1975; Kooi et al. 1978).

Although the spike and wave discharges appear to be bilaterally synchronous, there is an interhemispheric latency difference, with one side leading the other by 5–20 ms. This latency difference can shift from one side to the other without a consistent lateralization (Cohn 1954; Ogden et al. 1956; Lueders et al. 1980; Blume 1982).

Petsche and Rappelsberger (1973), using toposcopic displays, showed that the spike and slow waves are traveling waves that spread at different speeds over the cortex. The spike travels at 4–15 m/s and the slow wave at 2–7 m/s. In 1975, Daube and Westmoreland, using spatial display techniques, confirmed that the spike and slow waves are "two spatially distinct activities." The slow waves consist of a regular, symmetrical, bisynchronous, initially surface-positive fluctuation of voltage that occurs over the posterior frontal regions and shifts anteriorly in a symmetrical fashion. The spikes arise in a more focal fashion, either over the midline or over one hemisphere, as brief localized reductions in positivity with a more variable pattern of development, shifting to either hemisphere or anteriorly. These studies indicate that the spike and slow wave are different events and that the slow wave is the more stable component while the spikes represent a more variable pattern of rapid fluctuations of voltage (Petsche and Rappelsberger 1973; Daube and Westmoreland 1975). Direct-current studies also confirm that the slow wave is the more stable component, in which the 3-Hz spike and wave discharges are accompanied by a paroxysmal, negative direct-current shift that parallels the shift of the slow-wave component (Cohn 1964; Chatrian et al. 1968). The shift begins with the onset of the burst and reaches a maximal voltage (up to 600 μV) 1–5 s later over the frontal and anterior midline regions.

Activation

Hyperventilation is the most potent activator of the 3-Hz spike and wave pattern (Gastaut 1968; Sato 1983) (Fig. 6.3). The spike and wave bursts are particularly susceptible to the effects of altered O_2/CO_2 tension levels produced by hyperventilation (Kiloh et al. 1981). The electroencephalographic pattern is also influenced by the acid-base state, with alkalosis tending to facilitate the spike and wave bursts and acidosis inhibiting the discharges (Kiloh et al. 1981).

Photic stimulation can precipitate spike and wave bursts in some patients with absence seizures. Approximately 13% of Dalby's (1969) patients showed some light sensitivity. Usually, the photic-induced bursts occur at flash frequencies of 10–18 Hz (Lugaresi and Pazzaglia 1975; Gloor 1976; Niedermeyer and Lopes da

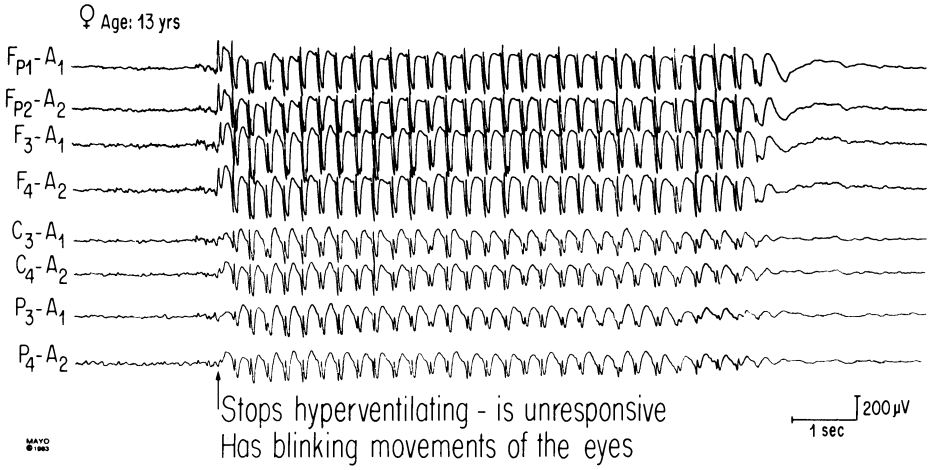

Fig. 6.3. Absence seizure with 3-Hz spike and wave burst induced by hyperventilation.

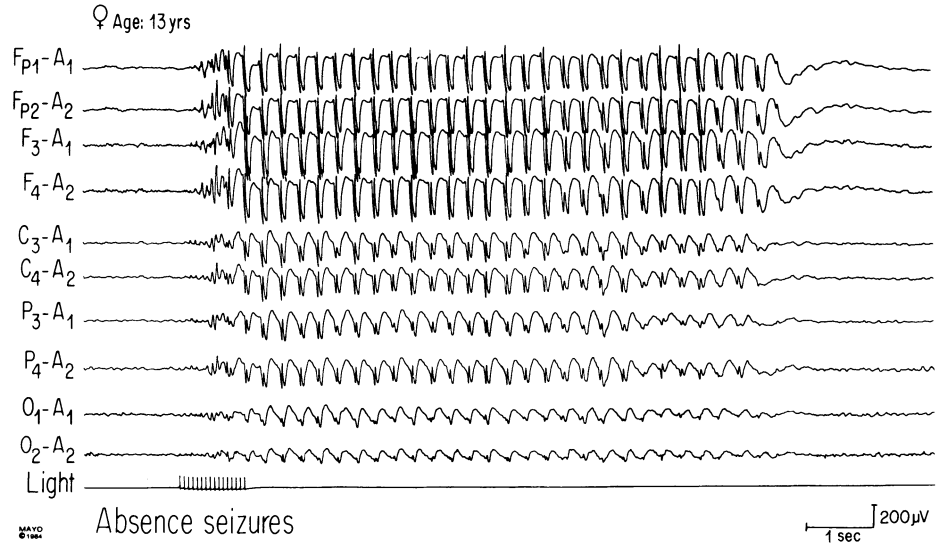

Fig. 6.4. Photic-induced 3-Hz spike and wave burst.

Silva 1982). Although the typical 3-Hz spike and wave pattern can be triggered by photic stimulation, the more common response consists of irregular or atypical spike and wave or multiple spikes and wave bursts (Gibbs and Gibbs 1952; Lugaresi and Pazzaglia 1975). Sometimes the bursts begin with an irregular repetition rate and then evolve into the regular 3-Hz spike and wave pattern (Fig. 6.4). The photic-induced spike and wave bursts are more likely to be seen in patients who also have myoclonic and generalized tonic–clonic seizures (Niedermeyer and Lopes da Silva 1982).

Hypoglycemia can potentiate 3-Hz spike and wave bursts, and sometimes relative hypoglycemia (such as that produced by tolbutamide) can precipitate the 3-Hz spike and wave pattern and absence seizures (Gibbs et al. 1939; Green 1963). Other drugs that have been used to activate, induce, or potentiate the 3-Hz spike and wave pattern include methohexital, an ultra-short-acting barbiturate, and pentylenetetrazol (Wilder et al. 1971; Gloor 1979).

Spike and wave bursts are also influenced by the degree of vigilance of the patient, being enhanced when the patient is in a less alert state and attenuated with eye opening (alerting the patient) or when the patient focuses his attention on a subject or a particular task (Guey et al. 1969; Gastaut et al. 1974; Daly 1979).

Effect of Sleep

Drowsiness and non-REM sleep facilitate epileptiform activity (Pompeiano 1969). In 1952, Gibbs and Gibbs reported that, in their series of patients, the 3-Hz spike and wave pattern was present in 84% of the wake tracings and that this increased to 89% during non-REM sleep. Some observers have noted a greater activation during stages 1 and 2 of non-REM sleep, while others have observed that the greatest number of discharges occurs during stages 3 and 4 (Ross et al. 1966; Daly 1973; Sato et al. 1973). Conversely, there is a marked attenuation of the spike and wave bursts during REM sleep (Ross et al. 1966; Sato et al. 1973). The discharge rate tends to be highest in the early night portion of sleep, particularly during the first sleep cycle, and lowest in the early morning hours (Ross et al. 1966; Sato et al. 1973). This in part may reflect the greater amount of non-REM sleep that occurs during the early night sleep, while more REM sleep is present during the early morning hours.

There is a change in the shape, frequency, amplitude, and pattern of the spike and wave discharges as the patient goes from one stage of sleep to another (Sato et al. 1973; Gastaut and Tassinari 1975). During drowsiness (stage 1), the bursts become shorter but retain a configuration similar to that of the wake tracing. During stage 2, the spike and wave bursts become briefer and assume a more irregular and less well-organized appearance, with some admixed multiple spikes (Fig. 6.5). More fragmented or focal spikes can be seen over the frontal regions (Gibbs and Gibbs 1952). The discharges also may occur in a quasiperiodic fashion. In stage 3, the rhythmicity and regularity decrease further, with a tendency toward single spikes or multiple spikes. During stage 4, the spike and wave bursts consist of less well-organized, irregular, and somewhat distorted slow-wave complexes with single or multiple spikes. The repetition rate of the spike and wave complexes slows to 0.5–2 per second, and the bursts may occur periodically every 2 or 3 s (Sato et al. 1973). Thus, as the depth of sleep increases, the spike and wave discharges become more irregular and assume more of an atypical spike and wave appearance: multiple spikes replace single spikes, the repetition rate slows, the duration of the bursts becomes shorter, and the bursts tend to occur periodically (Daly 1973).

The configuration of the spike and wave discharges during REM sleep is similar to the typical 3-Hz spike and wave pattern of the wake tracing; however, the frequency and duration of the bursts decrease (Ross et al. 1966; Sato et al. 1973).

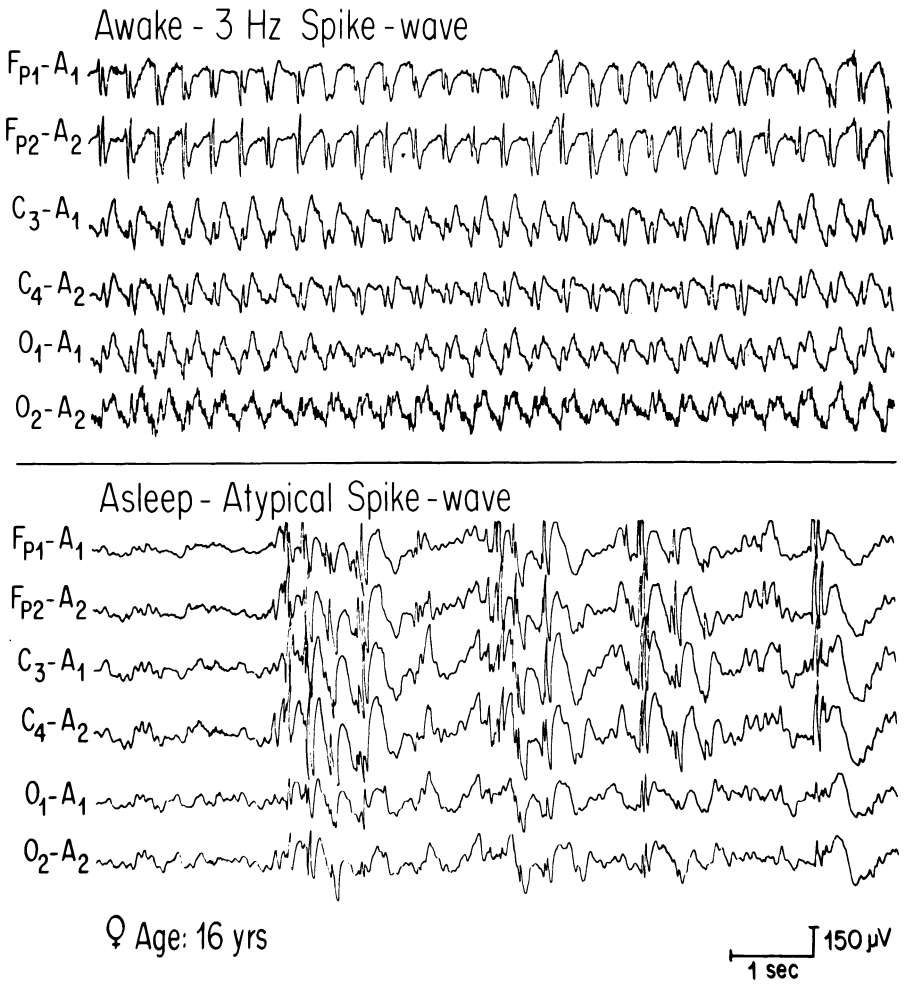

Fig. 6.5. Change in shape of spike and wave bursts during sleep to atypical spike and wave and multiple spike bursts.

Usually, little or no clinical or motor accompaniment is seen with the spike and wave bursts during sleep (Niedermeyer 1965; Ross et al. 1966; Sato et al. 1973), although there may be a slight arousal associated with a burst.

Other Features of the EEG

Between 55% and 75% of patients with absence seizures have normal interictal background activity (Gibbs and Gibbs 1952; O'Brien et al. 1959; Dalby 1969). An abnormal background is more likely to be seen in the EEGs of patients who have other types of seizures or signs of brain damage (Gibbs and Gibbs 1952; O'Brien et al. 1959; Dalby 1969).

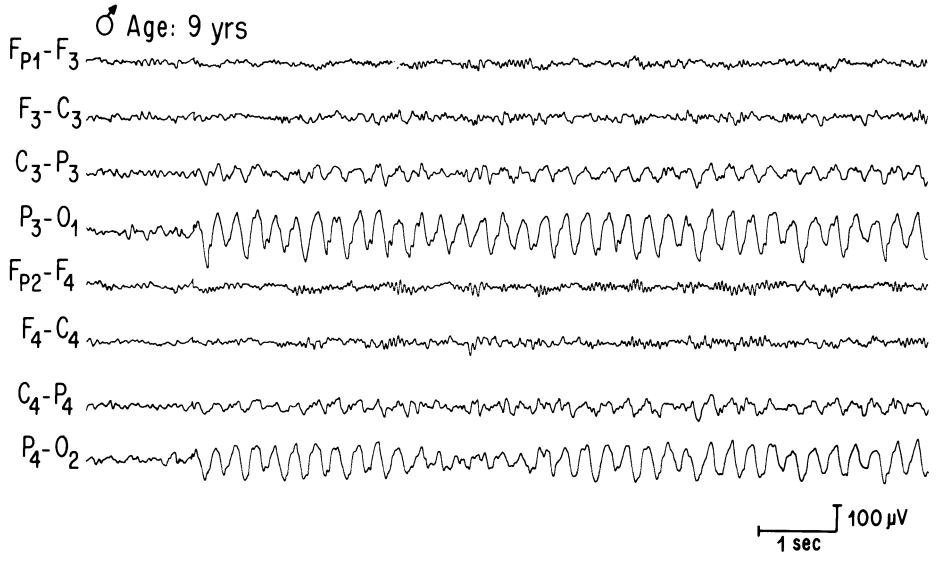

Fig. 6.6. Rhythmic slow-wave activity over the occipital head regions in a patient with absence seizures.

The main interictal findings in patients with absence seizures are prolonged trains of rhythmic fusiform 3-Hz slow waves over the posterior head regions (Fig. 6.6). Usually, this rhythm occurs in a bilaterally synchronous and symmetrical manner but occasionally it can be lateralized to one hemisphere. This rhythm was seen in 11%–60% of the various patient groups studied, with a peak occurrence in the 6- to 10-year age group (Dalby 1969; Niedermeyer 1972; Niedermeyer and Lopes da Silva 1982). Hyperventilation tends to induce or enhance this rhythm (Niedermeyer and Lopes da Silva 1982). In 1956, Elston et al. stated that patients with the occipital delta rhythm tended to have an earlier onset of absence seizures, fewer generalized tonic–clonic seizures, and more affected relatives than did those without this phenomenon. In 1969, Dalby stated that the occipital rhythm correlated with a longer duration and a greater frequency of spike and wave bursts and an otherwise normal interictal background. Several authors believed that the presence of the rhythm indicated a better prognosis with regard to therapy or less of a tendency to develop generalized tonic–clonic seizures, or both (Blume 1982; Niedermeyer and Lopes da Silva 1982; Loiseau et al. 1983).

Electroencephalographic changes that have been noted in cases of absence seizures in which generalized tonic–clonic (grand mal) seizures subsequently develop are (a) the appearance of more variable frequencies with slower (2.5 Hz) or faster (4 Hz) repetition rates of the spike and wave bursts, (b) the appearance of multiple spike (polyspike) discharges, (c) the occurrence of spike and wave status, (d) a decreased incidence of occipital delta slowing, and (e) photosensitivity (Dalby 1969; Gastaut and Tassinari 1975; Loiseau et al. 1983).

Clinical Correlates

The 3-Hz spike and wave pattern has one of the highest correlations of an electroencephalographic pattern occurring in association with a seizure disorder, with as many as 98% of patients with this pattern having absence seizures (Dalby 1969; Blume 1982). The electroencephalographic pattern is primarily seen in children who are between 3 and 15 years of age. It is rare in children who are 2 or 3 years of age and becomes less common in persons 20 years old or older, although it may persist through adulthood (Gibbs and Gibbs 1952; Gomez and Klass 1983). The expression and occurrence of the 3-Hz spike and wave pattern vary at different patient ages (Gastaut and Tassinari 1975). In childhood and early adolescence, the discharges occur spontaneously in the resting record, as well as being easily induced by hyperventilation. Also at this age, a significant number of patients activate spike and wave discharges during sleep recordings. In late adolescence and early adulthood, spontaneous discharges occur less frequently, and spike and wave bursts are less easily induced by hyperventilation. In later adulthood, the discharges become infrequent and are more difficult to induce by hyperventilation and other activating procedures. Thus, an age-dependent expression for the electroencephalographic abnormalities parallels that of the clinical seizures.

The spike and wave bursts usually last from 1 to 20 s but may persist for as long as a minute. Spike and wave bursts of less than 2 s can be associated with altered responsiveness and cognition; however, the patient is usually unaware of this if the burst is less than 1.5 s (Porter et al. 1973; Gastaut et al. 1974; Delgado-Escueta 1979). If the burst lasts longer than 3 s, then an arrest of movement or some type of motor accompaniment is usually apparent (Gastaut and Tassinari 1975; Kooi et al. 1978). Simple absence seizures are usually seen with bursts lasting 4–8 s, while spike and wave episodes of longer duration are often associated with automatisms (Dalby 1969; Gastaut and Tassinari 1975; Daly 1979).

Various studies have evaluated the patient's responsiveness during spike and wave bursts. In 1971, Selldén noted a delay in reaction times if the discharge lasted longer than 2.5 s. In 1970, Goode et al., using pursuit motor performance tasks, demonstrated a strong correlation between the duration of the spike and wave activity and the incidence in errors, with a greater number of errors being made during the longer bursts. Three seconds appeared to be the critical time, with a disruption of performance and complex behavior being seen if the burst lasted longer than this (Goode et al. 1970; Daly 1979; Sato 1983).

In 1947, Schwab showed that the reaction time to visual stimuli was increased during the spike and wave bursts and that there was some impairment of the responses with bursts of 3–6 s and a failure to respond if the burst lasted 8–20 s. In 1974, Browne et al. studied auditory reaction times and showed that the maximal disturbance of responses occurred within the first second of the spike and wave burst and that the response times decreased toward the end of the burst. In 1953, Shimazono et al., using verbal stimuli and observing verbal responses or the performance of simple motor tasks, showed that the degrees of altered consciousness varied during the bursts and that, during a given burst, the degree of the disturbance in consciousness is not constant but is altered in various ways, depending on the stimulus.

In 1965, Mirsky and Van Buren showed that errors in responses occurred during the spike and wave paroxysms but that the more correct responses tended to occur

during the latter part of the spike and wave burst. Using continuous performance tests, they also showed that a behavioral alteration and a disturbance of consciousness occurred *before* the burst was seen on the EEG. The percentage of correct responses decreased in the few seconds before the burst, the performance decreased with the onset of the spike and wave burst, and then there was a progressive improvement during the last 5 s of the burst. They observed that the gradual improvement in the performance was paralleled by a decline in the voltage of the discharges during the latter part of the burst and that the degree of alteration in responses was related to length of the burst and the frequency and type of discharge.

Others also have shown that the reaction time to stimuli is increased before the onset of the paroxysmal burst (Dalby 1969). In 1962, Jung noted a blocking effect on sensory arousal just before the spike and wave burst. In 1978, Orren showed that the visual evoked potential is altered in the 0.5 s before the onset of the spike and wave discharge, confirming that a behavioural alteration occurs before the discharge.

These studies indicate that the time courses for the motor and the sensory impairment are different, that the effects on sensory reception are apparent before the spike and wave bursts, and that the motor arrest follows the onset of the discharge (Mirsky and Van Buren 1965). These findings suggest that the seizure discharge may first involve the sensory structures and then spread to the motor pathways (Mirsky and Van Buren 1965). The recall of stimuli presented during a spike and wave burst was also significantly impaired, indicating an interference with the reception of stimuli and with the memory or consolidating process during the burst. Tasks requiring complete attention were impaired more than those of an automatic nature (Mirsky and Van Buren 1965). The behavioral alterations during spike and wave bursts thus represent a range of alterations that involve the sensory and motor structures, the central integrative mechanisms, memory, and the consciousness system and that depend, in part, on the duration, frequency, voltage, and type of discharge present (Mirsky and Van Buren 1965; Penry 1973).

Absence Status

Absence status, also referred to as petit mal status, nonconvulsive status, and spike–wave stupor (Niedermeyer and Khalifeh 1965), consists of prolonged episodes during which time there is a disturbance of mental function in association with a continuous repetitive or an intermittent spike and wave pattern on the EEG. Although the typical 3-Hz spike and wave pattern may be present (Fig. 6.7), generally the electrographic pattern consists of more irregular spike or multiple spike and slow wave complexes occurring at a rate slower than 3 Hz (Kooi et al. 1978; Sato 1983). In 1975, Gastaut and Tassinari described four main variations of status patterns:

1. Continuous 3-Hz spike and wave or polyspike and wave discharges.
2. Intermittent bursts of 3-Hz spike and wave or polyspike and wave discharges superimposed upon a slow background.

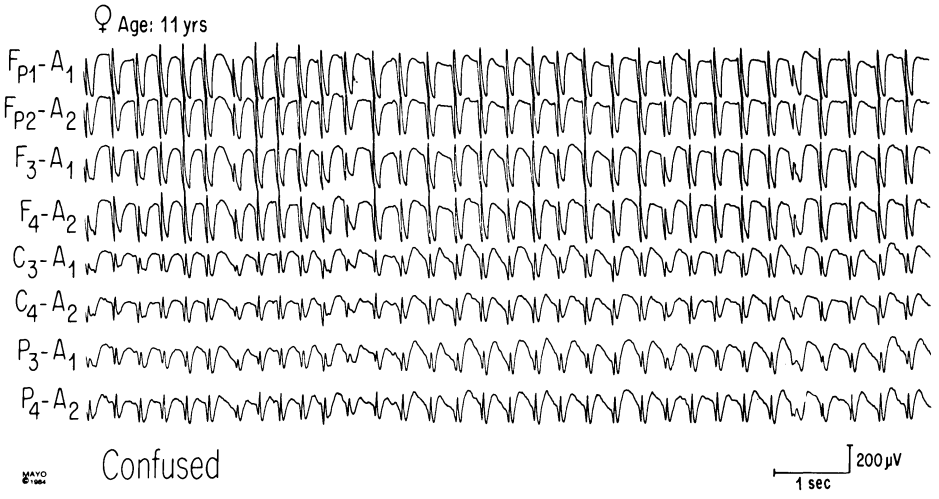

Fig. 6.7. Absence status with EEG showing continuous generalized 3-Hz spike and wave complexes.

3. Arrhythmic trains of spike and wave or polyspike and wave discharges.
4. A diffusely slow theta or delta frequency background with superimposed bursts of fast activity at 10–20 Hz and occasional bursts of spike and wave or polyspike and wave discharges.

One type of pattern can evolve into the other, and there is not a close correlation between the type of electroencephalographic pattern and the clinical presentation (Gastaut and Tassinari 1975). The trains of spike and wave may be interrupted by occasional brief periods of attenuation lasting 1 or 2 s (Kellaway and Chao 1955). A strong or repeated stimulus may result in a transient normalization of the record, whereas a weak stimulus will have little or no effect (Penry 1973; Gastaut and Tassinari 1975; Sato 1983).

During non-REM sleep, the continuous spike and wave pattern may be replaced by more intermittent bursts of polyspike or spike and wave discharges (Gastaut and Tassinari 1975). Rarely, a continuous spike and wave pattern can occur during slow-wave sleep and be attenuated upon arousal from sleep (Patry et al. 1971).

Etiological Factors

In 1961, Metrakos and Metrakos studied the genetic aspects of the 3-Hz spike and wave pattern. They stated that the electroencephalographic pattern was an expression of an autosomal dominant gene that varied with age of the patients, having a low expression at a very young age, a maximal expression at 4–16 years, and a gradual decline after that. In addition to the primary generalized type of absence seizures, the 3-Hz spike and wave pattern has been seen with other lesions or conditions. In 1952, Tükel and Jasper noted generalized spike and wave

discharges on the EEGs of patients with mesial frontal lesions and introduced the term "secondary bilateral synchrony." In 1960, Ajmome Marsan and Lewis described two patients with brain tumors who had a "centrencephalic" electroencephalographic pattern. Others have also noted a 3-Hz generalized spike and wave pattern in the EEGs of patients with focal structural lesions involving the cerebral hemispheres, the third ventricle, the hypothalamus, the rostral midbrain, and the cingulate gyrus (Madsen and Bray 1966; Stewart and Dreifuss 1967; Niedermeyer and Lopes da Silva 1982). In 1967, Andermann showed that diffuse neuronal disease can produce a generalized spike and wave pattern with associated absence seizures. Metabolic encephalopathies and acute drug withdrawal also can give rise to generalized bisynchronous discharges; however, these do not usually have the regular repetition rate of the typical 3-Hz spike and wave pattern (Gloor 1969; Niedermeyer and Lopes da Silva 1982).

Pathophysiological Factors

Two main theories have been proposed to explain the origin of the generalized bilaterally synchronous spike and wave discharges seen with absence seizures.

The first theory, popularized by Penfield and Jasper in 1947, was that the centrencephalon (consisting of the upper brain stem, thalamus, and the diffuse cortical projections) was the site of origin of the bisynchronous spike and wave pattern and that the cortex served as a passive follower. This theory was based on data from experimental animal studies in which a 3-Hz spike and wave pattern could be elicited by stimulation of the intralaminar and centrum medianum region of the thalamus (Jasper and Droogleever-Fortuyn 1947; Hunter and Jasper 1949). Pollen et al. in 1963 and Weir in 1964 showed that stimulation of the midbrain of cats induced a 3-Hz spike and wave pattern that was dependent on the state of arousal. In another experiment, Guerroro-Figueroa et al. (1963) implanted aluminum in the midbrain and intralaminar nuclei of the thalamus and evoked a generalized spike and wave pattern in kittens but not in cats.

The second theory proposes that cortical mechanisms play the major role in the genesis of the spike and wave pattern (Gloor 1968; Daly 1979). Various workers have shown that cortical lesions, particularly in the anterior parasagittal region and the mesial region of the cerebral hemispheres, could give rise to secondary generalized spike and wave discharges (Tükel and Jasper 1952). Bancaud in 1972 and Bancaud et al. in 1974 showed that electrical stimulation of the frontal cortex and, in particular, the mesial cortical region could produce generalized spike and wave bursts with clinical absence seizures. Depth studies by Niedermeyer et al. in 1969 also showed that frontal lesions could give rise to a generalized spike and wave pattern.

Based on their observations, Gibbs and Gibbs in 1952 stated that the bilateral spike and wave discharge was primarily a cortical phenomenon, both in its origin and propagation, and that the thalamus was not necessary for its production. In studies in which simultaneous recordings were performed from the thalamus and cortex, Hayne et al. in 1949 found that the spike and wave pattern appeared independently in the cortex, without a corresponding discharge in the thalamus. Depth studies by Niedermeyer et al. in 1969 also failed to yield evidence for a

primary focus in the thalamus. The point was also made that the 3-Hz spike and wave pattern was not seen in the EEGs of patients with lesions involving the thalamus (Gibbs and Gibbs 1952).

Other studies by Marcus and Watson in 1966 and Marcus et al. in 1968 showed that generalized spike and wave discharges could be produced in experimental animals with bilateral cortical lesions in the absence of a lesion in the brain stem or thalamus and that the capacity for generating generalized, bilaterally synchronous discharges was retained after ablation of the diencephalon and mesencephalon. These authors emphasized that the essential prerequisites for production of this spike and wave pattern were the presence and interaction of bilateral cortical lesions and that the diencephalon and brain stem were not needed for the production of the spike and wave pattern. They also showed that the corpus callosum was necessary for the synchronization of the discharges, because bilateral synchrony was lost after sectioning of the corpus callosum. In 1980, Musgrave and Gloor, in experiments using cats, also showed that the corpus callosum was the main, if not the only, pathway ensuring bilateral synchrony of the discharges.

In other electrophysiological studies, Pollen in 1964 and Pollen et al. in 1964 recorded cortical unit activity during the surface spike and wave burst induced by stimulation of intralaminar nuclei and showed that the spike discharge was generated by excitatory postsynaptic potentials in the apical dendrites in the superficial cortical region and that the surface-negative slow wave was generated by inhibitory postsynaptic potentials near the soma of neurons in deeper cortical layers. These authors concluded that the findings indicate that the cortex is the neuronal substrate for the generalized spike and wave pattern.

Gloor also believed that the primary physiological generators of the spike and wave pattern were cortical neurons (Gloor 1969; Gloor 1979). He showed that low-frequency stimulation of the midline regions of the thalamus could induce spike and wave discharges in cats given pencillin intramuscularly, whereas in control cats the same type of stimulus induced only spindles or a recruiting response (Gloor 1979). The question as to whether this represented an abnormal response of the cortex or an abnormal volley from the thalamus was answered by the experiment in which the diffuse cortical application of penicillin produced the spike and wave pattern but an injection of penicillin into the thalamus did not. Gloor believed that the crucial factor responsible for the spike and wave pattern was a diffuse increase in the excitability of the cortex and that, in this hyperexcitable state, the cortical neurons responded to the afferent thalamocortical volleys by producing a spike and wave burst which, in normal animals, resulted in spindles or a recruiting response. Gloor also showed that a depression of the desynchronizing drive of the reticular formation greatly facilitated the elaboration of the spike and wave discharges (Gloor and Testa 1974). Based on his studies, Gloor (1979) proposed the corticoreticular theory, in which three levels of the central nervous system interact to generate the generalized spike and wave pattern: (a) the *cortex*, in which the critical factor is an increased level of excitation or diffuse hyperexcitability and where spike and wave bursts can occur spontaneously or in response to triggering stimuli; (b) the *thalamus* and *midbrain*, which provide the trigger for eliciting the spike and wave bursts via thalamocortical volleys that activate the cortical neurons and which in turn produce the spike and wave bursts; and (c) the *reticular formation*, which modulates the excitability of the cortex and which can facilitate or depress spike and wave bursts (inhibition of the reticular formation facilitates the bursts, whereas activation of the reticular formation suppresses them).

Other Laboratory Studies

Results of laboratory tests in patients with absence seizures are either normal or irrelevant. Reports have noted increased amino acid excretion in the urine; however, this finding has not been confirmed. Computed tomography (CT) of the head usually shows no abnormality in patients with typical absence seizures and no neurological deficit or psychiatric disturbance (Moseley and Bull 1975; Gastaut and Gastaut 1976). However, in some reports it has revealed abnormalities in as many as 10% of patients with absence seizures (Browne and Mirksy 1983).

Treatment

There are two possible therapeutic approaches to absence seizures: pharmacotherapy and diet therapy. The two are not mutually exclusive.

Anticonvulsant Drugs

Of the drugs used for the treatment of absences, ethosuximide and valproate have been the most successful. Ethosuximide is considered by many to be the drug of choice because it is relatively free of undesirable side effects and serious complications, has a longer half-life than valproate, and costs less. Ethosuximide is more frequently used for the treatment of absence seizures than valproate, in part because it has been available for a longer time; and yet its mechanism of action is unknown. Among the dose-related side effects are gastrointestinal symptoms, anorexia, nausea and vomiting, dizziness, headache, drowsiness, changes in behavior, and euphoria. Non-dose-related reactions are leukopenia, skin rash, and a lupus erythematosus-like syndrome.

The dose, 20 mg/kg, should be halved and administered twice daily. One hour after a single dose, ethosuximide can be detected in plasma. Maximal plasma levels are reached 3–5 h after ingestion. A steady plasma level of ethosuximide is reached after 10–15 days of daily therapy. The volume of distribution is approximately 0.69 liter/kg in children and 0.62 liter/kg in adults (Buchanan et al. 1969). Protein binding is essentially absent. Ethosuximide equilibrates in plasma, cerebrospinal fluid, and saliva, is transferred transplacentally, and is secreted unchanged in breast milk. Ethosuximide is metabolized in the liver. Daily administration of 20 mg/kg in children will result in a mean plasma concentration of approximately 50 μg/ml. Since absence seizures often occur in children during rapid growth periods, it is important to monitor the plasma concentration once the seizures have been controlled, to try to maintain the therapeutic level necessary for the patient and to check for compliance (Sherwin et al. 1973). A concentration ranging between 40 and 100 μg/ml is considered therapeutic, but some patients require levels as high as 150 μg/ml. A commercial preparation is available in a syrupy-

flavored liquid containing 50 mg/ml and in capsules, each containing 250 mg. Ethosuximide should be given after meals in two divided doses. Because of the risk of generalized tonic–clonic seizures, a second anticonvulsant such as phenobarbital may be necessary.

Valproate is available as a sodium, calcium, or magnesium salt, and liquid valproic acid is available in a capsule. Valproate is most effective in the treatment of absence seizures but also can be used for other types of generalized seizure—hence the advantage of using it to avoid polytherapy in patients who have absence seizures and tonic–clonic seizures. In children, the recommended dose is between 30 and 60 mg/kg. Therapy should be started with only 15 mg/kg because many patients cannot tolerate the drug and may experience gastrointestinal symptoms, such as nausea and abdominal pain. Other side effects are drowsiness, tremor, ataxia, increased appetite and obesity, alopecia, transient amenorrhea, leukopenia, thrombocytopenia, transient elevation of the liver enzymes, depressed plasma fibrinogen levels, and rarely, hepatocellular necrosis (Dreifuss 1983). A few patients cannot tolerate valproate because they lack the normal enzymes for its metabolization in the liver. In some patients, valproate can cause liver damage, hyperammonemia, and a metabolic state similar to Reye's syndrome. The use of valproic acid is contraindicated in primary or secondary carnitine deficiency—that is, systemic or muscle carnitine deficiency, carnitine-palmityl-transferase deficiency, isovaleric acidemia, propionic acidemia, and methylmalonic aciduria.

Valproic acid is rapidly and nearly completely absorbed after oral ingestion. Plasma concentrations peak in $\frac{1}{2}$ to 2 h. Absorption is delayed when the drug is administered with meals, although this delay does not affect the extent of absorption. Monitoring of blood levels is recommended. The therapeutic range should be maintained between 50 and 100 μg/ml. The trough level, measured before the first morning dose, should not be less than 40 μg/ml. A plasma level of 120 or even 150 μg/ml should not be a cause for alarm, unless the patient has symptoms of overdosage, such as drowsiness. Valproic acid is approximately 90% protein bound. The control of seizures is relatively independent of the plasma concentration. Valproate is distributed mainly in extracellular space in a volume of 0.23 liter/kg (Klotz and Antonin 1977). Because valproic acid is 90% protein bound in therapeutic or toxic ranges, hemodialysis does not significantly diminish its concentration. The plasma half-life of valproate is 8–12 h, but it may be longer in patients with overdosage. Plasma concentrations fluctuate throughout the day unless administered three or four times daily. Although the elimination of valproate is chiefly through the kidneys, it is eliminated in smaller amounts in feces and expired air. Numerous drugs interact with valproate. Phenobarbital lowers the plasma concentration of valproate, whereas valproate increases the plasma level of barbiturate. Phenytoin interferes with the protein binding of valproate (and vice versa), so that one drug may cause elevation or depression of the other. Carbamazepine may lower the concentration of valproate.

When absence seizures are refractory, a combination of valproate and ethosuximide may be more effective than either drug by itself.

Clonazepam is effective in the treatment of absence seizures, but patients often develop a tolerance to the medication and recurrence of seizures after 2 or 3 months of treatment. The dose is 0.5–0.1 μg/kg. The half-life of clonazepam is between 22 and 33 h, peak levels are reached in 1–3 h, and a steady state is reached in 4–7 days. Therapeutic levels are between 10 and 50 ng/ml. Clonazepam is particularly effective in the treatment of absence seizures associated with myoclo-

nus, but because it does not prevent tonic–clonic seizures, it should be used with another anticonvulsant.

In a dose of 10 mg/kg, acetazolamide is effective in the prevention of absence seizures. Peak levels are reached in 2–3 h. Its half-life is between 48 and 96 h. Acetazolamide has few side effects, but its anticonvulsant effect in absence seizures may be only temporary. Valproate or clonazepam may be more effective in combination with ethosuximide than alone.

Methsuximide, trimethadione, and phensuximide are not as effective as the above-described anticonvulsants and have more severe toxic effects; this is particularly true for trimethadione.

Dietary Treatment

The ketogenic diet with natural foods or with artificial medium-chain triglycerides (MCT) as a fat substitute induces ketosis and may control absence seizures and other types of generalized seizure. Since the introduction of this diet in 1921, there has been much speculation as to its mechanism of action, which still remains unsolved. This diet is more effective in children than in adults because the infant brain has four times the capacity to oxidize ketones than the adult brain (Kraus et al. 1974). The effect of the ketogenic diet can be determined by measuring the amount of ketones excreted in the urine. If absence seizures continue after ketosis develops, the diet should be discontinued. When the ketogenic diet has been successful, interruption of the ketosis by the oral administration of glucose is followed by the reappearance of absence seizures.

The dangers of the ketogenic diet include hypoglycemia from ketosis (ketotic hypoglycemia), malnutrition, diarrhea and vomiting leading to dehydration and increase in the acidosis, and protein or vitamin malnutrition. The diet should be adjusted to the patient's ideal weight to provide the necessary amount of protein and calories and should be supplemented with calcium, iron, and vitamins. The need to prepare the diet carefully—weighing all food portions, avoiding indulgent and inadvertent ingestion of carbohydrates (sugar in candy and vitamin capsules, toothpaste, and syrupy medications), and observing the child carefully to prevent indulgence in extra foods not permitted in the diet—makes this treatment cumbersome and requires dedicated, understanding, and intelligent parents.

The MCT diet (Huttenlocher et al. 1971) is less cumbersome than the natural ketogenic diet and allows more carbohydrates and protein. Unfortunately, increased gastrointestinal motility, causing diarrhea and cramps, and the unpalatability of the MCT oil often result in failure to maintain the ketosis. The principles, the risks, and the need to supplement vitamins and minerals also are the same as for the ketogenic diet with natural foods.

Prognosis

The remission rate for simple absence seizures not accompanied by any other seizure types is greater than that for complex absences or absence seizures

associated with other seizure types; however, the rate of remission varies considerably in different series and still remains controversial (Rodin 1968). In a long-term follow-up study of 117 patients, 92 (78.6%) were in remission and almost all of those in remission were less than 20 years of age (Livingston et al. 1965). In another study in which patients' ages averaged 25 years at follow-up, 56% of the patients continued having seizures and 37% had acquired "grand mal" seizures, although none had seizures after the age of 18 years. The average age at onset of absence seizures in that series was 7 years, and the average age at cessation was 14 years (Currier et al. 1963). In a more recent prospective study of 48 patients, Sato et al. (1976) demonstrated that 90% of patients who did not have generalized tonic–clonic seizures, who were of average or above-average intelligence, and who had a negative family history of seizure disorders ceased having seizures. The most important factor in the prognosis of absence seizures was average or above-average intelligence. Also, when the response to drugs is good, the prognosis is better than when the response is poor (Gibberd 1966).

In 1969, Dalby found a correlation between the presence of spike and wave bursts on the EEG and the presence of clinical seizures. However, no correlation was noted between the absence of seizures and the absence of spike and wave bursts on the EEG (Dalby 1969). Some patients who have been seizure-free have a persistence of spike and wave bursts, even though they have stopped having seizures (Dalby 1969). Other electroencephalographic parameters that are of little value in predicting the cessation of seizures include frequency, duration, amplitude, type, and incidence of the spike–wave bursts; activation by hyperventilation or photic stimulation; and abnormal background activity (Dalby 1969; Loiseau et al. 1983; Sato et al. 1983).

In a longitudinal study of patients with epilepsy, Annegers et al. (1979) noted that the probability of remission (at least 5 years seizure-free) at 20 years after diagnosis was 80% for patients who had absence seizures with or without generalized tonic–clonic seizures. In another similar study, Sofijanov (1982) noted that 512 epileptic children, 4–10 years old, had a remission rate of 78% for simple absence seizures, which was better than that for "grand mal" seizures, elementary partial seizures, and complex partial seizures.

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Chapter 7

Juvenile Myoclonic Epilepsy

Dudley S. Dinner, Hans Lüders, Harold H. Morris III, and Ronald P. Lesser

Synonyms

Juvenile myoclonic epilepsy is an epileptic syndrome which has been referred to by various authors using the following terms:

Motor petit mal (Delasiauve 1854; Féré 1980)
Epileptic impulses, shocks, commotions (Herpin 1867)
Epileptic myclonias (Rabot 1899)
Intermittent sporadic myoclonus epilepsy (Lundborg 1903)
Regional twitchings (Muskens 1926)
Myoclonic epilepsy (Lennox 1945)
Benign or functional myoclonic epilepsy (Solé-Sagarra 1952)
Myoclonic petit mal (Penfield and Jasper 1954)
Impulsive petit mal (Janz and Mathes 1955)
Generalized epilepsy with intermittent or sporadic myoclonias (Lecasble 1958)
Bilateral and conscious myoclonic epilepsy (Castells and Mendilaharsu 1958)
Jerk epilepsy (Lennox 1960)

History

This syndrome of myoclonic epilepsy was first mentioned but not clearly defined by Heberden (1804), who wrote: "signa epielsiae remotoria sunt jactitatio et cetera." The first clear description was by Herpin (1867), who described myoclonic jerks ("secousses" or shocks) in a boy aged 14 years who later developed generalized tonic–clonic seizures. The description of myoclonic jerks as an aura of

a seizure or as abortive attacks (motor petit mal) was made by Delasiauve (1854), Reynolds (1861), Féré (1890), Binswanger (1899), and Gowers (1902).

In 1899 Rabot described myoclonic shocks ("secousses myocloniques") in patients who he classified as having "motor petit mal" to distinguish them from "intellectual petit mal," in which there was no myoclonic component. He indicated that his "motor petit mal" was equivalent to Herpin's description. In his paper he described how the jerks sometimes preceded the grand mal seizures by years, occurred mainly in the morning, in series, and tended to increase progressively days before the grand mal seizure.

In his description of patients with this epileptic syndrome, Lundborg (1903) referred to them as having "intermittent sporadic myoclonus epilepsy" and distinguished them from a second group with progressive familial myoclonus epilepsy, described previously by Unverricht (1891). Lennox (1945) referred to the syndrome as "myoclonic epilepsy," while Solé-Sagarra (1952) used the designation "benign myoclonic epilepsy" to distinguish it from the familial progressive myoclonus with epilepsy, which he termed the malignant form. Lecasble (1958) referred to it as "generalized epilepsy with intermittent or sporadic myoclonias," while Castells and Mendilaharsu (1958) used the term "bilateral and conscious myoclonic epilepsy." Lennox (1960), by contrast, proposed the concept of "jerk epilepsy," which coincides exactly with the "impulsive petit mal" described by Janz and Christian (1957).

Nosology

The myoclonic epilepsies consist of a heterogeneous group of epileptic syndromes within the primary generalized epilepsies. In the classification of the myoclonic epilepsies one must take into account not only the clinical manifestations but also the presence or absence of mental retardation, the age of onset, the response to therapy, and the prognosis. Table 7.1 shows a classification of the myoclonic epilepsies.

Table 7.1. Myoclonic epilepsies

A.	*Without mental retardation*
	1. Myoclonic absence
	2. Myoclonic seizures of early childhood without mental retardation
	3. Juvenile myoclonic epilepsy (myoclonic seizures of adolescence and late childhood)
B.	*With mental retardation*
	1. Infantile spasms (West's syndrome)
	2. Myoclonic astatic or atonic seizures (Lennox-Gastaut syndrome)
	3. Familial progressive myoclonic epilepsies (described by Unverricht, Lundborg, Lafora, Hartung, Hunt, and Kuf)

Juvenile myoclonic epilepsy (JME) was first differentiated as a distinct epileptic syndrome clinically and electroencephalographically by Janz and Mathes (1955) and was described in more detail in a subsequent publication (Janz and Christian 1957).

The main characteristics of the syndrome are:

1. Seizure onset in adolescence or early adulthood (in most cases just after puberty)
2. I.Q. within normal limits and no evidence of brain damage
3. Awakening myoclonic and generalized tonic–clonic seizures
4. Generalized spike and wave complexes in the EEG, typically polyspike and wave

The definition of this nosological entity is important because of the implications for prognosis. The EEG abnormality and seizure tendency persist for life, but the prognosis is very good in that patients are extremely responsive to anticonvulsants. From this point of view it can be regarded as benign, as was mentioned by Solé-Sagarra (1952) when distinguishing this syndrome from the progressive myoclonic epilepsies.

Clinical Manifestations

Myoclonic Seizures

The myoclonic seizures seen in JME are characterized by very brief bilateral muscle contractions that are usually symmetrical and synchronous. Primarily the shoulder girdles and arms are affected. The legs or head are affected only infrequently and never in isolation. Occasionally sudden flexion of the knees may occur, resulting in the patient falling, though he usually gets up again immediately. Frequently objects are thrown (Fig. 7.1). Involvement of the diaphragm and/or abdominal muscles is responsible for the production of an expiratory noise or cry. Very slight asynchrony of muscle involvement can only be detected with electromyography. Infrequently a single jerk may occur, as shown in Fig. 7.1; however, usually the jerks are repetitive and rhythmic, occurring in a sequence of two to four. They are described as being like an electric shock or lightning. The intensity is variable, ranging from just an "internal" shock not noticeable by observers to a massive contraction with major displacement and throwing of the arms, or even of the whole body. Occasionally these jerks may continue for minutes or hours, resulting in a series of myoclonic seizures or status. In this type of status there is very limited or no alteration of consciousness. Tachycardia and sweating may occur in association with myoclonic seizure status. Status may end in a generalized tonic–clonic seizure, as also may repetitive jerks (their frequency increasing and progressing into a seizure). Muskens (1926) was the first to observe that myoclonic jerks occur preferentially in the morning, after waking. Apparently the important

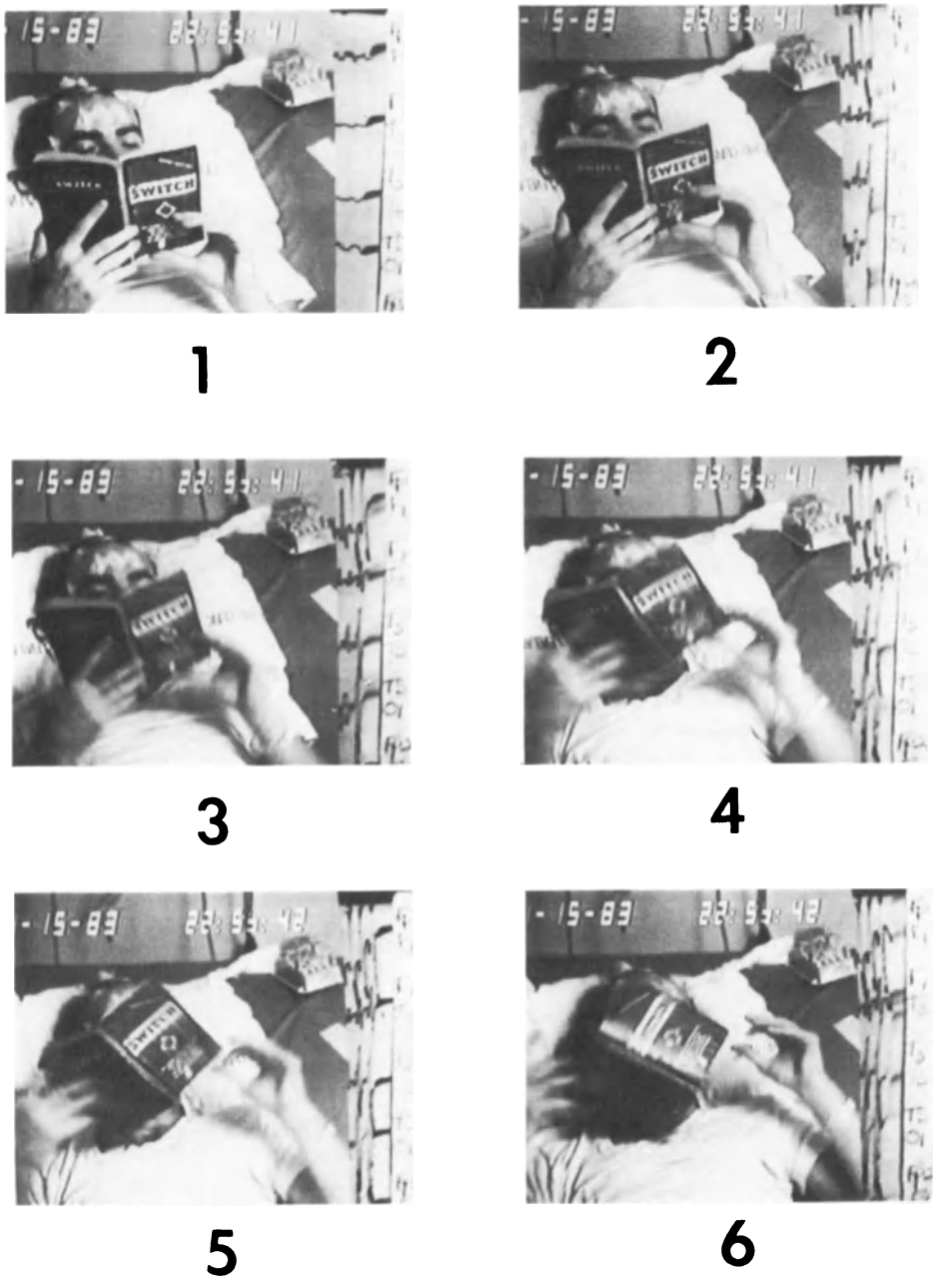

Fig. 7.1. A 23-year-old man with a 5-year history consistent with JME. The series of pictures demonstrates a myoclonic seizure. *1*, He is reading and a normal EEG pattern is recorded from the left hemisphere with bipolar montage FP1-F7, F7-T3, T3-T5, T5-O1. *2*, No clinical change; EEG shows onset of repetitive spikes which appeared in a generalized distribution. *3–8*, Sequence of the seizure, characterized by bilateral hand and then upper extremity myoclonic jerking, with the book being flung from the patient's grasp; there are associated spikes on the EEG (in a generalized distribution). *9–10*, Cessation of the seizure clinically and on EEG. *11–12*, The patient picks up his book upside down.

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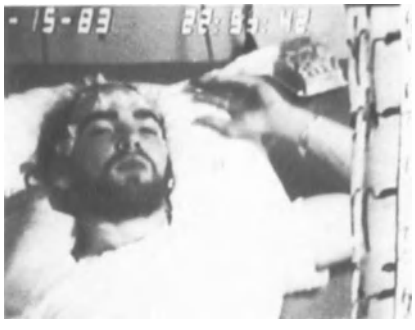

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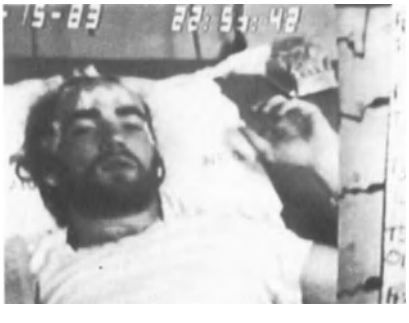

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Fig. 7.1 (*continued*)

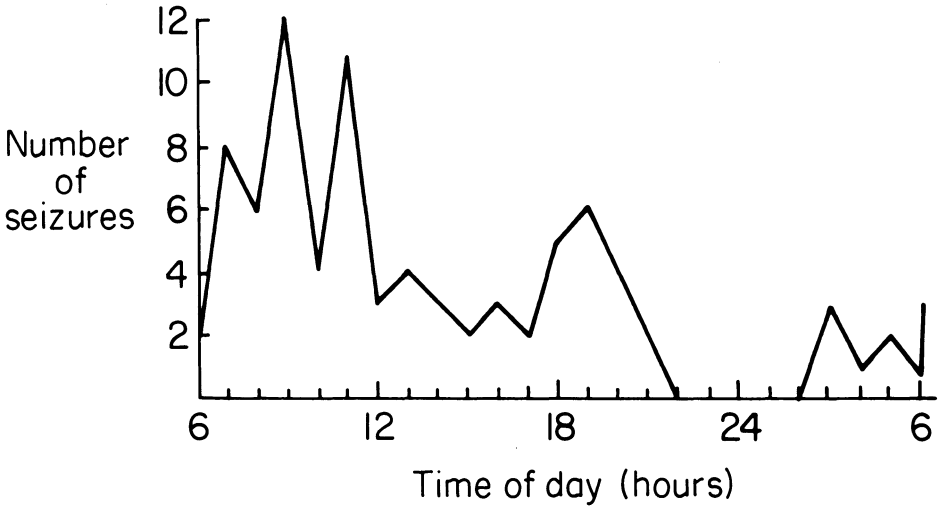

Fig. 7.2. Time of day of 73 myoclonic seizures over the course of 12 days in a man with JME (modified from Janz 1969).

factor is the state after waking rather than the time of day, as they also occur on awakening from a nap during the day (Fig. 7.2). The jerks may occur while the person is still in bed; therefore getting up is not the critical factor. The patient may be afraid to wake up, particularly suddenly. Janz and Christian (1957) reported that four of their patients experienced jerks in the evening when they were tired, and this has also been our experience. Myoclonic jerks of JME are thought not to occur during sleep. The myoclonic jerks can be provoked by sleep deprivation, alcohol intake, or emotional stress.

Alteration of Consciousness

Alteration of consciousness does not usually occur in association with the myoclonic seizures and in general there is no alteration of consciousness before the myoclonus. Delgado-Escueta and Enrile-Bacsal (1984) recorded myoclonic seizures in eight patients on closed circuit television with simultaneous EEG monitoring. Alteration of consciousness was evaluated by instructing the patients to respond to auditory stimuli, by asking them to repeat nursery rhymes or lines from a poem, by assessing responses to simple questions, or by observing for pauses while counting. Consciousness was not impaired in these patients. However, occasionally when patients fall to the floor with a sudden single massive jerk, they remain there for a few seconds, unresponsive. This may be due to a short period of loss of consciousness. The alteration of consciousness is thought to depend on the intensity of the myoclonus, not the duration. This is exactly the opposite of typical generalized absence (petit mal epilepsy), where the loss of consciousness constitutes the major manifestation of the seizure and if myoclonic jerks are present, e.g., of the shoulders, they are of minor importance.

Generalized Tonic–Clonic Seizures

Generalized tonic–clonic seizures (GTCSs) in patients with JME frequently follow a series of myoclonic jerks of increasing intensity. The tonic phase consists of a symmetrical, very intense tonic contraction of long duration and frequently opisthotonic in nature, which is associated with severe cyanosis. Tongue biting occurs frequently and foaming at the mouth is seen in 50% of patients, but sphincter incontinence is seen only infrequently. The GTCSs of JME usually occur when patients awaken, but occasionally also in the evening. In Janz's series of 251 patients (1969) (excluding 27 who had only myoclonic seizures and 2 who had < 5 GTCSs), 238 (95%) had awakening GTCSs and only 5 (2%) had sleeping GTCSs. Therefore, myoclonic seizures have a close relationship with awakening GTCSs (similar to typical and nontypical petit mal epilepsy).

Absence Seizures

Absence seizures are not infrequently associated with the myoclonic and generalized tonic–clonic seizures of JME. Simple absences were described as occurring in 15%–40% in four of the series shown in Table 7.2. The absence seizures seen in JME are usually of short duration. Sometimes the absences are only detected by clinical and EEG correlation, the patient or observer being unaware of the seizure. In Delgado-Escueta's series, five patients had absence seizures manifested by loss of consciousness recorded on simultaneous video and EEG monitoring. Two of the patients showed 3-Hz spike and wave complexes and three showed 4- to 6-Hz polyspike and wave complexes during the absence. The complaint in these patients of being "sleepy" or "absent" in the morning may correspond to a series or status of simple absences. In Janz's cases (1969) of combined myoclonic seizures and simple absences, either one of the attacks could occur first. In 13 of 461 patients with typical absence (petit mal epilepsy) he found associated JME. In these cases the myoclonic seizures developed after the patient had had typical absence seizures for many years. Occasionally there may be a seizure-free interval between the absence and myoclonic seizures; these patients usually have infrequent GTCSs.

Table 7.2. Seizure types in JME

Author	No. of cases	Myoclonic seizures only	Generalized tonic–clonic seizures	Absence seizures
Janz and Christian (1957)	47	4%	96%	–
Janz (1969)	280	10%	88%	15%
Tsuboi and Christian (1973)	399	–	95%	8%
Loiseau et al. (1974)	100	–	87%	22%
Delgado-Escueta and Enrile-Bacsal (1984)	43	2%	95%	40%
Asconapé and Penry (1984)	12	17%	83%	25%

Type of First Seizure

In Janz's series (1969) myoclonic seizures occurred first in 50%, simultaneous onset of myoclonic seizures and GTCSs occurred in 13%, and GTCSs occurred first in 37%. Myoclonic seizures preceded GTCSs by an average of 3.3 years; in only 10% was the interval between the onset of myoclonic and grand mal seizures long, up to 20 years in one case. In his series only two patients had myoclonic seizures alone; one was a medical student and the other a person who worked at the clinic, in whom jerks were noted by the epileptologist and the diagnosis documented by EEG. Similarly, other authors report an extremely low incidence of isolated myoclonic seizures (Table 7.2). However, myoclonic seizures as the sole manifestation of JME are probably much more frequent than is reported, the seizures being ignored by the patient or possibly not recognized by the physician as being epileptic in nature.

Precipitating Factors

Juvenile myoclonic epilepsy is very sensitive to external factors. Sleep deprivation is an extremely important factor, as is alcohol. In Janz and Christian's original series (1957) sleep deprivation was a triggering factor in 85% of the patients, and excessive alcohol in 40%. Awakening or arising too early is a less important factor. Sleep is not an activator for EEG discharges in this type of epilepsy. Janz and Christian (1957) reported a relationship with menstrual periods in 42% of 19 females. Physical exertion and psychological problems are not prominent precipitating factors in JME. It is not infrequent for attacks to occur only after a triggering factor like sleep deprivation or alcohol ingestion. This fact can sometimes be exploited in the management of this type of epilepsy. Janz also used triggering factors as a provocative test in the evaluation of this type of epilepsy, in the form of sleep deprivation for 1–2 days prior to recording the EEG as well as ingestion of coffee or a liter of wine just before the study. These he found successfully produced clinical and EEG seizures in nine of ten patients (1969). One patient had only EEG activation.

Pregnancy

There appears to be no consistent effect of pregnancy on the seizures of JME. In one study of 36 pregnant women with JME 52% showed no change in their seizure pattern, 28% showed improvement, and 20% showed deterioration (Fuchs 1965).

Age of Onset

The typical age of onset is adolescence through young adulthood, with the majority of cases starting shortly after puberty.

Table 7.3. Age of onset of myoclonic seizures in JME

Author	No. of cases	Age range (yrs)	Mean age (yrs)	Highest frequency	
				Age range (yrs)	% cases
Janz and Christian (1957)	47	10–23		14–18	66
Castelles and Mendilaharsu (1958)	70	1–31		11–20	71
Lecasble (1958)	138			11–20	73
Aigner and Mulder (1960)	45		15.5		
Janz (1969)	280	9–27		13–19	79
Tsuboi and Christian (1973)	319	1–54		12–19	70
Loiseau et al. (1974)	100	1–20		10–20	72
Delgado-Escueta and Enrile-Bacsal (1984)	43	8–24	13.6		
Asconapé and Penry (1984)	12	11–18	14.75		

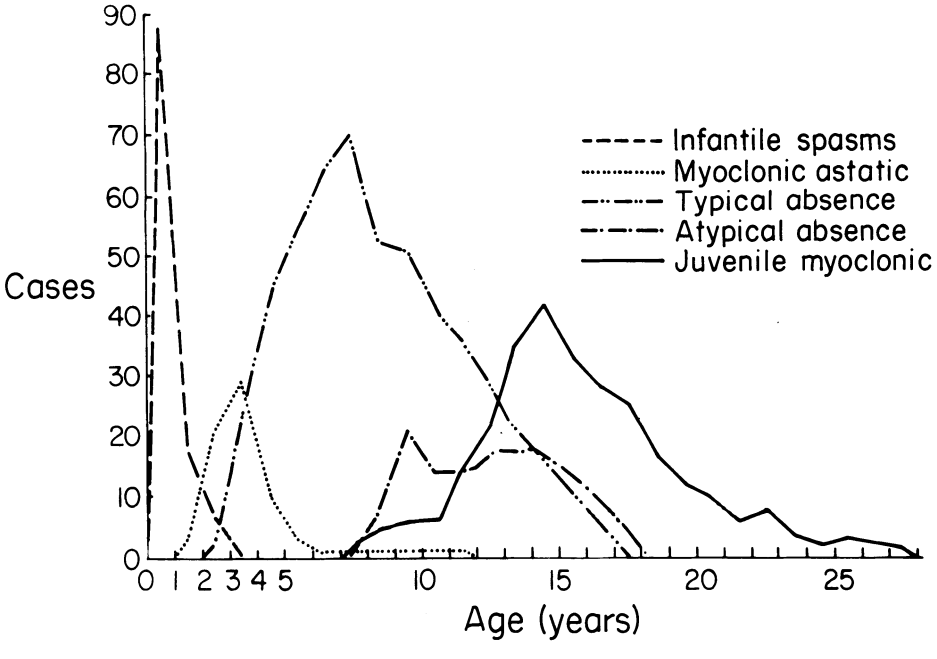

Fig. 7.3. Age of onset of JME and of other types of epilepsy that involve myoclonic seizures and must be differentiated from JME (modified from Janz 1969).

The age of onset of myoclonic seizures in the various case studies is shown in Table 7.3. The peak onset was in the second decade in all the studies. In six of the studies the seizure onset was between 10 and 20 years in 66%–79% of the cases. The other two studies, by Delgado-Escueta and Enrile-Bacsal (1984) and Asconapé and Penry (1984), did not give the peak age of onset in their cases but rather the mean, which was 13.6 and 14.75 years respectively. This conforms well with the other studies. The age of onset of the first myoclonic seizure in Janz's experience (1969) is shown in Fig. 7.3. This is very different from the age of onset in infantile spasms (1–5 years), absence (petit mal) seizures (4–12 years), or myoclonic epilepsy of Unverricht-Lundborg (6–15 years).

Sex

The sex distribution of JME is approximately equal, as shown in Table 7.4. Five of the studies show the percentage of females as ranging from 46.8% to 53.5%. There were a total of 916 patients in the eight studies, with the percentage of females being 50.1%. One study (Loiseau et al. 1974) showed a marked preponderance of females in their 100 cases, 61%. Although 75% of Asconapé and Penry's cases were females, they had a sample of only 12 cases.

Table 7.4. Sex distribution of JME

Author	No. of cases	No. of males	No. of females	% of females
Janz and Christian (1957)	47	23	24	51.1
Castells and Mendilaharsu (1958)	70	34	36	51.4
Aigner and Mulder (1960)	45	21	24	53.0
Janz (1969)	280	149	131	46.8
Tsuboi and Christian (1973)	319	161	158	49.5
Loiseau et al. (1974)	100	39	61	61.0
Delgado-Escueta and Enrile-Bacsal (1984)	43	20	23	53.5
Asconapé and Penry (1984)	12	3	9	75.0

Clinical Profile

All the patients tend to get up late in the morning, tend to wake up slowly, and frequently have breakfast in bed. They are often difficult to wake up, need considerable sleep, and tend to be deep sleepers. Apparently they tend to go to bed

late. Schulte (1955) thought these sleep habits were most probably primary and not secondary to the seizures.

Incidence

Although JME appears to be rarely diagnosed, it is not an uncommon form of epilepsy. However, there is often a delay in the proper recognition and diagnosis of this type of epilepsy. In their study, Delgado-Escueta and Enrile-Bacsal (1984) mention that the myoclonic seizures were not recognized for years in 12 of their 43 patients, usually because attention had been directed to the refractory generalized tonic–clonic seizures. The incidence of JME in the different studies does not vary greatly, being 3.1%–4.3% (Table 7.5). One exception is the study of Lennox (1960), who referred to JME as "jerk epilepsy" and found an incidence of 7%. In Janz and Christian's (1957) study JME represented 2.7% of their patients with both idiopathic and symptomatic epilepsy but 3.75% of the patients with idiopathic epilepsy.

Table 7.5. Incidence of JME

Authors	No. of epileptics	No. of JME	Percentage JME
Janz and Christian (1957)	1712	47	2.7
Bamberger and Matthes (1959)	349	11	3.1
Lennox (1960)	1900	–	7.0
Janz (1969)	6500	280	4.3
Gastaut and Tassinari (1975)	6000	187	4.1
Asconapé and Penry (1984)	276	12	4.3

Etiology

Pathology

Juvenile myoclonic epilepsy is idiopathic. In 1957 Janz and Christian reported 47 patients with JME, and none had evidence of brain damage. In 1969 only 1 of 280 had a history of brain damage; this was due to birth trauma and there was residual hemiplegia. All the changes were most probably the result of the GTCSs, with the most severe abnormalities occurring in the mediobasal temporal lobe and insula. Microdysgenesis was described in seven of eight patients with primary generalized

epilepsy, including two with JME (Meenke and Janz 1984). These changes included:

1. Rows of uni- and bipolar cells immediately subpially
2. An increased density of nerve cells in the stratum moleculare
3. An indistinct boundary between lamina 2 and stratum moleculare
4. Protrusions into the pia of tissue containing well-differentiated neurons
5. Displaced columnar neuronal architecture
6. Increased nerve cells in the white matter
7. An increase of large nerve cells with satellitosis in stratum radiatum of hippocampus
8. Purkinje cell dystopias

The pathological significance of these findings is not confirmed. They have been found in 4% of normals (Veith and Schwindt 1976) and in 37% of 279 patients with epilepsy (Veith and Wicke 1968). Meenke and Janz (1984) hypothesized that the cortical microdysgenesis in primary generalized epilepsy (including JME) may be the pathological substrate.

Heredity

Genetic factors certainly appear to be significant in predisposing an individual to develop this type of epilepsy. Table 7.6 shows the incidence of a positive history of epilepsy in families and first-degree relatives (parents, siblings, or children) of probands with JME in the various studies. A family history is high in all the studies, ranging from 13% to 50%. The study by Tsuboi and Christian (1973) of 319 probands with JME is outstanding as the only systematic study on the genetics of this disease. They found the incidence of genetic predisposition to be 27% among their JME patients, which was significantly higher than the incidence of 9.9% in 466 nonselected epileptics from their clinic. It was also higher than the family history of seizures in patients with benign focal epilepsy of childhood

Table 7.6. Heredity and JME

Authors	No. of cases	Family history of seizures	First-degree relatives
Janz and Christian (1957)	47	17%	8.5%
Castells and Mendilaharsu (1958)	70	37%	20%
Aigner and Mulder (1960)	45	13%	–
Janz (1969)	280	25%	17%
Tsuboi and Christian (1973)	319	27%	4%
Loiseau et al. (1974)	100	14%	–
Delgado-Escueta and Enrile-Bacsal (1984)	43	39%	25%
Asconapé and Penry (1984)	12	50%	–

(13%), absence seizures (10%), generalized epilepsy (3%), and partial epilepsy (1%) in the study of Beausart (1972).

The incidence of epilepsy in first-degree relatives (4.1%: Tsuboi and Christian 1973) was higher than that among the general population (0.38%: Hauser and Kurland 1975).

In the study by Janz (1969) 17% of the first-degree relatives of the probands had JME. Of the 116 epileptic relatives of the probands in the study by Tsuboi and Christian (1973), myoclonic seizures were found in 15% and awakening GTCSs in 17%.

In the study by Tsuboi and Christian (1973) the EEGs of 390 first-degree relatives (asymptomatic and symptomatic) of 136 probands were examined and 15% showed specific epileptiform abnormalities (spike and wave complexes and/or spikes). The frequency was highest among sons and daughters (24.6%), intermediate among siblings (13.3%), and lowest among parents (9.4%). These results further support the view that a genetic factor is important in the pathogenesis of this type of epilepsy and are consistent with the extremely low incidence of brain pathology in this type of epilepsy.

The low incidence of epilepsy (4.1%) and specific EEG epileptiform abnormalities (15%) in first-degree relatives militates against the possibility of autosomal recessive inheritance. Sex-linked inheritance can be excluded because males and females are equally affected. It is very difficult to distinguish autosomal dominant inheritance with low penetrance from polygenic inheritance. Either of these two modes of inheritance is possible in JME. Tsuboi and Christian calculated a low penetrance of 10% among first-degree relatives of probands in their study and thus hypothesized polygenic inheritance as the likely mode of transmission.

Electroencephalographic Manifestations

Interictal

Juvenile myoclonic epilepsy has a typical EEG pattern, the polyspike and wave complex (Fig. 7.4). Although this is a characteristic EEG finding, it is not pathognomonic of JME as it is seen in many of the different types of myoclonic and other generalized epilepsies. Numerous spikes precede the slow wave in the polyspike and wave complex. The frequency of the slow waves in the complex was described as 3.5–4.5 Hz by Janz (1969) and as up to 6 Hz by Delgado-Escueta and Enrile-Bacsal (1984). The distribution is generalized and usually bilaterally symmetrical. However, the EEG may show only generalized spike and wave complexes and not the typical polyspike and wave complexes. If bursts of 3-Hz spike and slow-wave complexes are seen in the EEG, the patient will usually have a history of typical absence seizures in addition to the history of awakening myoclonic or generalized tonic–clonic seizures. Thus the two of Janz and Christian's (1957) original series of 47 patients who showed a combination of polyspike and wave bursts and 3-Hz spike and wave complexes had both JME and typical absence seizures. The typical EEG abnormality in JME (see in 68 EEGs of 38 patients in

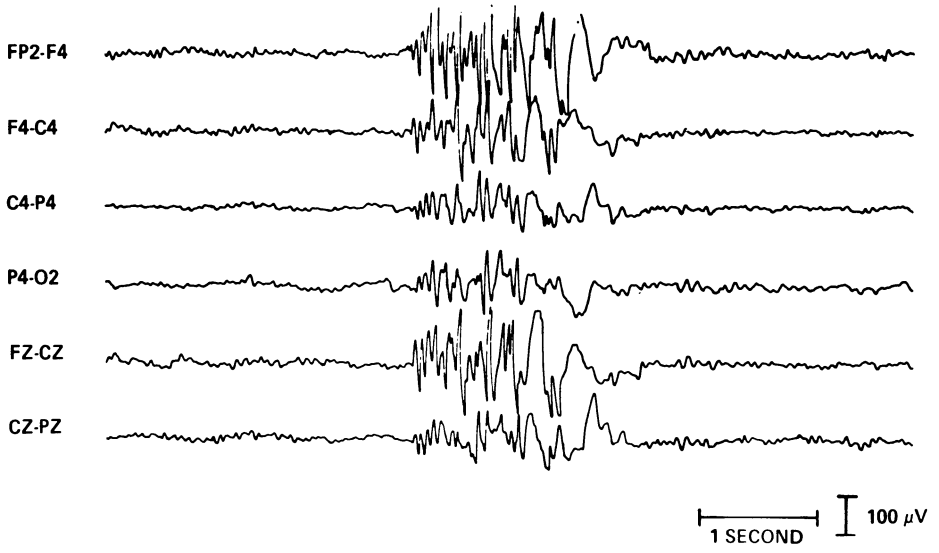

Fig. 7.4. Interictal generalized polyspike and wave complex from EEG recording of a 15-year-old girl with JME. Only the activity over the right parasagittal and midline regions is shown.

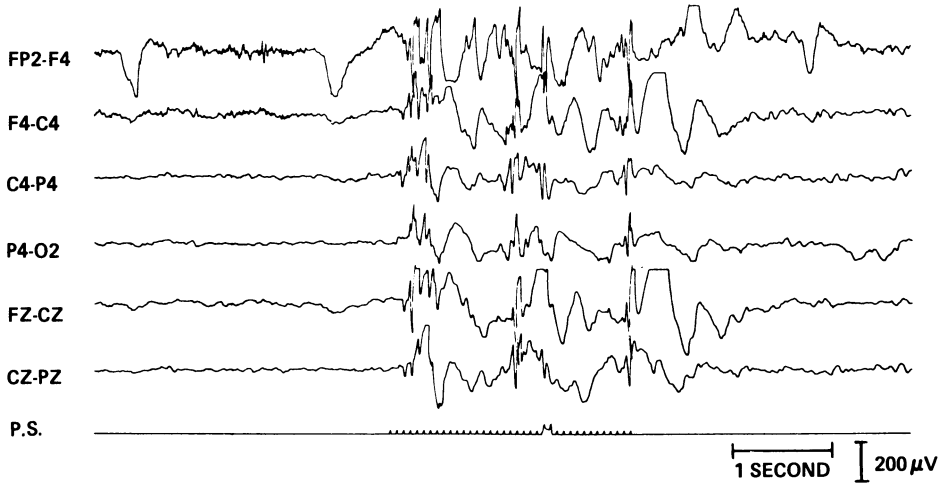

Fig. 7.5. Generalized polyspike and wave complex elicited by photic stimulation in the same 15-year-old girl as in Fig. 7.4. The activity over the right parasagittal and midline regions is shown.

Janz and Christian's study) is very stereotyped, with no great change from one EEG to another in a particular patient. Ninety-two percent of Janz and Christian's patients had typical interictal epileptiform discharges, and only two patients on anticonvulsants had no epileptiform discharges. Therefore, there is a very high

percentage of EEG abnormalities. With provocation by hyperventilation and sleep deprivation, positive findings increased to 96%. Sleep alone is not usually effective in inducing epileptiform activity in this syndrome, and a special induction procedure including sleep deprivation preceded by alcohol and/or coffee was used by Janz and Christian. Hyperventilation in Janz and Christian's series (1957) elicited seizures in only three cases. Photosensitivity is a common feature in this disorder. Thus photic stimulation elicited epileptiform activity in 30.5% of 121 cases of JME (Goosses 1984) and in 33% of 12 cases studied by Asconapé and Penry (1984). Figure 7.5 shows epileptiform activity in response to photic stimulation in one of our cases. There is usually a normal background rhythm and there are no focal abnormalities. Only 2 of 38 patients studied by Janz and Christian (1957) had a mild abnormality of background rhythms. This is in contrast to patients with generalized tonic–clonic seizures without myoclonic seizures, 76% of whom have generalized slow activity.

Ictal

The ictal EEG pattern is characterized by abrupt onset of a series of spikes of increasing amplitude followed by slow waves of variable frequency and amplitude. According to Delgado-Escueta and Enrile-Bacsal (1984) the spikes are usually at a frequency of 10–16 Hz. Complexes with slow waves at 2–5 Hz occur with, preceding, following, or superimposed on spikes or polyspikes. The number of spikes is related to the intensity of the myoclonus, but not to the duration of the attack. Severe jerks are associated with more spikes and lower amplitude slow waves than are seen in milder jerks. Spikes are negative polarity and may have an amplitude of 150–300 μV. The slow waves have an average amplitude of 200–330 μV, the amplitude seldom being more than 400 μV. The polyspikes are bilateral and symmetrical, and maximal frontocentrally. They are much less well synchronized than 3-Hz spike and wave complexes.

There are no clinical myoclonic jerks without polyspikes. The burst of polyspike and wave complexes is usually 2–10 s in duration, even when the clinical attack lasts only 1–1.5 s.

Differential Diagnosis

It is important to make a specific diagnosis of a particular epileptic syndrome because of the implications for prognosis, choice of treatment, and possible genetic counselling. This is particularly true for JME.

Juvenile myoclonic epilepsy should be differentiated from various forms of nonepileptic myoclonus. If myoclonic jerks occur in isolation in relation to sleep, then JME must be differentiated from physiological sleep-related myoclonic jerks. If the jerks are restricted to the time of sleep onset, they may be confused with hypnagogic myoclonic jerks. Physiological hypnagogic myoclonus occurs in the

normal subject as he/she is falling asleep and is not associated with any change in the EEG other than a vertex transient of K-complex signifying arousal. There is no epileptiform activity. This contrasts with the myoclonic jerks of JME, which occur mainly in the morning on awakening and are associated with prominent polyspike and wave complexes in the majority of cases.

Nocturnal myoclonus may be considered in the differential diagnosis if the myoclonus occurs at night. Nocturnal myoclonus is characterized by periodic leg movements during sleep (Symmonds 1953), and can be either rhythmic or irregular in its periodicity. The form associated with an irregular periodicity is more likely to cause arousal (Coleman 1982) and is thus more likely to have associated EEG features of arousal in the form of K-complexes. However, there is no associated epileptiform activity. Myoclonic jerks of JME are thought not to occur during sleep, as shown in Fig. 7.2.

If the myoclonic jerks occur during the day, "surprise" or "startle" myoclonus should be considered. Unsuspected motor or sensory stimuli may startle the subject and result in a myoclonic jerk. Startle jerks are not associated with EEG changes like sharp transients or epileptiform activity.

When GTCSs occur in association with myoclonic jerks, the myoclonic jerks are often neglected, most attention being brought to bear on the GTCSs both by the patient and by the attending physician. Thus, the diagnosis of JME is frequently missed and a diagnosis of idiopathic generalized epilepsy made instead.

It is also important to distinguish JME from other types of epilepsy that are associated with myoclonus presenting in this age group.

Typical absence seizures (petit mal epilepsy) frequently have associated myoclonus involving the eyelids and periorbital muscles (Penry et al. 1975). There may also be associated myoclonus of the shoulder girdle. This form of absence, myoclonic absence, is easily distinguished from myoclonic seizures in that there is prominent loss of consciousness and less significant myoclonus. Also the ictal EEG manifestations of typical absence, 3-Hz spike and wave complexes, clearly distinguish the two types of epilepsy.

Myoclonic seizures of early childhood (Aicardi and Chevrie 1971) do not really enter into the differential diagnosis by virtue of the age of onset of this form of epilepsy. This is also true for infantile spasms (West's syndrome).

Myoclonic astatic or atonic seizures (Lennox-Gastaut syndrome) (Gastaut and Tassinari 1975) are characterized by the presence of a typical triad of an intractable seizure disorder, encephalopathy with mental retardation, and a characteristic EEG pattern of generalized slow spike and wave complexes. The intractable seizures include myoclonic, atonic, atypical absence, and generalized tonic–clonic. The slow spike and wave complexes occur at a frequency of 2.5 Hz or less in a generalized distribution, typically in runs of greater than 3 s duration and with a slow background rhythm.

The familial progressive myoclonic epilepsies (Unverricht, etc.) are characterized by the presence of progressive encephalopathy with mental retardation, a positive family history, and presence of epilepsy and myoclonus. The age of onset is 6–15 years (most frequently 9–11 years), and the GTCSs usually occur in sleep. The myoclonus is asynchronous and asymmetrical with no preference for a particular time of day. The myoclonus increases with intentional movement, sensory stimuli, and psychic excitement. It can affect isolated muscles, frequently with no visible movements, and muscles of the face, tongue, or pharynx. The EEG shows slowing of background rhythms, often to a severe degree, with bursts of

spike and wave complexes which are poorly correlated with the myoclonus. EMG activity may follow or precede spike and wave complexes but usually does not coincide with them.

Management

Once a definitive diagnosis of JME is established one must first pay particular attention to potential precipitating factors of this type of seizure. Alcohol may be an important precipitant, as is sleep deprivation; thus the subject should be encouraged to obtain adequate nocturnal sleep and abstain from alcohol. Also caffeinated beverages, such as coffee and tea, may act as precipitants and should be avoided in the evening hours.

Today the drug of choice in the treatment of JME appears to be valproic acid (VPA) (Jeavons et al. 1977; Delgado-Escueta and Enrile-Bacsal 1984). In Jeavons' et al. series (1977) 10 of 12 patients with JME became seizure free, while one had >80% reduction and one >30% reduction in seizure frequency. In Delgado-Escueta and Enrile-Bacsal's group (1984), 41 of 43 received this drug. In one patient VPA was discontinued owing to the development of exfoliative dermatitis. VPA completely controlled the myoclonic, absence, tonic–clonic, and clonic–tonic–clonic seizures in 32 of the 40 patients who had adequate trials and reduced the seizure frequency in five others. In three cases therapy with VPA failed. Sixteen patients eventually were controlled on VPA as the sole anticonvulsant; 14 of these were seizure free for at least 2 years. Twenty-four patients took VPA in combination with other anticonvulsants, either because they refused to discontinue these other anticonvulsants or because discontinuation of other drugs precipitated seizures.

Primidone and phenobarbital are other agents which may be effective in the management of JME. Janz (1969) compared primidone, phenobarbital, and phenytoin in the management of JME. The most effective agent was primidone. Of 84 patients treated with this agent, 82% became seizure-free and 16% had a reduction in seizures by >75%. The response to phenobarbital was also good, with 67% seizure-free and 25% with a >75% reduction. The results with phenytoin, however, were poor, only 32% being seizure-free and only 36% having a >75% reduction.

Clonazepam is an anticonvulsant which may be an effective adjunctive agent in the treatment of JME. Nanda et al. (1977) reported on its use in combination with phenytoin, phenobarbital, or primidone. In a double-blind crossover add-on study of clonazepam versus placebo in 15 patients with a diagnosis consistent with JME (3 with myoclonic jerks alone and 12 with myoclonic jerks and GTCSs), they found myoclonic seizures to be completely controlled in 80% and reduced by at least 80% in the remaining 20%. They treated an additional seven patients with myoclonic jerks and GTCSs in an open study of clonazepam as an adjunctive agent, and in every case the seizures were completely controlled. We have used clonazepam in combination with Tegretol in two patients with good effect, completely suppressing the myoclonic seizures with the addition of clonazepam.

Prognosis

Juvenile myoclonic epilepsy has a very good prognosis insofar as it can generally be well controlled by medication. Thus it is important to identify this epileptic syndrome and to treat it appropriately. Unfortunately, as noted above, the myoclonic seizures often are not recognized for years, usually because attention is directed to uncontrolled GTCSs (Delgado-Escueta and Enrile-Bacsal 1984).

In JME the electroclinical trait appears to persist for life. This is consistent with reports of a high incidence of relapse of seizures after withdrawal of anticonvulsants: seizures return within 5 years after medication withdrawal in 75%–100% of cases of JME (Janz 1982; Lund et al. 1976; Delgado-Escueta and Enrile-Bacsal 1984). This has led Delgado-Escueta and Enrile-Bacsal to advocate that in this type of epilepsy, when seizures are well controlled, withdrawal of anticonvulsants should not be considered.

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Chapter 8

Generalized Tonic–Clonic Epilepsies

Bruce J. Fisch and Timothy A. Pedley

Introduction

This chapter focuses on generalized tonic–clonic seizures, including both those of nonfocal origin (primarily generalized tonic–clonic seizures) and those generalized by propagation from a lateralized or restricted cortical area (secondarily generalized tonic–clonic seizures). Although Merlis (1970) defined generalized tonic–clonic epilepsy as a "chronic disorder of recurrent seizures that are clinically and electrographically generalized from the outset," few published studies have rigorously separated primarily from secondarily generalized convulsions.

Synonyms

Early attempts at classification grouped tonic–clonic seizures with other convulsive fits, and all were referred to as "le grand mal" (Esquirol 1838). Subsequently, "grand mal" became virtually synonymous with the generalized tonic–clonic attack. Use of the term, however, is now discouraged because it does not infer presence or absence of a sequence of events which may be of help in discriminating clinically between primarily and secondarily generalized seizures. Other similarly ambiguous designations include "generalized convulsion" and "major motor seizure." Even the descriptive "tonic–clonic" must be qualified, since a tonic–clonic sequence of motor events may be generalized, asymmetrical, unilateral, or focal.

The most widely accepted current nomenclature of epileptic seizures was formulated by the Commission on Classification and Terminology of the International League Against Epilepsy (1981). This classification emphasizes the easily observed sequence of a generalized tonic phase followed by a clonic phase. Close

observation of individual attacks, however, reveals that there is often considerable variation in the absolute and relative durations of these phases. Furthermore, generalized tonic–clonic seizures regularly demonstrate a tonic postictal motor phase (Gastaut and Broughton 1972), and there are often one or more myoclonic jerks preceding the tonic part of the ictus. Some investigators believe that special syndromes of generalized convulsive seizures can be identified partly on the basis of the exact sequence of motor events (Delgado-Escueta et al. 1983; see below).

Nosology

Bilateral tonic–clonic epilepsies are commonly divided into primary (cryptogenic, essential, idiopathic) and secondary (symptomatic) categories (Merlis 1970). Secondary epilepsies have a presumed etiology based on a known disturbance of brain function. Primary tonic–clonic seizures are always generalized from onset, although oscillographic or other special recording methods reveal that ictal electrographic patterns are rarely, if ever, truly bisynchronous. Instead, shifting asynchronies occur. Secondary tonic–clonic seizures may be clinically and electrographically nonfocal in origin, but more often the ictal discharge arises focally or within one hemisphere. Demonstration of such a unifocal origin may require use of computerized display techniques and other methods that permit detailed timing analyses (Klass 1975; Lüders et al. 1980; Gotman 1981). Under such circumstances, a consistent lateralized asynchrony of greater than 10–20 ms may be demonstrated even in cases where the routine EEG appears generalized from the beginning. In patients whose seizures are related to bilateral and multifocal cortical lesions, the distinction between focal and generalized onset can be unresolvable as there may be no consistent lateralization, and interhemispheric asynchronies may be less than 20 ms. Such situations elude the resolving power of present testing methods, and as a result such seizures are considered generalized by definition (see also Pathophysiology, below).

Recent attempts to subdivide primary generalized tonic–clonic epilepsies have emphasized differences between tonic–clonic and clonic–tonic–clonic seizures that occur alone or in combination with other types of primarily generalized fit (Delgado-Escueta et al. 1983). Evidence for the existence of these subtypes is difficult to obtain for several reasons. First, many investigators have proceeded on the assumption that generalized tonic–clonic seizures, regardless of etiology, frequently begin with a succession of bilateral myoclonic jerks (Gastaut and Broughton 1972; Browne 1983). Second, other investigators classify myoclonic jerks occurring hours or days before a tonic–clonic seizure as a nonspecific prodrome seen in about 10%–50% of all patients with generalized convulsions (Marsden and Reynolds 1982). Third, epidemiological studies have usually defined tonic–clonic epilepsy without attention to preictal myoclonus or consistent EEG information. Finally, other investigations of epilepsy have in the past not distinguished between tonic–clonic, clonic–tonic–clonic, or other "grand mal" patterns.

The most comprehensive epidemiological study of epilepsy in the United States was conducted by Hauser and Kurland (1975) in Rochester, Minnesota. Epilepsy type was classified mainly by clinical presentation. The mean annual incidence of

patients presenting exclusively with generalized tonic–clonic seizures was 12.5/100 000 population, which represented about 23% of the overall yearly incidence of epilepsy between 1945 and 1964. The incidence did not vary significantly with age in contrast to other seizure types and the results of some previous studies. Prevalence analyses showed that patients with only generalized tonic–clonic seizures accounted for 20.6% of all patients with epilepsy. Over half of all patients with epilepsy, however, eventually experienced one or more generalized seizure. Within the population (244 800) of Greater Aarhus, Denmark, "grand mal" seizures accounted for 25.6% of all seizure types (Juul-Jensen and Foldspang 1983).

Gastaut et al. (1975) performed the largest nonepidemiological survey of epilepsy which categorized patients by both clinical and electroencephalographic criteria. Of 4591 patients, 11.3% had primary generalized epilepsy characterized mainly or wholly by tonic–clonic seizures. This figure is lower than expected from the data of Hauser and Kurland (1975), but some differences would be expected considering the different methods of case selection and classification. Patients with secondary (symptomatic) generalized nonfocal tonic–clonic seizures were rare.

Gastaut et al. (1973) grouped together all patients with primary generalized tonic–clonic epilepsy and analyzed the features of this population. Seizure onset occurred during puberty in 68% of patients. One-third had isolated bilateral massive myoclonic jerks. Evolution and prognosis were favorable since the majority eventually experienced complete remission, and seizure frequency declined over time in the remainder. Provoking or facilitating factors were present in 84% of patients and included falling asleep or awakening (57.5%), menstruation (40%), and intermittent light stimulation (13%).

Delgado-Escueta et al. (1983) propose distinguishing two subgroups of primary generalized tonic–clonic epilepsy. The first group shares many features of juvenile myoclonic epilepsy [Delgado-Escueta and Enrile-Bascal 1984; Asconapé and Penry 1984; also termed "impulsive petit mal" (Janz and Christian 1957) and "benign adolescent myoclonus" (Porter 1984)]. This form of "awakening grand mal epilepsy" usually begins at puberty. The only type of attack is a clonic–tonic–clonic convulsion that typically occurs upon awakening. Unlike juvenile myoclonic epilepsy, isolated myoclonic jerks and absence seizures do not occur. The interictal epileptiform EEG pattern is bursts of 4- to 6-Hz multiple spike and wave paroxysms. Although a majority of patients relapse if anticonvulsants are withdrawn, prognosis remains favorable since almost all patients can be completely controlled with valproate. Because of the many obvious similarities to juvenile myoclonic epilepsy, Delgado-Escueta et al. (1983) speculate that this entity represents a phenotypic variant of a similar genetic substrate.

The second group is characterized by so-called "pure grand mal epilepsy" in which generalized tonic–clonic seizures occur as the only type of attack. A preceding clonic phase is not present. Seizures usually present during both wakefulness and sleep, but occasionally they are confined to sleep ("nocturnal grand mal"). Interictal EEG epileptiform activity consists of well-formed diffuse 3-Hz spike and slow wave complexes. Prognosis is excellent, with 80%–90% of patients remaining seizure-free off drugs.

The existence of these forms as truly distinct categories of tonic–clonic epilepsy is still controversial. Most major prognostic studies have not attempted to identify specific types of grand mal epilepsy. Even some studies cited in support of the subvariety concept (Gastaut and Tassinari 1975; Delgado-Escueta and Greenberg

1984) do not really provide enough information to permit clinical and EEG discrimination. Futhermore, there are inherent difficulties in making critical distinctions that depend on verification of whether isolated myoclonic jerks are present or not. Finally, the precise point at which tonic–clonic seizures preceded by myoclonus become classified as clonic–tonic–clonic seizures has not been clearly defined by any investigator.

While primary generalized tonic–clonic epilepsy is considered an idiopathic disorder, there is substantial evidence indicating that genetic factors play a major role (Newmark and Penry 1980, for review). The studies by Eisner and colleagues (1959, 1960) described a significant familial aggregation in patients with generalized tonic–clonic seizures, in contrast to other epilepsies. In their data, a familial tendency was only present with probands whose seizures began before age $15\frac{1}{2}$, with the strongest association seen with probands whose seizures began before age 4. Tonic–clonic seizures occurred in 8.3% of probands' relatives, in contrast to 2.2% of relatives of the control population. Tsuboi and Endo (1977) considered their evidence of a genetic basis for idiopathic grand mal epilepsy conclusive. They found that patients with this type of seizure disorder had the highest rate of offspring with either febrile or afebrile seizures (16.8%), but a control population was not studied.

Patients with primary generalized epilepsy commonly have more than one type of seizure. Most often there is some combination of absence, bilateral myoclonic, and tonic–clonic attacks. Absence attacks may be accompanied by brief, symmetrical tonic, atonic, or clonic motor activity. Generalized tonic–clonic seizures occur in 37%–66% of patients with absence attacks (Currier et al. 1963; Charlton and Yahr 1967; Livingston et al. 1965; Dalby 1969; Sato et al. 1976). Most of these patients will continue to have tonic–clonic seizures into adulthood (Sato et al. 1976, 1983). About one-half of this group will present with tonic–clonic seizures only (Sato et al. 1983). There is, at present, no way of reliably predicting which patients with absence attacks will go on to develop tonic–clonic seizures. Tonic–clonic seizures also occur frequently in association with myoclonic seizures, as in juvenile myoclonic epilepsy (Janz and Christian 1957; Delgado-Escueta and Enrile-Bascal 1984; Asconapé and Penry 1984) and certain subgroups of other patients with myoclonic seizures (Loiseau et al. 1974).

Diseases of the central nervous system that result in chronic epilepsy are legion, but the prevalence of tonic–clonic seizures in these disorders is extremely variable. For instance, generalized tonic–clonic seizures may be seen in 5% of patients with juvenile-onset Huntington's disease, whereas in patients with multiple sclerosis they occur only slightly more frequently than in the population at large (Niedermeyer 1982a). Although some neurological diseases are said to manifest generalized tonic–clonic seizures (e.g., Alzheimer's disease), in most cases careful clinical observation and electrographic data are lacking. More rigorous scrutiny may reveal that clinical attacks in such patients are actually tonic, clonic, or myoclonic (Gastaut and Tassinari 1975). In adults, the great majority of clinically generalized tonic-clonic seizures are secondarily generalized partial fits (Porter 1984). Extensive lists of various etiologies are provided by Gastaut and Tassinari (1975), Laidlaw and Richens (1982), Gastaut and Broughton (1972), and Niedermeyer (1982b).

Clinical Manifestations

The Tonic–Clonic Seizure Proper

The detailed observations of Gastaut and Broughton (1972) provide the basis for the following description. It should be remembered, however, that phases of individual seizures may vary somewhat, especially in intensity and duration.

The primarily generalized tonic–clonic convulsion begins with brief tonic flexion of the axial musculature accompanied by superior deviation of the eyes and pupillary dilation. The muscular contraction spreads to the limb girdles, forcing the arms into an elevated, abducted posture with the elbows semiflexed and the hands rotated so the palms face forward. The lower extremities assume a position of flexion, abduction, and external rotation. Muscular contraction in the limbs is greatest proximally. The mouth is characteristically held in a half-open position, rigidly fixed. This brief flexor spasm is followed by a longer period of tonic extension which also begins in the axial musculature. This is accompanied by forced closure of the mouth which sometimes produces oral trauma. The tonic extension causes forceful expiration of air, resulting in a 2- to 12-s "epileptic cry." Next, the arms assume an attitude of semiflexion and abduction, with the forearms partially crossed in front of the chest. The legs are adducted and extended, and fixed in external rotation with the feet and great toes in extension.

The tonic phase does not end abruptly with onset of clonic activity. Rather, inhibition of the tetanic contraction begins as a diffuse tremor with a rate approximating 8 Hz which gradually slows to 4 Hz. With slowing of this tremor, the clonic pattern appears, and the muscular movements increase in amplitude. This transition from tonic to clonic phase has been referred to as the "intermediate vibratory period." The clonic phase is established when each recurrent inhibition of tetanic contraction produces complete atonia, thus resulting in violent flexor spasms. The intervals of atonia gradually become longer until a final massive jerk occurs. With each clonic spasm the pupils contract and dilate.

About 5 s after the clonic phase ends, there is another episode of generalized increased tone that occurs with onset of the postictal period. This lasts a few seconds to several minutes. The final tonic contraction predominates rostrally, with mild to marked increased tone in the extensor muscles of arms or legs, or both. There may be opisthotonus, and trismus occasionally causes tongue laceration. Respiration, which ceases at the beginning of the initial tonic phase, returns. Ajmone-Marsan and Ralston (1971) suggested that the postictal tonic phase represents a functional decerebrate state.

Consciousness returns gradually. As the patient begins to awaken, a confusional state with automatic behavior may ensue. Often the individual falls asleep directly and then awakens, feeling tired, after a variable period of time. Complaints of generalized muscle soreness and headache are frequent. The actual ictus lasts 1–2 min, but patients often measure seizure duration through the initial part of the postictal period, usually 5–15 min.

Premonitory Symptoms and Variations in Initial Manifestations

A number of nonspecific premonitory symptoms may appear hours or days before a primarily generalized tonic–clonic seizure (Table 8.1). These nonspecific manifestations of heightened cortical excitability must be distinguished from the localizing signature provided by a partial seizure's "aura." Occasionally such epileptic prodromata enable patients to predict occurrence of the subsequent seizure with some accuracy. Patients with secondarily generalized tonic–clonic seizures may be forewarned by frequent isolated specific auras which, of course, represent brief partial seizures. Myoclonus of the arms and trunk upon awakening may precede a generalized convulsion by minutes or hours. In other cases seizures may be anticipated on the basis of known specific and consistent precipitating factors (Bickford and Klass 1969). Unfortunately, the majority of patients are unable to identify warning signs reliably. When primary generalized tonic–clonic seizures occur at night, it is usually near the beginning or end of sleep, rarely during REM sleep (Kawahara et al. 1977; Baldy-Moulinier et al. 1984). Light-sensitive epilepsies are particularly activated by sleep deprivation.

Table 8.1. Common neurological premonitory symptoms

Headache	Decreased concentration
Mood change	Sleep disturbance
Emotional instability	Unusual appetite
Anxiousness	Myoclonus
Irritability	Dizziness and light headedness
Lethargy	

Generalized tonic-clonic seizures usually involve both sides of the body symmetrically, but slight turning movements at seizure onset have been recognized for many years (Penfield and Jasper 1954). Ajmone-Marsan and Ralston (1971) first questioned the localizing value of conjugate lateral eye deviation. More recently Ochs et al. (1984) and Robillard et al. (1983) independently investigated the localizing or lateralizing value of head turning. Both studies showed that forced head turning occurred in partial (frontal, temporal, and unilateral foci) and primarily generalized seizures. Furthermore, ipsilateral head turning was as common as contralateral rotation. Despite traditional teaching, this is not altogether surprising considering the different complex cortical and subcortical mechanisms that may produce adversive movements. Ochs et al. (1984) conclude that "... the direction of head-turning is probably dependent on the distribution of excitation within cortical and subcortical motor systems, rather than on the site of seizure origin." An opposing view by Wyllie et al. (1986) has recently appeared which supports the lateralizing significance of true versive head and eye movements if these are distinguished from nonversive turnings.

In the unusual circumstances where convulsive activity on the two sides of the body is actually asynchronous, Gastaut and Broughton (1972) suggest that the convulsion be considered two independent unilateral seizures rather than a single generalized one.

Autonomic Changes

Although apnea persists throughout the convulsion and shortly into the immediate postictal period, other autonomic changes, including increased blood pressure, heart rate, and intravesicular bladder pressure peak at the end of the tonic phase and decrease thereafter (Fig. 8.1). During the ictal tonic phase, heart rate and blood pressure more than double, and intravesicular bladder pressure may increase to 5 times normal. Enuresis is blocked until the end of the clonic phase by contraction of sphincter muscles. Incontinence, when present, occurs between the end of the clonic phase and the beginning of the postictal tonic phase. Ejaculation and fecal incontinence are rare, occurring in the immediate postictal period. Diffuse skin color changes are probably the result of venous congestion due to impaired venous return or to cyanosis caused by apnea-induced hypoxia. Occasionally piloerection and petechial hemorrhages are seen. Sweating is a regular occurrence and results in a measurable drop in skin resistance.

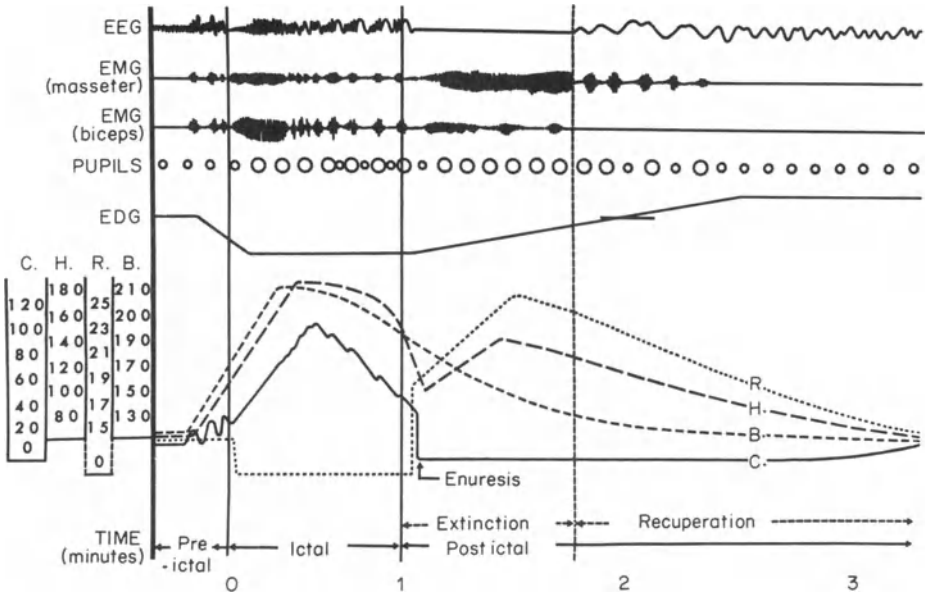

Fig. 8.1. Schematic representation of a generalized tonic–clonic seizure depicting EEG, EMG activity, pupillary size, skin resistance (*EDG*, electrodermogram), and changes in intravesicular bladder pressure (*C*), heart rate (*H*), respiratory rate (*R*), and systolic blood pressure (*B*). Except for the apnea, note that all autonomic changes attain their maximum at the end of the tonic phase and then progressively attenuate. See text for further details. (Gastaut and Broughton 1972)

Metabolic and Hormonal Changes

Immediately after a generalized tonic–clonic seizure, there are marked alterations in acid–base equilibrium (Orringer et al. 1977). Mean arterial pH drops to 7.14 ± 0.06 associated with a venous lactate concentration of 12.7 ± 1.0 mEq/liter and a mean CO_2 content of 17.1 ± 1.1 mmol/liter. Spontaneous resolution takes place over the next 60 min from metabolism of the lactic acid and removal of hydrogen ion.

Recent reports have emphasized seizure-related hormonal changes (for review, see Mattson and Cramer 1985). Following spontaneous generalized tonic–clonic seizures, there are elevations in plasma levels of prolactin, ACTH, vasopressin, norepinephrine, epinephrine, β-endorphin, β-lipotropin, and plasma cortisol (Aminoff et al. 1984; Simon et al. 1984; Trimble 1978). There is no consistent change in plasma renin activity, growth hormone, luteinizing hormone, or follicular stimulating hormone (Aminoff et al. 1984). The pattern of hormonal responses suggests direct seizure activation of the hypothalamus, either electrically or by specific changes in release of neurotransmitters and other neuromodulatory substances.

Trimble (1978) has proposed that serum prolactin measurements are of help in distinguishing epileptic seizures from psychogenic attacks by failing to increase as expected with pseudoseizures. There are, however, reports of both electroconvulsive and spontaneous tonic–clonic seizures not accompanied by a significant change in serum or plasma prolactin concentration (Öhman et al. 1976; Dana-Haeri et al. 1983; Abbott et al. 1980; Aminoff et al. 1984). Conversely, a mild increase in serum prolactin may follow heavy physical exertion (Höppener et al. 1981), and there is one reported case of significant increase after a psychogenic seizure (Oxley et al. 1981).

Complications

Complications of single seizures occurring in a reasonably protected environment include oral trauma, aspiration pneumonia, stress fractures, pulmonary edema, and sudden death. Complications increase with prolonged seizures or multiple seizures occurring in close succession.

Aspiration pneumonia results from accumulation of saliva and tracheal bronchial secretions, particularly in patients who are debilitated and remain supine in the postictal period. It may also be caused by aspiration of vomitus during the initial postictal period.

Vertebral compression fractures are the most common skeletal injury. They seem to complicate nocturnal seizures especially, and are more common in older patients (Vasconcelos 1973). Although most compression fractures due to external trauma are located near the thoracolumbar junction (Worthing and Kalinowsky 1942), those resulting from spontaneous seizures are almost evenly distributed between the third and eighth thoracic vertebrae and the thoracolumbar area (Vasconcelos 1973). The incidence of symptomatic vertebral compression fractures

is about 1%. However, Vasconcelos (1973) has estimated that the overall incidence of seizure-related fractures in unselected cases may be as high as 15%.

Sudden death occurs most often in young adults with longstanding generalized tonic–clonic seizure disorders. Subtherapeutic anticonvulsant serum levels are a frequent finding, but autopsies usually fail to provide other anatomical or chemical causes of death (Terrence et al. 1975; Leestma et al. 1984). Most often, death is presumed to result from suffocation, cardiac arrhythmia, or pulmonary edema. Suffocation is usually considered when there are obvious environmental contributing factors. Ictal increases in plasma epinephrine sufficient to produce cardiac arrhythmias may account for some cases of sudden death (Clutter et al. 1980; Simon et al. 1984). The most recent information on mortality in epilepsy comes from a major epidemiological study by Annegers et al. (1984). They studied mortality, and specifically the relationship of cardiac-related causes, in patients with epilepsy in Rochester, Minnesota from 1935 to 1979. Death rates were twice those in the general population. Heart disease was a significant factor only in patients below 65 years of age, and the incidence of myocardial infarction was increased in patients with both idiopathic and symptomatic epilepsy. Sudden cardiac death, however, was increased only in patients with symptomatic epilepsy in which cerebrovascular disease was the presumed cause. Sudden cardiac death was not increased in patients with idiopathic seizures. No data were provided about anticonvulsant drug levels at the time of death.

Pulmonary edema is said to be an infrequent complication and, indeed, relatively few well-documented cases have been reported in the English literature (Archibald and Armstrong 1978; Terrence et al. 1975). It is likely to be more common than believed, however (Simon 1985). A diagnosis of postictal pulmonary edema is not usually made, first because it is not frequently thought of, and second because the chest X-ray, if obtained, may be misinterpreted as showing pneumonia. This latter diagnosis may seem to be supported by the fever and leukocytosis which can be present postictally. The salient diagnostic manifestations include hemoptysis and a chest X-ray showing either the classic "butterfly" pattern or, less often, increased vascularity restricted to the upper lung fields. Very rarely, the chest X-ray shows a unilateral pattern of involvement (Greene et al. 1975). The EKG is usually normal (Archibald and Armstrong 1978). Most cases resolve rapidly with supplemental oxygen regardless of whether diuretics, digitalis, or antibiotics are used. Pulmonary edema is probably secondary to a seizure-induced increase in pulmonary vascular pressure (Simon 1985). Vascular pressures increase with the number of seizures, thus accounting for the observation that postictal pulmonary edema is more likely to be seen in the setting of multiple rather than single convulsions (Darnell and Jay 1982). Seizure-induced neuroendocrine effects probably mediate the increase in vascular pressure. Animal studies demonstrate that pulmonary deterioration can be largely prevented by sympatholytic agents, hypophysectomy, or adrenalectomy, but not by eliminating skeletal muscle activity by curarization (Bean et al. 1966).

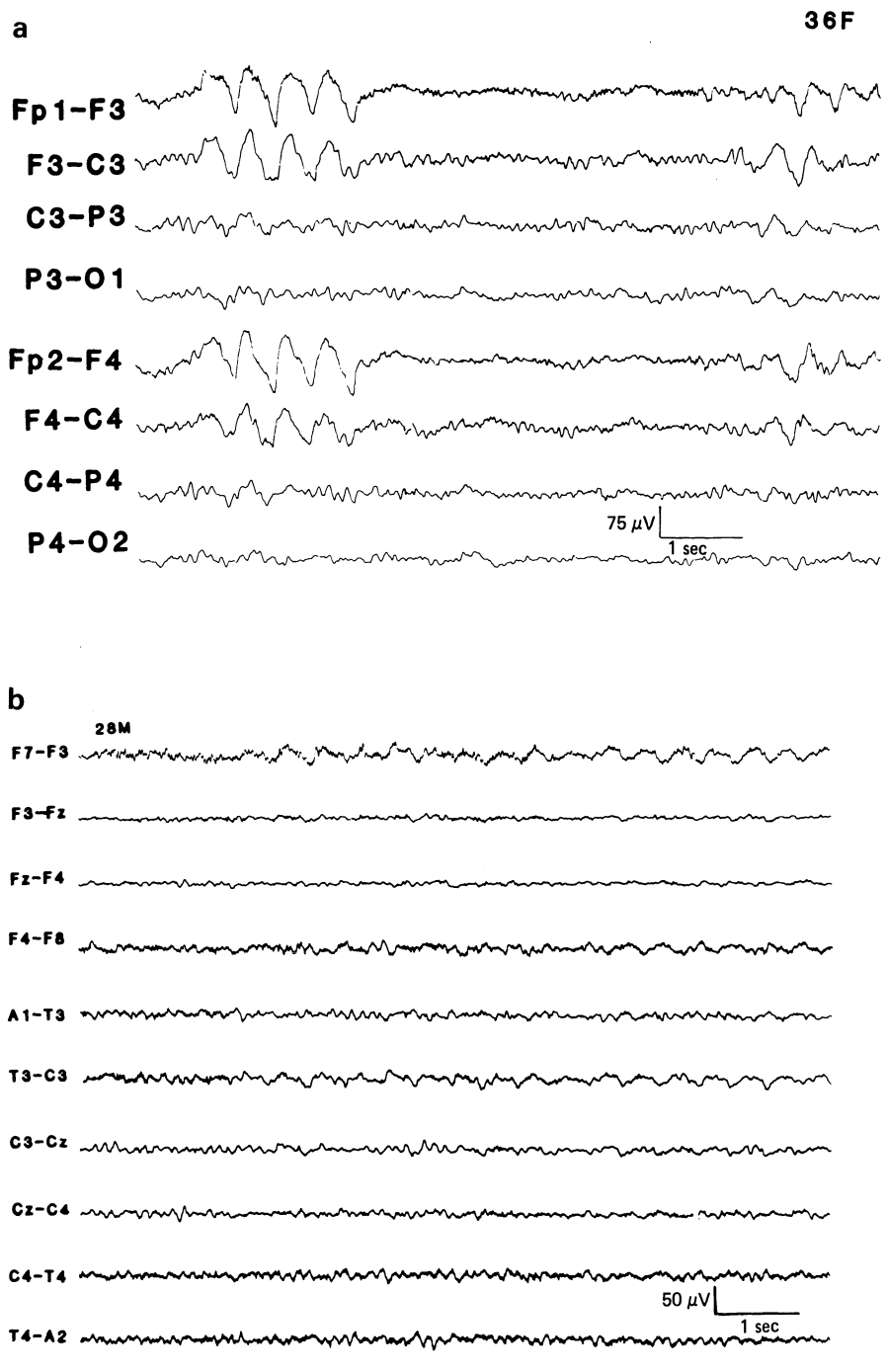

Fig. 8.2a,b. Nonspecific interictal EEG findings in two patients with generalized tonic–clonic seizures. In **a**, bursts of bisynchronous rhythmic delta waves occur, a nonspecific indication of dysfunction of thalamocortical interconnections. In **b**, runs of rhythmic delta waves appear focally over the left temporal region. Sphenoidal leads demonstrated rhythmic interictal spiking from the mesial temporal area coincident with most of the surface delta activity. Even with video monitoring, however, there were no clinical clues to the focal origin of the seizures.

EEG Manifestations

Interictal Findings

Nonspecific Changes

Background activity of patients with primary generalized tonic–clonic seizures is usually unremarkable. A common abnormal finding is bursts of intermittent medium- to high-voltage rhythmic delta waves occurring in a generalized distribution but with a clear frontal accentuation (Fig. 8.2). There may also be a mild diffuse increase in slower frequencies which are intermixed randomly with ongoing normal background rhythms. A moderate to marked increase in slower frequencies is seen postictally. The degree of slowing is in large part related to how soon after the seizure the EEG is obtained. Anticonvulsant drugs, particularly phenytoin, may slow the mean frequency of the basic posterior rhythm. Barbiturates and benzodiazepine derivatives produce an increase in synchronized rhythmic beta activity. This is usually generalized but most prominent over the anterior head regions. When tonic–clonic seizures occur in association with absence attacks, intermittent bursts of bioccipital 3-Hz rhythmic delta waves are common (Gastaut and Tassinari 1975). These patients also exhibit prolonged runs of 4- to 7-Hz parietal rhythms (Doose et al. 1973). All of these findings, while common in patients with primary generalized epilepsy, are non-specific and thus, by themselves, provide no support for the diagnosis of epilepsy.

In secondary (symptomatic) epilepsies, nonspecific abnormalities of background rhythms are the rule, and usually consist of varying degrees of diffuse excessive slowing and disorganization.

In patients with secondarily generalized tonic–clonic seizures, focal or lateralized slow activity, or voltage asymmetries, provide a clue to the partial origin (Fig. 8.2b).

Epileptiform Activity

Gibbs and Gibbs (1952) found epileptiform activity in 49% of 2430 patients with a history of generalized tonic–clonic seizures. Ajmone-Marsan and Zivin (1970) reported epileptiform discharges on the first EEG in 58% of 228 patients with generalized tonic–clonic seizures. thirty-two percent of these had epileptiform activity on every recording when serial examinations were performed. They also observed that EEGs recorded between 1 and 5 days following a seizure increased the likelihood of obtaining a positive record.

The most common interictal epileptiform pattern is generalized spike–wave activity. This takes several forms, including single generalized spikes, 4- to 5-Hz spike–wave complexes, spike–wave bursts of more irregular frequency, and multiple spike ("polyspike")–wave paroxysms (Fig. 8.3). Bursts of epileptiform discharges usually last 1–4 s. The EEG of a given patient may include one form predominately or show a combination of two or more variants. To the extent such

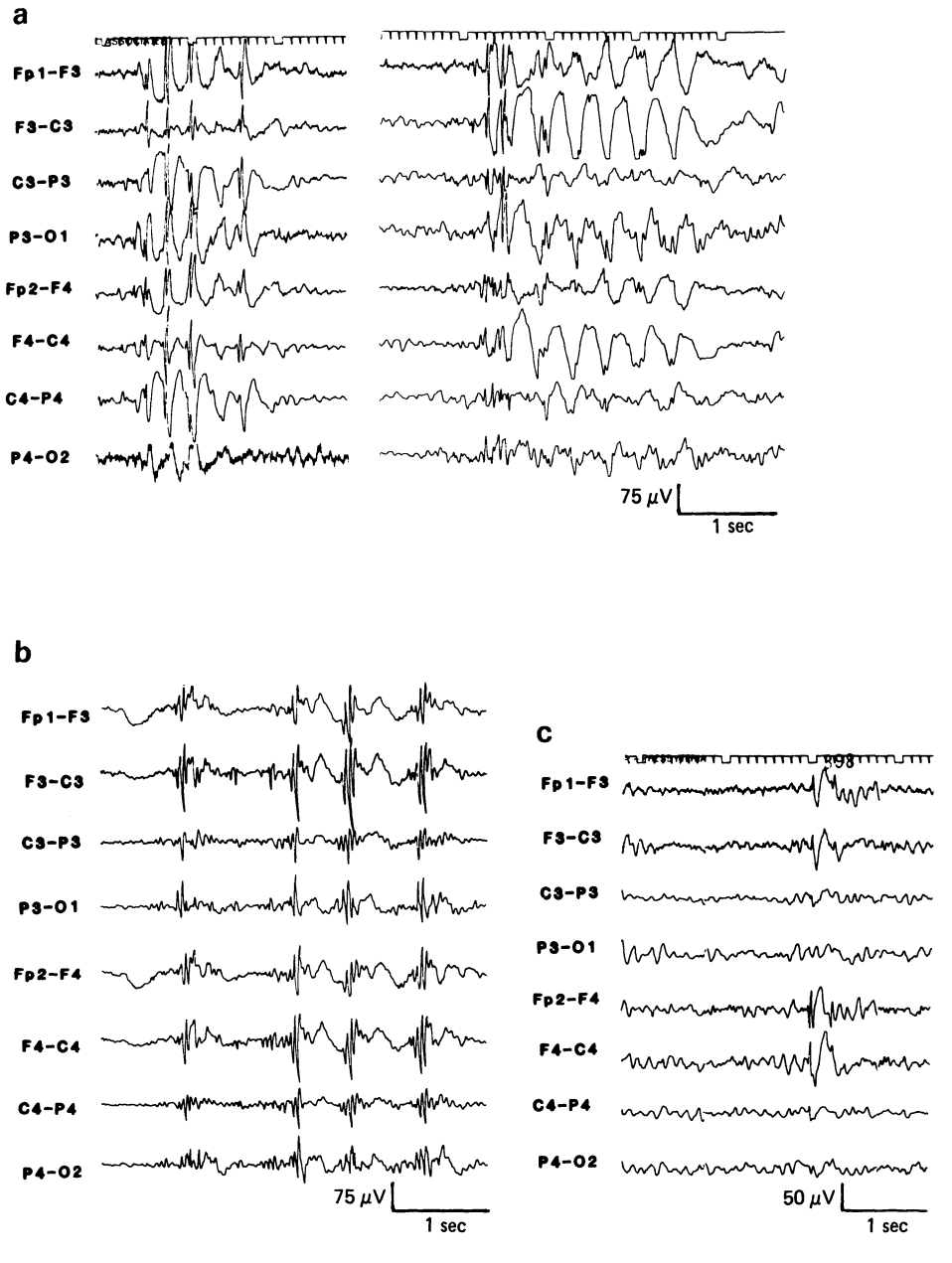

Fig. 8.3a–c. Various interictal epileptiform patterns recorded in different patients with generalized tonic–clonic seizures. Generalized, bisynchronous spikes and irregular spike–wave discharges are most common **a.** Multiple spike bursts ("polyspikes") can also occur **b.** Sometimes, the generalized abnormality is only partially expressed, usually as isolated bifrontal spike–wave events as shown here **c.** These may be transiently quite asymmetrical, and by themselves should not be taken as an indication of focal seizure onset.

epileptiform activity differs in morphology and frequency from the classic 3-Hz spike–wave pattern of absence seizures, it is sometimes referred to as "atypical spike–wave" or "rapid spike–wave." Epileptiform activity that is primarily generalized appears bilaterally symmetrical and synchronous. Rarely, the epileptiform discharges may appear lateralized or be otherwise asymmetrical. In such cases the EEG should be repeated to reduce the possibility of errors in electrode placement or the possibility that the apparent asymmetry is a sampling effect since all epileptiform patterns show some variability over time.

Spikes are usually polyphasic, and have a voltage maxima over the frontal regions. Aftergoing slow waves are also maximal over the anterior head areas but may have a different topography than the spikes. Rarely and usually in children, spike–wave complexes may be maximal over the posterior scalp. Typical 3-Hz spike–wave discharges may occasionally be seen in patients with only tonic–clonic seizures ("pure grand mal") (Gastaut and Tassinari 1975). Usually, however, they occur in combination with "atypical" spike–wave patterns, and clinically such patients have mixed seizures (e.g., tonic–clonic and absence attacks). When epileptiform activity consists largely or exclusively of fast multiple spike–wave bursts, myoclonic seizures are the rule.

Sleep has a characteristic modifying effect on the morphology of generalized spike–wave activity. During non-REM sleep, epileptiform bursts become fragmented, multiple spikes are more likely to occur, and the generalized epileptic susceptibility may be only partially expressed as focal or lateralized spikes (Niedermeyer 1966; Broughton 1984). Under such circumstances, care must be taken not to interpret a primarily generalized disturbance as focal, multifocal, or secondary bilateral synchrony. Generalized epileptiform activity is markedly depressed or disappears altogether during REM sleep (Cadilhac et al. 1965; Broughton 1984).

Primary vs. Secondary Bilateral Synchrony

Tükel and Jasper (1952) introduced the term "secondary bilateral synchrony" to describe the phenomenon of a unilateral cortical focus giving rise to apparently generalized bisynchronous spike–wave bursts. Specifically, they studied a group of patients with mesial hemispheric epileptogenic lesions whose scalp EEGs showed only bilateral paroxysmal activity. They hypothesized that the bilateral discharges were "secondary" to a centrencephalic pathogenetic mechanism that had been triggered by a cortical focus. They contrasted this with the then current concept of "primary" bilateral synchrony, where generalized spike–wave activity was initiated exclusively through the centrencephalic system. Unfortunately, the concept has been applied so indiscriminately that it has lost much of its original meaning. For example, inexperienced electroencephalographers commonly misinterpret focal frontal spikes in the context of otherwise typical generalized spike–wave activity as evidence of secondary bilateral synchrony. Furthermore, the entire concept must be reconsidered in the light of present concepts of the pathogenesis of generalized epilepsy (see below).

Nonetheless, it is clear that under some circumstances, bilateral spike–wave discharges may indeed be secondary to an isolated epileptogenic cortical focus, removal of which has the potential for eliminating all EEG epileptiform activity

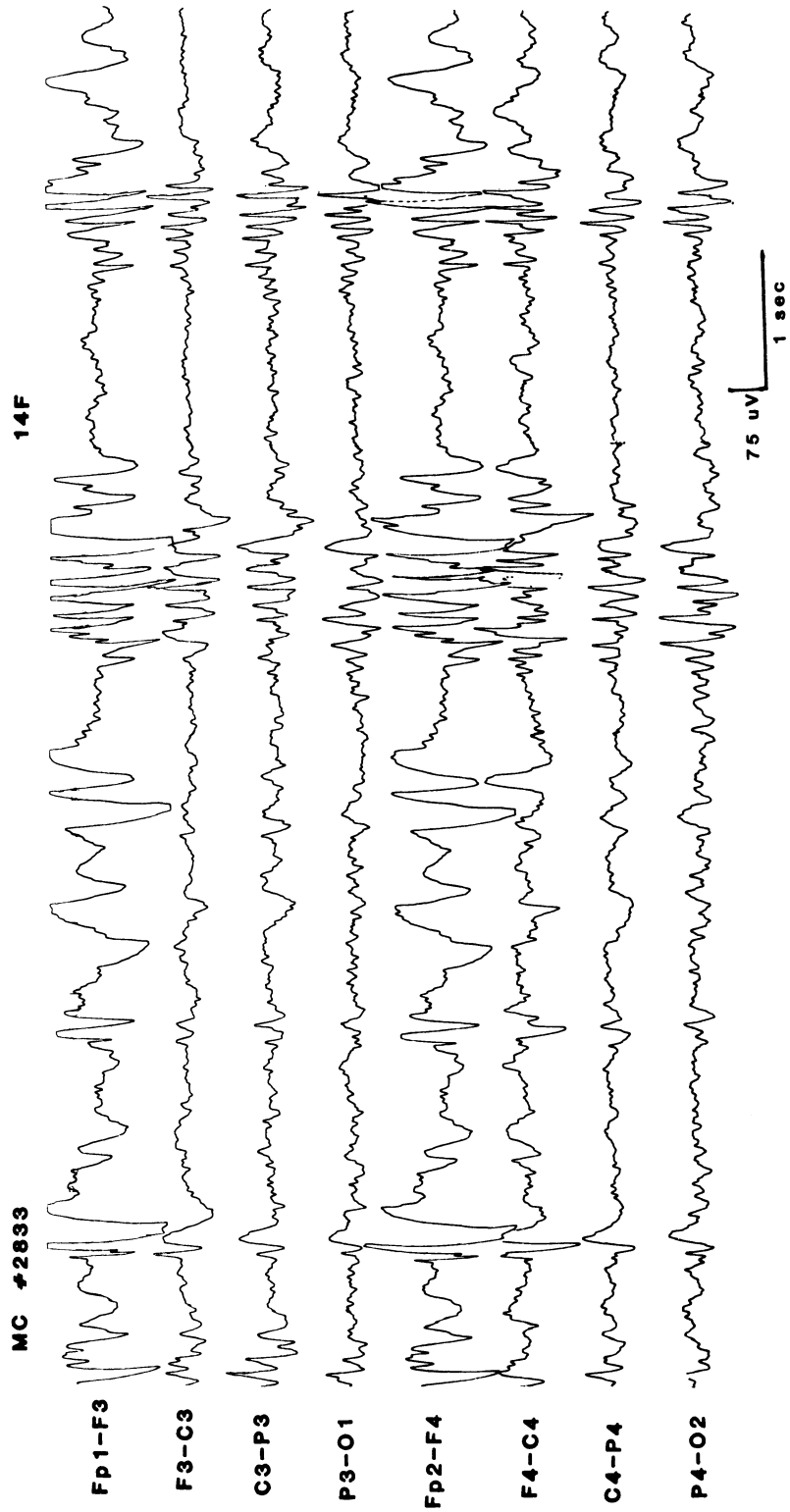
MC #2833
14F
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
75 uV
1 sec

Fig. 8.4a

(Fig. 8.4). Lesions giving rise to secondary bilateral synchrony are classically located in the mesial frontal cortex (Tükel and Jasper 1952; Pedley et al. 1981), but other cortical areas, including the temporal lobe, may be involved (Klass 1975). We believe that specific electrographic criteria are necessary to classify a generalized discharge as secondary bilateral synchrony. The coexistence of focal spikes and generalized epileptiform discharges should never, by itself, be taken to indicate a focal onset for seizures with secondary generalization. Additional features to be looked for that suggest secondary bilateral synchrony include (a) frequent spikes or sharp waves that occur repetitively in a localized area; (b) a different morphology of the focal spikes compared with the generalized paroxysms; (c) a lateralized focal build up that appears to precede and initiate the generalized disturbance; and (d) other evidence of focal dysfunction such as localized slowing or attenuation of

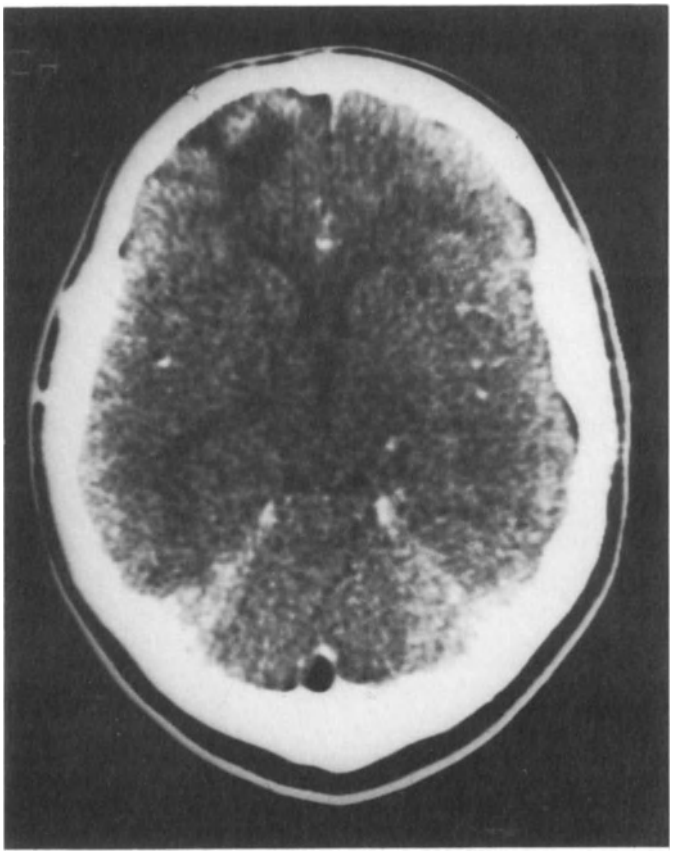

Fig. 8.4b

Fig. 8.4. **a** Secondary bilateral synchrony from a right frontal epileptogenic focus. The lesion shown on CT **b** was a cystic ganglioglioma. Resection of the lesion and surrounding gliotic epileptogenic cortex eliminated the generalized spike bursts. The EEG sample in **a** shows somewhat greater slowing over the right frontal region. Other parts of the recording more clearly showed right frontal focal delta, attenuation of background faster frequencies, and localized spikes and sharp waves.

background rhythms. At times, the surface reflection of a discharging epileptogenic focus may appear as localized rhythmic delta waves (Fig. 8.2b). Indeed, prolonged runs of focal rhythmic delta activity should always suggest this possibility. Clinical or radiographic evidence of a focal cerebral lesion provides other evidence in difficult situations. It must be recognized that a longitudinal parasagittal bipolar montage may not optimally display a mesial parasagittal focus; transverse montages which include midline electrodes should be used routinely.

Several special methods have been devised to help distinguish between primary and secondary bilateral sunchrony. Noninvasive techniques rely mainly on computerized analysis of interhemispheric synchrony (Daube et al. 1973). Secondary bilateral synchrony can probably be inferred with assurance if a localized spike or sharp wave precedes each diffuse epileptiform burst by at least 20 ms (Klass 1975). Invasive tests include intracarotid injection of pentylenetetrazole or amobarbital (Gloor et al. 1964; Rovit et al. 1961) and intravenous thiopental (Lombroso and Erba 1970). Ideally, pentylenetetrazole will selectively activate a focal or generalized seizure discharge when injected into the carotid circulation ipsilateral to an initiating epileptogenic focus. In contrast, administration of an equivalent dosage contralaterally will fail to induce a seizure. Similarly, amobarbital will suppress bilateral spike–wave activity when injected into the carotid circulation ipsilateral to the triggering focus, but a comparable injection into the uninvolved hemisphere has no effect. Use of intravenous thiopental is based on a similar concept, but small amounts are employed to suppress generalized epileptiform activity while allowing focal discharges to persist in cases of secondary bilateral synchrony.

Asymptomatic or Incidental Epileptiform Activity

Generalized spike–wave bursts may occur in individuals without a history of seizures. In adults this is rare. Zivin and Ajmone-Marsan (1968) found that only 0.7% of 6497 patients without epilepsy had generalized epileptiform activity. The situation is more complicated in children, in part because in the past, a variety of normal patterns (e.g., hypnagogic bursts, V-waves of light sleep, arousal responses, and hyperventilation-induced paroxysmal slowing) have been interpreted as epileptiform. Figures based on spontaneous waking EEGs alone underestimate the incidence of epileptiform abnormalities compared with results obtained if sleep is recorded as well. In addition, the incidence of epileptiform activity within childhood is strongly age specific. Finally, recent data suggest that epileptiform responses elicited by photic stimulation are related to, but under separate genetic control and therefore additive to, spontaneous spike–wave discharges (Doose et al. 1973; Hauser et al. 1983). With these reservations in mind, the following observations are pertinent to children. Metrakos (1961) and Metrakos and Metrakos (1961) reported that 37% of siblings of probands with spike–wave epilepsy had EEGs demonstrating generalized epileptiform activity compared with a 5% incidence in controls. These figures are clearly overestimates because of reservations alluded to earlier. Gerken and Doose (1973) found generalized spike–wave bursts in 1.8% of the EEGs of 685 normal children. If the child had a first-degree relative with spike–wave epilepsy, however, the incidence peaked at 12%–13% at 3–6 years of age, fell to 1.4% at 9–10 years, and rose again to 9.7% at 15 years. Their data suggested that a "regular" spike–wave pattern was more strongly linked than was an "irregular" spike–wave pattern. Recently, Cavazzuti et al.

(1980) recorded EEGs in 3726 normal children, none of whom had a history of epilepsy. There was a 3.54% incidence of all types of epileptiform activity; the incidence of spike–wave discharges in particular was 1.1%.

Bifrontal or diffuse spike–wave bursts can occur within 1–10 days of anticonvulsant drug withdrawal (Ludwig and Ajmone-Marsan 1975). Under these circumstances, the epileptiform activity should be viewed as nonspecific activation probably related to metabolic changes precipitated by drug discontinuation. Thus, caution is warranted in interpreting diffuse spike–wave activity during anticonvulsant, especially barbiturate, withdrawal so that a patient is not diagnosed erroneously as having generalized epilepsy.

Photosensitivity

Intermittent visual stimulation is a well-known precipitant of epileptiform activity, or even seizures, in susceptible individuals. The three main categories of effective stimuli are (a) a flickering diffuse light source such as a stroboscopic light or television; (b) a stationary or moving specific pattern [or rarely an object (Klass and Daly 1960)] presented at constant luminance (Bickford et al. 1953; Chatrian et al. 1975; Wilkins et al. 1975); and (c) a pattern (or object) intermittently illuminated (Engel 1974; Jeavons and Harding 1975; Stefannson et al. 1977; Takahashi 1983). Individuals may be susceptible to any one of these stimuli alone or in any combination (Bickford et al. 1953; Gastaut and Tassinari 1966; Wilkins and Lindsay 1984). The EEG responses to stroboscopic stimulation are classified as photic driving, photomyogenic (photomyoclonic), and photoparoxysmal (photoconvulsive).

Photic driving is normal bioccipital rhythmic activity that is time locked or harmonically related to the stimulus frequency.

The photomyogenic response occurs in about 20% of normal individuals (Bickford 1979). It is not of cortical origin, but instead comprises repetitive muscle spikes that are maximally recorded from frontal electrodes. The muscle activity appears to recruit after the photic stimulus starts, but disappears promptly when the stimulus is stopped. It is often attenuated by eye opening. Accompanying eye flutter and discrete jerking of the head and neck are common. Although the incidence of photomyogenic responses is increased in some metabolic and toxic encephalopathies, such as uremia or drug withdrawal, the finding has no useful clinical significance, and certainly no relationship to epilepsy.

The photoparoxysmal response is characterized by symmetrical, bisynchronous, generalized bursts of irregular spikes and spike–wave discharges which are not time locked or harmonically related to the flash frequency (Fig. 8.5). Flash frequencies most effective in eliciting a photoparoxysmal responses range from 10 to 20 per second. The degree of photosensitivity is directly related to the intensity of the light stimulus, and monocular occlusion will attenuate or even obliterate the response in some individuals (Procopis and Jameson 1974). Sometimes a photosensitive patient will demonstrate differential responses to specific colors, with red usually being the most provocative (Troupin 1966; Brausch and Ferguson 1965). Typically, the induced epileptiform activity is not associated with clinical manifestations, but if an effective stimulus is continued, or if the individual is unusually photosensitive, myoclonic jerks, absence attacks, or even a tonic–clonic convulsion may occur. Most patients with photoparoxysmal responses do not have light-

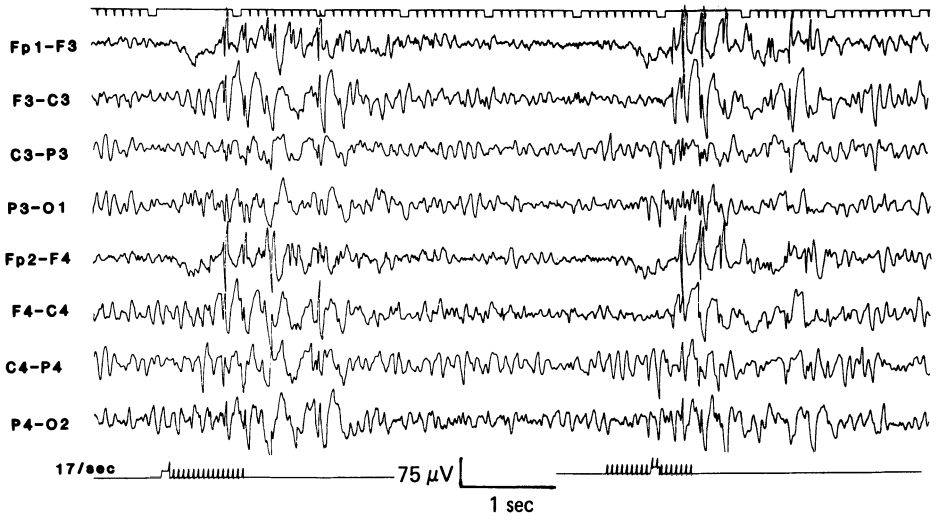

Fig. 8.5. Photoparoxysmal response consistently elicited by intermittent flash frequencies in a patient with generalized tonic–clonic seizures but no clinical photosensitivity.

sensitive epilepsy. Rather, the photoparoxysmal response may be viewed as a genetic marker in patients with primary generalized epilepsy or in individuals with a family history of seizures. The incidence of photoparoxysmal responses is clearly age dependent, although exact figures vary from study to study. In adults, it is estimated that fewer than 2% of normal individuals without a personal or family history of epilepsy have a photoparoxysmal response (for review, see Newmark and Penry 1979).

Ictal Findings

Patients with primary generalized epilepsy often have a normal EEG until onset of the tonic phase. In many patients, generalized bursts of rapid multiple spikes and spike–wave bursts associated with bilateral myoclonic jerks precede the attack. Infrequently, the seizure evolves from one or more typical absence attacks accompanied by 3-Hz spike and slow wave (Fig. 8.6).

Regardless of any changes in preceding background activity, the electrographic onset of the generalized tonic–clonic seizure is always characterized by generalized voltage attenuation (desynchronization), with symmetrical very low voltage rhythms in the 20- to 40-Hz range being recorded simultaneously from all leads (Fig. 8.7). Later electrographic events are usually obscured by muscle artifact. This may be reduced by partial muscular paralysis with curare, as in Fig. 8.7. As the seizure progresses, synchronized monorhythmic activity emerges that gradually increases in voltage as the frequency of the electrical discharge slows to approximately 10 Hz. Gastaut and Fischer-Williams (1959) named this 10-Hz discharge the "epileptic recruiting rhythm" because its initial increase in voltage and

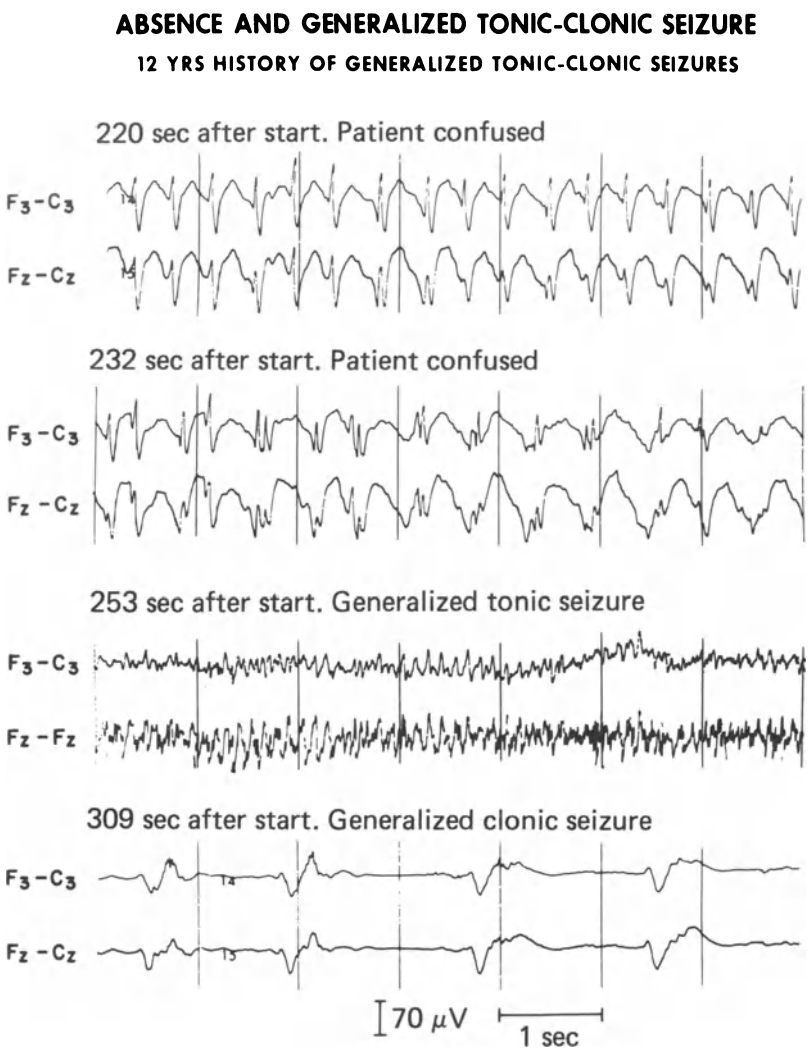

Fig. 8.6. Evolution from absence to generalized tonic–clonic seizure (Lüders et al. 1984)

subsequent modulation seemed similar to the thalamic recruiting rhythm of Dempsey and Morison (1942). Using frequency analysis techniques, a 10-Hz rhythm has also been noted during other types of generalized seizure (Gastaut and Tassinari 1975). After about 10 s, an intermixed rhythm approximating 8 Hz appears, gradually slowing to about 1 Hz as it replaces the epileptic recruiting rhythm. The intermixture of rhythmic slow waves and fragments of the recruiting rhythm appears on the EEG as periodic bursts of multiple spikes followed by slow waves. Tonic muscle contractions give way to interrupted muscle tone when the slower EEG rhythm reaches about 4 Hz. The progressive decrease in frequency of the rhythmic EEG discharge paces the increasingly longer intervals of muscle atonia which characterize the clonic phase of the fit.

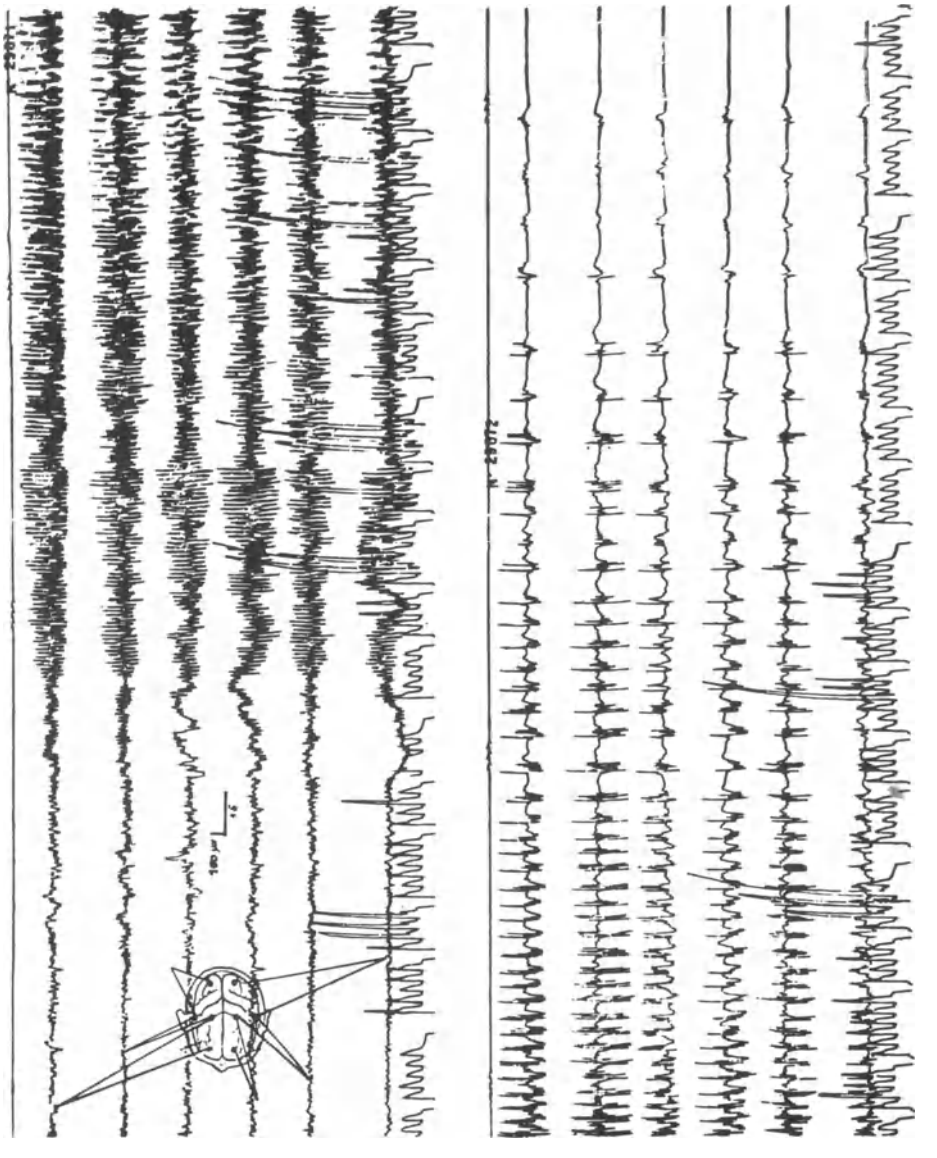

Fig. 8.7. EEG discharge during a generalized tonic-clonic seizure. The patient was partially paralyzed with curare so there is relatively little muscle contamination. See text for further details. The bottom recording channel is a continuous print-out from a Grey Walter frequency analyzer connected to the left temporo-occipital derivation. (Gastaut and Broughton 1972).

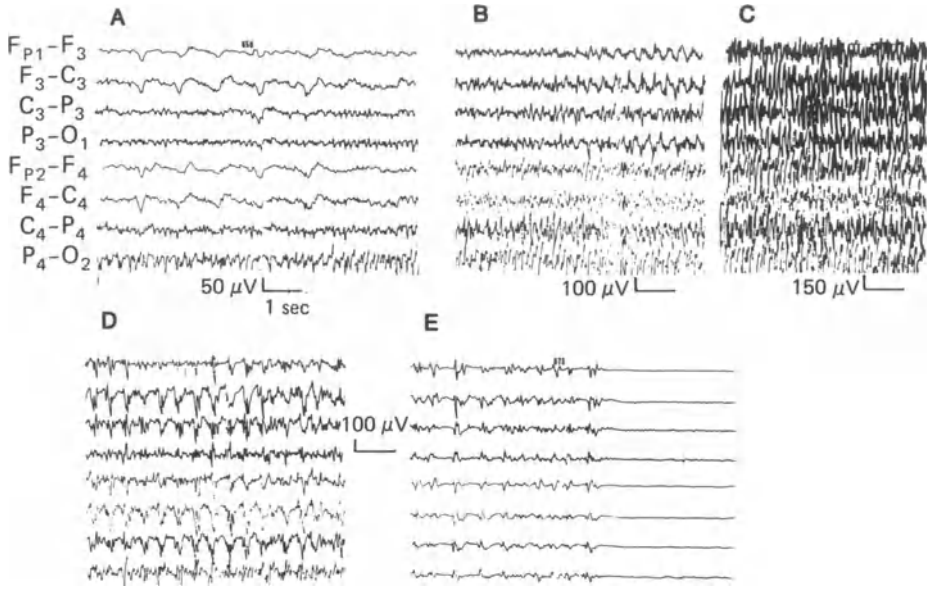

Fig. 8.8a–e. EEG discharge from a secondarily generalized tonic–clonic seizure. This patient had a right occipital metastasis. The ictal episode begins focally in the right occipital region with subsequent ipsilateral and contralateral homologous spread. The tonic and clonic phases are identical to a primarily generalized tonic–clonic convulsion. The patient was completely paralyzed with curare so no muscle artifact is present.

Secondarily generalized tonic–clonic seizures have three main patterns of onset: (a) brief, localized voltage attentuation or low voltage, fast activity; (b) a build-up of focal rhythmic activity; and (c) focal rhythmic or arrhythmic epileptiform spiking (Fig. 8.8). Other less reliable findings include local or lateralized arrhythmic slowing, or a build-up of interictal epileptiform discharges preceding the seizure in the absence of a clear ictal onset. Once the tonic phase is established, the ictal patterns of primarily and secondarily generalized seizures are virtually identical (Fig. 8.8).

Following the last clonic movement, the EEG is bilaterally depressed, showing only polymorphic delta averaging less than 20 μV. The duration of this flattening is related to the length of the seizure and the number of preceding convulsions. Although the EEG may return to preictal baseline almost immediately after generalized myoclonic and tonic fits, it never does after a generalized tonic–clonic seizure. This is an important point in differentiating nonepileptic paroxysmal behaviors (e.g., psychogenic seizures) from epileptic seizures.

Several seconds after the onset of postictal EEG depression, the postictal tonic phase begins (Fig. 8.1). This persists into and disappears during the phase when EEG activity becomes characterized by higher voltage delta waves. The subsequent return of EEG activity to normal closely mirrors the clinical progression as

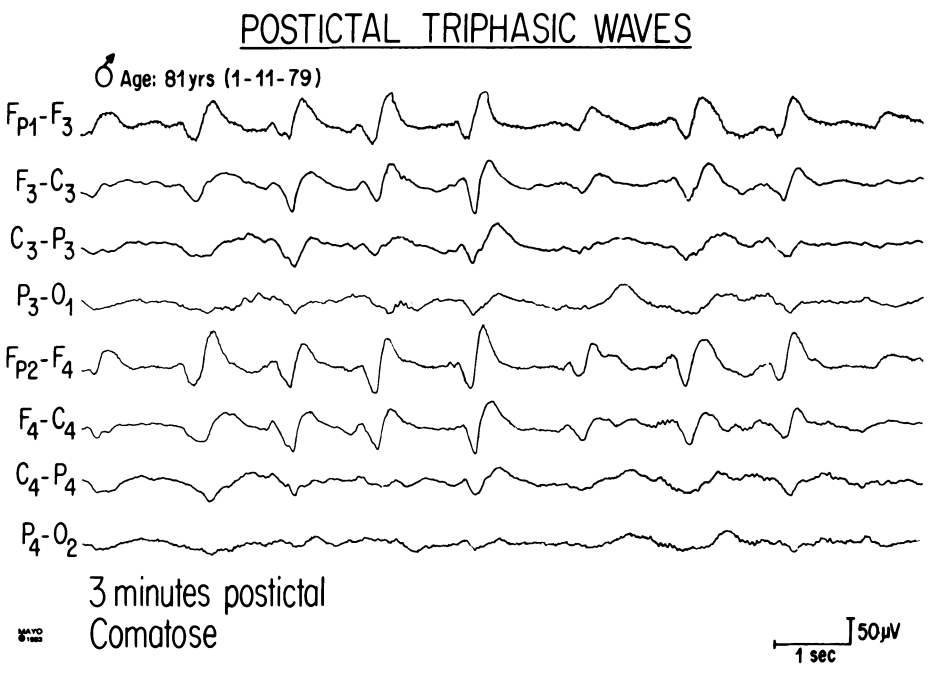

Fig. 8.9. Triphasic waves occurring in the immediate postictal period of a generalized tonic–clonic seizure.

the patient evolves from coma to normal consciousness. Infrequently, a burst suppression pattern (Lüders et al. 1984) or periodic triphasic waves (Fig. 8.9; Fisch and Klass 1986, and in preparation) can be seen postictally. Secondarily generalized seizures may be followed by predominantly focal or lateralized postictal slowing. When a focal signature is not appreciated at seizure onset, postictal focality has the same meaning. Some degree of postictal EEG slowing may persist for many hours, especially in children or when multiple seizures have occurred. In adults, however, most EEG changes resulting from a single typical tonic–clonic seizure lasting 1–2 min will resolve within 30 min. There are many exceptions, however, and as a practical interpretive point, it is best to accept mild degrees of diffuse slow activity as being probably postictal in origin for 24 h after a single tonic–clonic seizure. This interval will be longer in young children or in the setting of multiple frequent convulsions.

Pathophysiology

There is considerably more information about the cellular mechanisms of focal epileptogenesis than about those of generalized seizures. Factors important in seizure initiation, propagation, and termination are all poorly understood. The newer techniques of neurobiology have yet to be applied successfully to a model of

generalized epilepsy in ways that are analogous to the extensive sophisticated investigations undertaken successfully with various models of focal epilepsy.

Unlike the chronic focal epileptogenic lesion in animals or humans, which shows characteristic neuropathological features (Westrum et al. 1964; Scheibel et al. 1974; Mathieson 1975), the brains of patients with primary generalized epilepsy have not revealed any consistent specific anatomical or biochemical abnormalities. Recently, however, Meencke and Janz (1984) reported neuropathological findings in eight patients with clinical and EEG features of primary generalized epilepsy. None of the specimens showed changes that could be attributed to epileptic (hypoxic-ischemic) brain damage. In seven brains, there were significant degrees of "microdysgenesis" which included abnormally located groups of neurons, immaturity of cortical columnar organization, regional changes in cell density, indistinct boundaries between histological zones, and protrusions of brain tissue into the pia. The functional implications of these changes for epileptogenesis are unclear, and further quantitative studies of larger numbers of patients will be required before any conclusions can be drawn.

Some insight into factors necessary for generalization of epileptic discharge is provided by ontogenetic studies. Generalized tonic–clonic seizures do not occur in newborn infants, and are rare in the first 6 months of life (Dreyfus-Brisac and Monod 1964; Gomez and Klass 1983; Niedermeyer 1982b). Similar observations have been made on the immature young of other species using experimentally induced cortical epileptogenic lesions. Developmental factors preventing the elaboration of tonic–clonic activity include (a) the immaturity of important pathways of propagation, including corpus callosum and intracortical arcuate fibers (Caveness 1969); (b) incomplete myelination which would affect the rapidity and synchrony with which neuronal interactions can develop (Hess 1954; Huttenlocher 1970); (c) alteration in the relationship between excitatory and inhibitory synaptogenesis (Purpura 1969; Schwartzkroin and Altschuler 1977; Schwartzkroin 1982); (d) reduced maximum spike frequency in immature neurons (Prince and Gutnick, 1972); and (e) structural immaturity of synaptic connections (Dyson and Jones 1976).

The first major modern theory of primary generalized seizure propagation proposed that the critical factor was an epileptogenic discharge originating in a "central integrating system of the higher brainstem" (Penfield and Jasper 1954). Such seizures were called "centrencephalic seizures" in accord with their proposed site of origin. The centrencephalic theory had its origin in several important observations. First, the apparently bisynchronous onset involving every area of cortex simultaneously seemed to require a subcortical generator. Second, the seminal studies of Dempsey and Morison (1942), demonstrating the existence of a diffuse nonspecific projection system of thalamocortical connections by which medial and intralaminar thalamic nuclei could induce widespread cortical rhythmic activity, were having an enormous influence on the thinking of cortical neurophysiologists. Such a system seemed to provide at least part of the substrate required to explain the origin of generalized seizures. Finally, an electrographic pattern approximating 3-Hz spike and slow-wave complexes could be produced in anesthetized or cervical isolé-prepared cats by electrical stimulation of the medial intralaminar region of the thalamus (Jasper and Droogleever-Fortuyn 1946). Later, additional support for a centrencephalic origin of primary generalized tonic–clonic seizures was provided by Rodin et al. (1969). They recorded a midbrain reticular discharge of frequencies greater than 1000 Hz at the beginning

of the tonic phase of megimide-induced seizures in cats. Thalamic and cortical structures became involved only after the very fast firing was recorded in the brain stem. Browne (1983) has recently emphasized these findings in advocating a brain stem origin for generalized tonic–clonic seizures.

In recent years, the centrencephalic theory has been considerably modified in the light of findings that the clinical and electrographic features of absence seizures can be reproduced experimentally without direct involvement of subcortical structures. This new emphasis on a primary role for neocortical involvement in generalized epileptogenesis has largely been the work of Gloor and his colleagues (for reviews, see Gloor 1968, 1984). The evidence for a "corticoreticular" mechanism may be summarized as follows. High doses of parenteral penicillin induce bilaterally synchronous bursts of 3- to 5-Hz diffuse spike–wave discharges in cats. These are often accompanied by staring, repetitive eye blinks and facial myclonus. Spike–wave activity always appears first in cortex, never in thalamus or brain stem (Fisher and Prince 1977; Avoli et al. 1983). Detailed timing studies demonstrate that the interhemispheric synchrony is only approximate, and any one cortical area may appear first to lead a spike–wave burst and then follow other cortical areas in subsequent bursts (Fisher and Prince 1977). The spike–wave activity results from a direct action of penicillin on the cortex; application to the thalamus is ineffective in producing epileptiform discharges. Maintenance of intrahemispheric synchrony requires an intact corpus callosum (Musgrave and Gloor 1980).

Although abnormal cortical excitability or reactivity is an essential requirement for generation of spike–wave epilepsy, the feline model indicates the importance of thalamus and brain stem reticular formation as well. Electrographic discharges that sometimes mimic those of a tonic–clonic seizure can arise in isolated cortex (Ingvar 1955; Halpern 1972), but intact thalamocortical connections are necessary for penicillin-treated cortex to develop rhythmic 3- to 5-Hz spike–wave complexes (Pellegrini et al. 1979). Furthermore, thalamic input appears to be the trigger mechanism for spike–wave bursts. Thalamic stimuli which under ordinary circumstances induce spindles or recruiting responses elicit spike–wave bursts in the penicillin model. Depression of thalamic function, either by thalamectomy or by intrathalamic injection of potassium chloride, eliminates the occurrence of spike–wave discharges.

Finally, the brain stem reticular formation appears to be an important modulator of spike–wave activity by modifying the level of cortical excitability (Gloor 1984).

Clinical evidence in support of a primary cortical role for generalized epilepsy comes from cases of secondary generalized epilepsy in which a focal cortical lesion, usually frontal or mesial frontal, has resulted in the clinical and EEG picture of generalized absence, tonic, or tonic–clonic seizures (Tükel and Jasper 1952; Gloor 1968; Farwell and Stuntz 1984).

We believe that pathophysiological theories of generalized seizures, in the absence of contradictory experimental evidence, should conform to a unified concept of epileptogenesis that encompasses acute and chronic focal seizures, and primary and secondary epilepsies as well. We are impressed by evidence that indicates the fundamental abnormality is one of excessive cortical excitability. It is our hypothesis that in the generalized epilepsies, genetic or acquired pathological processes diffusely but selectively alter cortical inhibition, perhaps differentially in a laminar or topographic fashion. The extent and severity of the basic disturbance would then determine whether a patient has only absence seizures, tonic–clonic

convulsions, or other types of generalized seizure (Benardo and Pedley 1984; Pedley and Traub 1985).

The mechanisms whereby tonic–clonic seizures are terminated are especially poorly understood, and no coherent explanation is possible at this time. At the cellular level, sustained depolarization during the clonic period is followed by postictal hyperpolarization that corresponds to the period of EEG depression (Oakley et al. 1972; Ward 1983). Recovery of normal EEG activity is associated with return of cell membrane potential and EPSP and IPSP activities to normal. These phenomenological observations, however, do not provide insights into the actual events that terminate seizures. There is no evidence for activation of a widely projecting inhibitory system, and "neuronal exhaustion" is also unlikely.

Prognosis

Recent studies of prognosis in epilepsy (Annegers et al. 1979; Group for the Study of the Prognosis of Epilepsy in Japan 1981; Sofijanov 1982; Goodridge and Shovron 1983; Elwes et al. 1984) show an almost twofold increase in the chances of a greater than 1-year seizure-free remission compared with previous studies (Rodin 1968; Juul-Jensen 1964; Trolle 1961; Alstroem 1950). Unfortunately this probably reflects improved study methodology rather than improved treatment. This conclusion is supported by the comprehensive epidemiological study of Annegers and colleagues (1979), which found similar remission rates for patients with epilepsy in the periods 1935–1959 and 1960–1974.

About 85% of patients with idiopathic generalized tonic–clonic seizures experience a 5-year continuous remission in the first 20 years after onset (Annegers et al. 1979). Juul-Jensen and Foldspang (1983) found that 47% of patients with "grand mal" epilepsy were seizure-free more than 2 years from diagnosis. In addition, the prognosis of patients with only idiopathic tonic–clonic seizures is superior to that of patients with focal seizures or secondarily generalized seizures (Fig. 8.10) (Annegers et al. 1979; Group for the Study of the Prognosis of Epilepsy in Japan, 1981; Elwes et al. 1984). For patients with idiopathic tonic–clonic seizures who have been in remission for 5 years, there is a 21% chance of relapse within 20 years (Annegers et al. 1979).

Secondarily generalized tonic–clonic seizures have a less favorable prognosis. Some authors have reported a particularly poor prognosis for the association of complex partial seizures and secondarily generalized convulsions (Juul-Jensen 1964; Rodin 1968; Group for the Study of the Prognosis of Epilepsy in Japan 1981), although this has been disputed by others (Currie et al. 1971; Schmidt et al. 1983). Two recent studies suggest that the frequency of generalized tonic–clonic seizures strongly affects the prognosis of individuals with complex partial and other types of seizure (Emerson et al. 1981; Schmidt et al. 1983). Emerson et al. (1981) found that the number of tonic–clonic seizures was one of the most significant prognostic indicators for likelihood of remission in all types of childhood epilepsy (Fig. 8.11).

Chance of remission among all patients with epilepsy is reduced if there are associated neurological deficits, especially if identified from birth, or if onset is in adult life (Fig. 8.12) (Annegers et al. 1979) Frequent seizures prior to initiation of

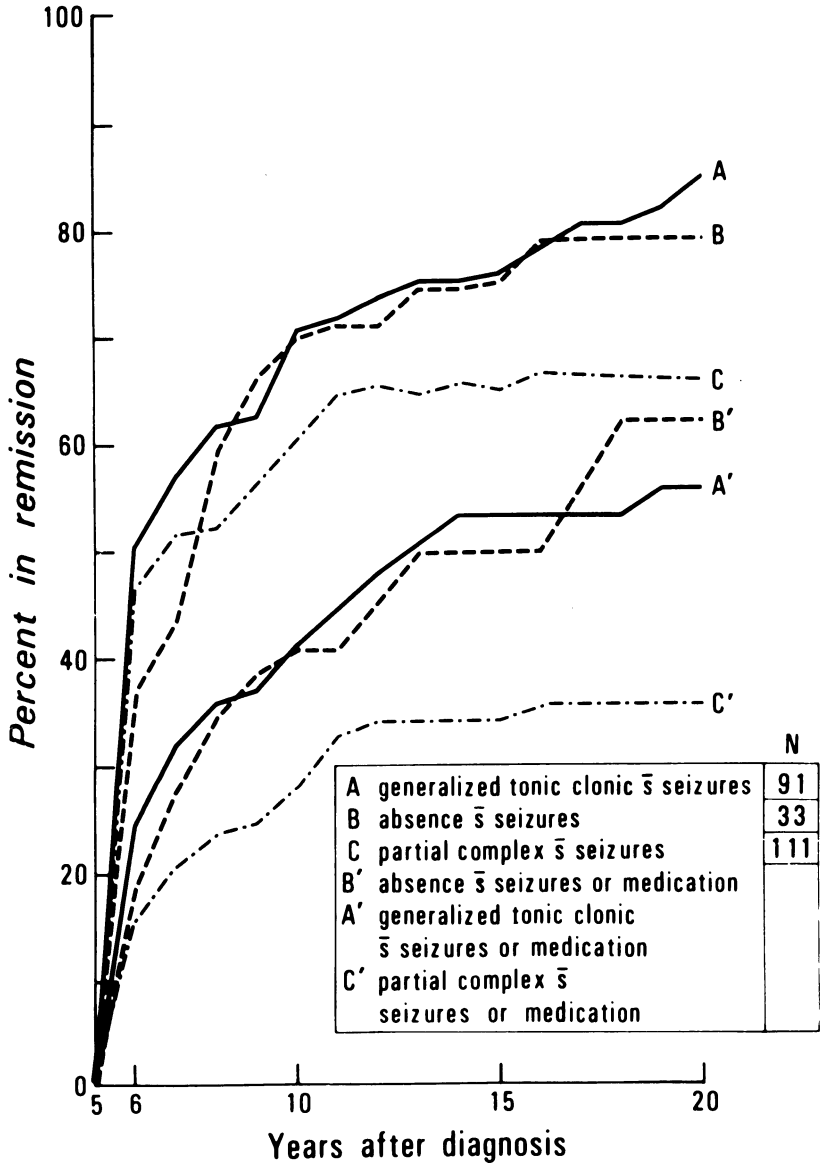

Fig. 8.10. Percentage of patients with idiopathic seizures in remission, by seizure type and medication status. (Annegers et al. 1979)

treatment adversely effect prognosis (Group for the Study of the Prognosis of Epilepsy in Japan 1981; Holowach Thurston et al. 1982; Elwes et al. 1984). In children with only tonic–clonic seizures, failure to enter remission within 2 years of onset appears to reduce significantly the chances of a subsequent remission within the next 3 years (Elwes et al. 1984). Among all patients with epilepsy, probability of

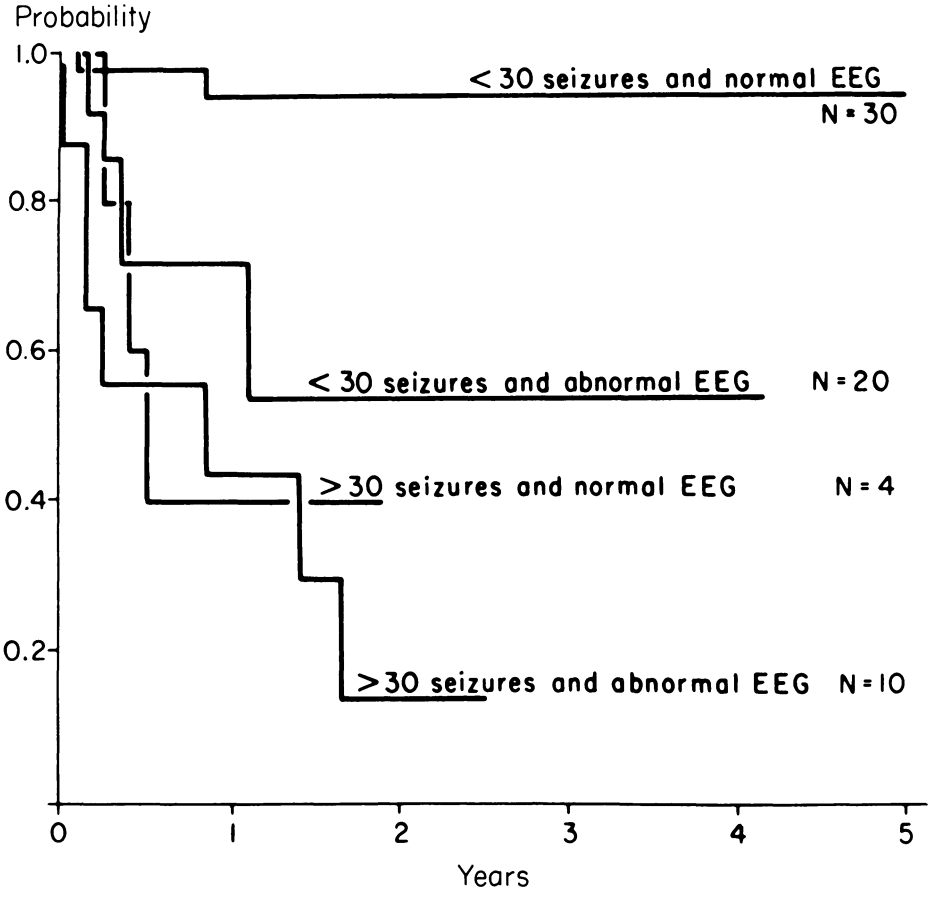

Fig. 8.11. Cumulative probability of relapse plotted as a function of elapsed time following discontinuation of anticonvulsant drugs. The effect of generalized seizure frequency and EEG findings on relapse rate are shown in four different combinations. (Emerson et al. 1981)

remission is highest in those with only generalized tonic–clonic seizures with onset before 10 years of age.

The data of Elwes et al. (1984) and Shorvon (1984) strongly indicate that the patterns of epilepsy are established early, probably within the first 2 years of treatment. Of even greater interest is their suggestion that early aggressive and appropriate treatment reduces the likelihood of chronicity (Reynolds et al. 1983). This is supported by their prospective investigation of newly diagnosed epileptic patients and factors influencing their response to treatment (Elwes et al. 1984), and their observation that the time intervals between tonic–clonic seizures become shorter with time, as if a learning process were taking place favoring the escalation of seizure frequency (Reynolds et al. 1983; Reynolds 1985). This clearly deserves further study.

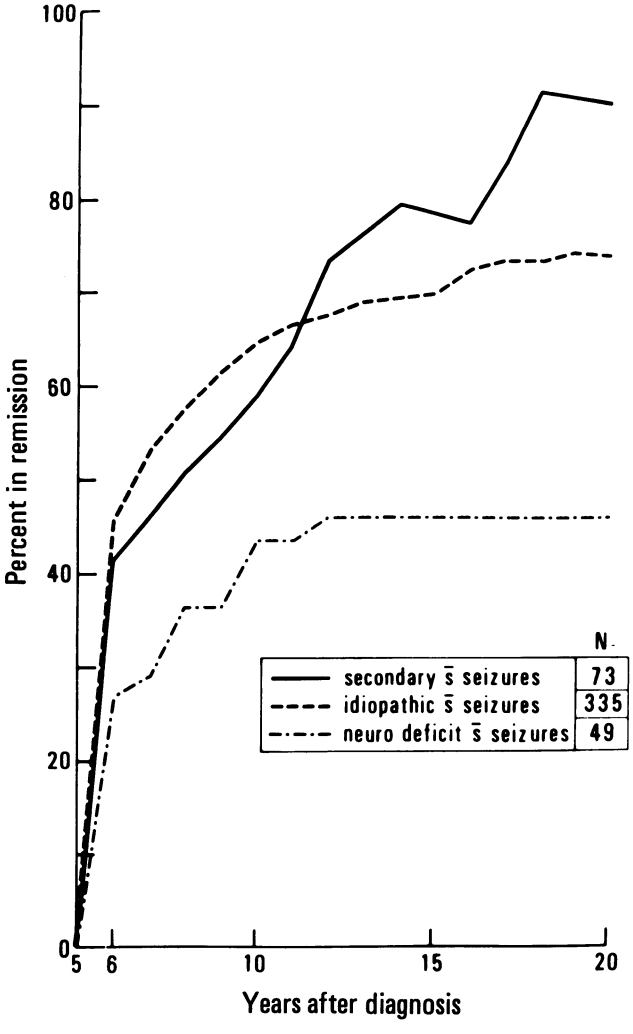

Fig. 8.12. Percentage of patients in remission by seizure type. (Annegers et al. 1979)

Therapy

Specific questions related to treatment are when, with what, and for how long. Institution of drug treatment requires knowledge of the natural history of epilepsy in order to estimate accurately the risk and frequency of recurrence. There is no consensus as to when a patient should be started on anticonvulsant drugs. Hauser et al. (1982) found that the cumulative risks of seizure recurrence after a first unprovoked seizure among 244 patients were 18% at 1 year, 21% at 2 years, and

27% at 3 years. They were unable to find a difference in outcome, whether patients received treatment for the first seizure or not. Recurrence risk was substantially increased by a neurological cause (secondary or "symptomatic" epilepsy), a family history of epilepsy, and an epileptiform EEG. Consideration of precipitating factors (environmental, systemic, and neurological) will also influence the decision. At this time, we prefer to defer drug treatment in patients with a single generalized tonic–clonic seizure if their neurological examination and EEG are normal, there are no significant causative or antecedent factors, and there is no family history of epilepsy. We also delay initiating therapy if there is any question about the diagnosis. With recurrent seizures, we believe that early drug treatment is desirable, not only to enable the patient to lead a normal life as soon as possible, but perhaps also to reduce the chance of developing chronic epilepsy.

If the decision is made to begin drug treatment, choice of "best" drug is hampered by the relatively few comparative studies of antiepileptic agents in homogeneous seizure types. Valproate is most widely used to treat primarily generalized tonic–clonic seizures in Europe, but because of concerns about its possible toxicity, phenytoin or carbamazepine are more often tried first in the United States. Nonetheless, available evidence suggests that valproate is as effective as phenytoin (Voelzke and Doose 1973; Turnbull et al. 1982) or carbamazepine (Callaghan et al. 1985), and we believe that when absence or myoclonic seizures coexist with tonic–clonic fits, valproate monotherapy may be used successfully in the majority of patients. Phenobarbital is now rarely used as drug of first choice because of adverse effects on cognitive function and behavior (Trimble and Reynolds 1984). Carbamazepine and phenytoin are the drugs of choice for secondarily generalized tonic–clonic seizures (Porter 1984), which constitute the vast majority of grand mal attacks in adults. We prefer carbamazepine because of the absence of undesirable cosmetic effects and the lower incidence of cognitive depression and memory impairment (Trimble and Thompson 1983; Trimble and Reynolds 1984). It should be emphasized, however, that available evidence indicates that carbamazepine, phenytoin, phenobarbital, and primidone are approximately equipotent antiepileptic agents in the treatment of secondarily generalized tonic–clonic seizures (Mattson et al. 1985). Therefore, preference of initial drug must be based in part on analysis of relative acute and long-term toxicity, cost, and ease of dosage schedule.

There is almost no role for surgery in the treatment of primary generalized tonic–clonic epilepsy. Early reports of success with chronic cerebellar stimulation (Cooper 1973; Cooper et al. 1976) have not been reproduced (Van Buren et al. 1978), and the procedure has been largely abandoned. Focal cortical excision should be considered in selected patients with secondarily generalized convulsions. The clinical utility of forebrain commissurotomy (corpus callosotomy) is still under investigation. This procedure may play a role in patients with secondary tonic–clonic seizures or with secondarily generalized convulsions not associated with a well-defined single focus (Wilson et al. 1982; Spencer et al. 1984).

There are no generally accepted guidelines for when or how to discontinue antiepileptic therapy. This lack can only be addressed by carefully designed studies focused on individual electroclinical epilepsy syndromes. In general, relapse rates are low in children who have been seizure-free for 4 years (Emerson et al. 1981; Holowach Thurston et al. 1982). To what extent this interval can be shortened depending on specific variables is unknown. Likewise, it is not known whether the success of remaining seizure-free off medication is influenced by prolonging the

duration of remission while on treatment. Indeed, despite the widespread assumption among physicians, it has not been proved that continuation of drugs in seizure-free patients guarantees continued remission. The value of the EEG in helping to predict which patients may be withdrawn from anticonvulsants safely is controversial. Available evidence, however, suggests that the more abnormal the EEG at the time of medication withdrawal, the greater the likelihood of seizure relapse. In our clinic, we attempt drug withdrawal in children or adults with pure primary tonic–clonic seizures after a seizure-free period of 2 years. If other seizure types are present, or if the tonic–clonic seizures are secondarily generalized or secondary to demonstrable brain pathology, we prefer to wait a minimum of 4 years before attempting to reduce or eliminate drugs. We are less likely to initiate drug withdrawal if the EEG remains significantly abnormal, excluding genetically determined epileptiform patterns.

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Chapter 9

Progressive Myoclonic Epilepsy

Hiroshi Shibasaki

Synonyms and Nosology

Progressive myoclonic epilepsy or progressive myoclonus epilepsy (PME) is a rare condition. It is commonly hereditary, is characterized by generalized convulsive seizures and myoclonic jerks frequently provoked by volitional movements, and is frequently associated with cerebellar ataxia, mental deterioration, pyramidal signs, and rigidity. PME is regarded as a syndrome having various causes (Table 9.1), not as an independent disease entity.

The term "myoclonus" originates from Friedreich's description (1881) of "paramyoclonus multiplex" in a 50-year-old man who had shown, since the age of 45, generalized small muscle jerks, without seizures or organic brain disease, which occurred most frequently at rest and were inhibited by volitional activity. Myoclonus can be defined as an involuntary, sudden, jerky, irregular contraction of a group of muscles or a muscle, unassociated with loss of consciousness (Halliday 1975).

At the end of the nineteenth century, Unverricht (1891, 1895) in Germany described a progressive familial syndrome of myoclonus epilepsy affecting five siblings in his first paper (1891) and three brothers in the second (1895). The disease commonly started with convulsive seizures between the ages of 10 and 20 years, and a few years later lightning-like muscle jerks developed. The muscle jerks were similar to the "myoclonus" described by Friedreich (1881) except that they were exacerbated by psychic excitation or volitional movement and diminished during sleep. Patients in the advanced clinical stage also manifested progressive dementia, pseudobulbar palsy, rigidity, and finally quadriplegia in flexion.

At the beginning of the twentieth century, Lundborg (1903, 1904, 1912) in Sweden reported patients similar to those reported by Unverricht. He proposed the term "progressive Myoklonusepilepsie." The disease appeared to be transmitted through an autosomal recessive inheritance (Lundborg 1912), but there were some sporadic cases showing a less progressive clinical course as compared with Unverricht's cases (Lundborg 1904). Following the original reports by these two

Table 9.1. Causes of progressive myoclonic epilepsy and their clinical features

Disease	Age of onset (years)	Heredity	Other manifestations	Diagnosis
Lafora's disease	10–20	Aut. rec.	Dementia Ataxia	Lafora body in muscle or liver
Lipidosis				
Cherry-red spot–myoclonus syndrome	7–20	Aut. rec.	Ataxia Cherry-red spot	
Sialidosis type 1				Sialidase deficiency
Sialidosis type 2			Coarse facies	Sialidase and β-galactosidase deficiency
GM_2-gangliosidosis		Aut. rec.	Dementia Visual loss Cherry-red spot	Hexosaminidase deficiency
Tay-Sachs	6 mo.			
Juvenile	1–4			
Gaucher's disease (noninfantile)	10–40	Aut. rec.	Dementia Spasticity Ataxia Visceromegaly	Gaucher cells in bone marrow, glucocerebrosidase deficiency
Neuronal ceroid lipofuscinosis		Aut. rec.	Dementia Visual loss (except for Kufs)	Curvilinear and fingerprint bodies in rectal mucosa, bone marrow cells, lymphocytes and fibroblasts
Jansky-Bielschowsky	1.5–4			
Batten-Spielmeyer-Vogt	5–10			
Kufs	10–40			
Juvenile neuroaxonal dystrophy	9–10	Aut. rec.	Dementia Ataxia	Spheroids in peripheral nerve
Myoclonus epilepsy with mitochondrial myopathy	10–40	Aut. dom.	Muscle atrophy	Ragged-red fibers in muscle biopsy
Dentatorubropallidoluysian atrophy	5–60	Aut. dom.	Choreoathetosis Dementia	
Unverricht-Lundborg syndrome	10–20	Aut. rec.	Dementia Spasticity Rigidity Ataxia	
Ramsay Hunt syndrome	7–17	Sporadic	Ataxia	

authors, this syndrome has been called "progressive myoclonus epilepsy" or Unverricht-Lundborg syndrome.

Lafora and Glueck (1911) in Spain reported the first pathological findings of PME (in a 17-year-old boy), finding cytoplasmic amyloid inclusions in neurons of many structures of the central nervous system. Since then, a variety of pathological findings have been reported in patients with PME, but Lafora's disease is one of the most distinct clinicopathological forms of this syndrome (Schwarz and Yanoff 1965). Sioli (1913) found a deposit of lipid in the brain of a 17-year-old patient with PME and paid special attention to a marked involvement of the cerebellar dentate nucleus.

In 1914–15, Hunt reported three cases characterized by generalized intention tremor, dyssynergia, dysmetria, adiadochokinesia, and hypotonia, and called them "dyssynergia cerebellaris progressiva or chronic progressive cerebellar tremor." Later, Hunt (1921) reported six cases of progressive cerebellar tremor associated with myoclonus epilepsy, and proposed the term "dyssynergia cerebellaris myoclonica." Two of his six cases, twin brothers, also had evidence of Friedreich's ataxia, and in one of them this was confirmed pathologically. Hunt (1921) directed special attention to marked atrophy and neuronal loss of the cerebellar dentate nucleus in the autopsied case. The clinical picture of Hunt's cases was similar to that described by Unverricht and Lundborg, but the family history was negative in Hunt's cases.

Myoclonic jerks and convulsive seizures are seen in various forms of lipidoses, especially in Tay-Sachs disease and the noninfantile form of Gaucher's disease (King 1975; Nishimura and Barranger 1980; Winkelman et al. 1983). PME has also been described in some cases of neuronal ceroid lipofuscinosis, especially the juvenile (Batten-Spielmeyer-Vogt) and adult forms (Kufs) (Pallis et al. 1967; Chou and Thompson 1970).

Recently cherry-red spot–myoclonus syndrome has attracted particular attention (Engel et al. 1977). The age of onset and the clinical picture of this syndrome are quite similar to those of Ramsay Hunt syndrome except for the presence of cherry-red spots. Increased excretion of sialyl oligosaccharides in urine (Rapin et al. 1978) and deficiency of α-neuraminidase (sialidase) in fibroblasts (Miyatake et al. 1979; Thomas et al. 1979) gave evidence of an underlying chemical abnormality. Patients with similar symptoms, but associated with a gargoyle-like appearance, were shown to have deficiency of both β-galactosidase and neuraminidase (Kobayashi et al. 1979; Sakuraba et al. 1983).

Dorfman et al. (1978) reported PME in two brothers with juvenile neuroaxonal dystrophy with characteristic axonal spheroids in the nervous system. Fukuhara et al. (1980) reported two cases manifesting a combination of dyssynergia cerebellaris myoclonica, Friedreich's ataxia, and mitochondrial myopathy, and similar cases have been reported by other investigators (Feit et al. 1983; Sasaki et al. 1983). This syndrome is considered to be a type of mitochondrial encephalomyopathy. Takahata et al. (1978) and Naito and Oyanagi (1982) reported a familial syndrome of PME and choreoathetosis. This syndrome seems to be pathologically compatible with dentatorubropallidoluysian atrophy (Smith et al. 1958), although the patient reported by Smith et al. (1958) did not show myoclonus epilepsy.

Thus, a syndrome of PME is associated with a variety of different pathological or chemical abnormalities of the central nervous system and seems to be a manifestation of diffuse neuronal disease, as pointed out by Watson and Denny-Brown (1953). As already indicated, the term "progressive myoclonic epilepsy"

(Noad and Lance 1960; Halliday 1967a) has been used with the same meaning as "progressive myoclonus epilepsy."

Clinical Manifestations

The cardinal clinical symptoms of PME are progressive myoclonic jerks and generalized convulsive seizures. The age of onset is usually under 20 years, although there are some differences depending on the etiology (Table 9.1). Some patients first have a generalized convulsion with loss of consciousness, myoclonic jerks only developing later, whereas others first notice myoclonic jerks and later start having generalized convulsions. In addition, PME patients commonly show cerebellar ataxia and/or intellectual deterioration, although the former is frequently difficult to distinguish from myoclonic jerks enhanced by volitional movements. Patients with dyssynergia cerebellaris myoclonica (Ramsay Hunt) may show unsteady gait as an initial symptom, and those with Lafora's disease may show intellectual deterioration and motor disturbances before myoclonic jerks or convulsive seizures appear.

Myoclonic jerks are usually of the postural and/or intention (action) type, and are rarely seen at complete rest or during sleep. Jerks are provoked as soon as the patient initiates any kind of volitional movement, including speech. These intention myoclonia are commonly stimulus sensitive, the most effective stimuli being proprioceptive, such as tendon tap or passive joint movement, and in some cases auditory or flash stimuli as well. A myoclonic jerk elicited by tendon tap may appear indistinguishable, at least clinically, from an enhanced deep tendon reflex, but in contrast to the monosynaptic spinal reflex, the myoclonic response appears to spread to involve other muscles of the corresponding extremity and those of other extremities at increasing latencies. Myoclonic jerks occurring in association with volitional movement are usually irregular and asynchronous, although they may look quite symmetrical. A myoclonic response following an unexpected auditory stimulus, however, may involve both sides synchronously. A vigorous jerk involving the truncal and leg muscles, as occurs upon starting to walk, may cause a sudden drop attack.

In addition, attacks of generalized convulsions may occur after myoclonic jerks have accumulated over a period of hours or days; these are followed by a myoclonus-free period of several days' duration. Consciousness may or may not be lost during the convulsive seizure.

Diagnosis of PME itself is not difficult, but its cause often remains undetermined. As shown in Table 9.1, the age of onset is quite similar among different disease groups. The mode of inheritance is usually autosomal recessive, although cases of autosomal dominant inheritance have been reported, especially in association with other neurological features (May and White 1968; Smith et al. 1978; Takahata et al. 1978; Jankovic and Rivera 1979; Fukuhara et al. 1980; Naito and Oyanagi 1982; Sasaki et al. 1983). Cherry-red spots should be looked for in every case of PME, because demonstration of this particular retinal abnormality strongly suggests a kind of lipidosis or mucolipidosis. Progressive visual failure from the early clinical stage suggests a possibility of neuronal ceroid lipofuscinosis. These clinical diagnoses can be confirmed by demonstrating characteristic intracy-

toplasmic inclusions in various biopsied tissues (Table 9.1), by proving a deficiency of those enzymes related to lipid metabolism in either peripheral leukocytes or serum or skin fibroblasts, or by other specific tests. Demonstration of amyloid inclusions in biopsied muscle or liver is helpful in the diagnosis of Lafora's disease (Schwarz and Yanoff 1965; Carpenter et al. 1974). Biopsy of rectal mucosa may also be helpful in finding cytoplasmic inclusions in the autonomic neurons.

As the postural tremor seen in hepatolenticular degeneration (Wilson's disease) is often vigorous enough to resemble action myoclonus (Wohlfart and Höök 1951), its possibility should always be taken into consideration.

Cases of PME without any specific laboratory abnormalities are frequently encountered. At present, such cases must be categorized into a nonspecific degenerative group. The diagnostic significance of PME of Unverricht-Lundborg and of dyssynergia cerebellaris myoclonica of Ramsay Hunt is obscure, because none of the original cases was pathologically studied except for one of Hunt's cases associated with Friedreich's ataxia (Hunt 1921). In fact, those patients described by Unverricht (1891, 1895) and by Lundborg (1903, 1904, 1912) could have had Lafora's disease. On the other hand, there are some patients who show a clinical picture quite similar to that of Unverricht-Lundborg syndrome and yet lack Lafora bodies (Koskiniemi et al. 1974a). Therefore, it seems appropriate to continue using the term Unverricht-Lundborg syndrome until more specific morphological or chemical abnormalities are discovered.

The distinction between Unverricht-Lundborg syndrome and Ramsay Hunt syndrome is even more obscure (Wohlfart and Höök 1951; de Barsy et al. 1968). If we follow the original descriptions, familial cases of autosomal recessive inheritance could be called Unverricht-Lundborg syndrome and sporadic cases could be called Ramsay Hunt syndrome. Among associated neurological symptoms, however, there seems to be a predominance of dementia in the former and of cerebellar ataxia in the latter.

Patients with PME can manifest clinical features seen in other neurological diseases. These include dyssynergia cerebellaris myoclonica associated with Friedreich's ataxia (Hunt 1921), myoclonus epilepsy with mitochondrial myopathy (Fukuhara et al. 1980; Sasaki et al. 1983), familial myoclonus epilepsy with choreoathetosis or dentatorubropallidoluysian atrophy (Takahata et al. 1978; Naito and Oyanagi 1982), familial myoclonic epilepsy with Friedreich's ataxia and peroneal muscular atrophy (Smith et al. 1978; Jankovic and Rivera 1979), familial olivopontocerebellar atrophy with action myoclonus (Bonduelle et al. 1976), and familial myoclonus epilepsy with deafness (May and White 1968; Chayasirisobhon and Walters 1984).

Related Disorders

Posthypoxic Myoclonus (Lance-Adams Syndrome)

Posthypoxic myoclonus is a well-known syndrome characterized by intention or stimulus-sensitive myoclonus and cerebellar ataxia starting immediately after

anoxic encephalopathy (Lance and Adams 1963). Clinical and electrophysiological features of this syndrome are quite similar to those of PME, and especially to those of dyssynergia cerebellaris myoclonica (Ramsay Hunt syndrome), except that posthypoxic myoclonus is commonly seen among middle-aged or elderly people. This syndrome, therefore, has been dealt with similarly to PME in terms of electrophysiological and neuropharmacological investigations (Chadwick et al. 1977; Van Woert et al. 1977).

Creutzfeldt-Jakob Disease

The most common form of myoclonus seen in this slow virus infection is a periodic, non-stimulus-sensitive myoclonus continuously occurring at rest. This myoclonus is frequently associated with periodic synchronous EEG discharges, although these two phenomena appear to be only loosely fixed in this particular condition (v. Koschitzky et al. 1980; Shibasaki et al. 1981). These patients can, however, show stimulus-sensitive myoclonus time locked to EEG spikes during the clinical course, although generalized convulsive attacks are rare.

Subacute Sclerosing Panencephalitis

Myoclonus commonly observed in this slow virus infection of childhood is a slow muscle jerk involving facial or limb muscles which is associated with EEG discharges occurring periodically once every 4–13 s.

Epilepsy with Myoclonus (Myoclonic Epilepsy)

Some epileptic patients show occasional myoclonic jerks between major attacks. Paroxysmal EEG abnormalities may be photosensitive, but myoclonus is neither progressive nor disabling at all. Moreover, there are no other associated neurological symptoms.

Essential Myoclonus

Myoclonus in this condition is usually irregular, multiple or generalized, and not stimulus sensitive. The age of onset is under 20 years, and the clinical course is not progressive. There are neither convulsive seizures nor other neurological symptoms, although there may be mild cerebellar ataxia. EEG is usually normal. The original case reported by Friedreich (1881) seems to belong to this category.

Hereditary essential myoclonus of autosomal dominant transmission has been reported (Przuntek and Muhr 1983).

Startle Disease

Startle disease or hyperekplexia is a rare condition. It is often hereditary, with autosomal dominant transmission, and is characterized by sudden jumps in response to unexpected stimuli, most frequently auditory (Andermann et al. 1980). The age of onset is under 25 years. EEG may show mild paroxysmal abnormalities.

Epilepsia Partialis Continua (Kojewnikow's Syndrome)

Epilepsia partialis continua is a prolonged rhythmically repeated twitching of a group of muscles, usually involving a distal limb (Thomas et al. 1977). Muscle jerks continue for days or weeks at a rate of 20–60 per minute. EEG shows focal sharp waves or periodic lateralized epileptiform discharges over the contralateral hemisphere in association with muscle jerks. This condition is always based on structural lesions involving the motor cortex or a closely adjacent area, and is considered to be cortical in origin (Thomas et al. 1977).

Electrophysiological Aspects

EEG Abnormalities and Correlation with Myoclonus

In spite of a great diversity of clinical manifestations, EEG abnormalities in patients with PME are rather uniform. The abnormalities are usually characterized by a train of spikes, spike and wave complexes, or a short burst of generalized multiple spikes and waves which appear to occur bilaterally and symmetrically over the scalp (Fig. 9.1) (Grinker et al. 1938; Gastaut and Rémond 1952; Kreindler et al. 1959; Halliday 1967b; Hambert and Petersen 1970; Koskiniemi et al. 1974b; Engel et al. 1977; Westmoreland et al. 1979). The EEG is quite photosensitive in many cases (Watson and Denny-Brown 1955; Koskiniemi et al. 1974b; Westmoreland et al. 1979).

In most cases, the background activity of the EEG is disorganized, with a variable amount of intermixed slow waves. In cases of α-neuraminidase deficiency (sialidosis), however, the waking EEG consists of low-voltage fast activity interspersed with paroxysmal bursts (Engel et al. 1977), or the record may even lack paroxysmal abnormalities (Fig. 9.2).

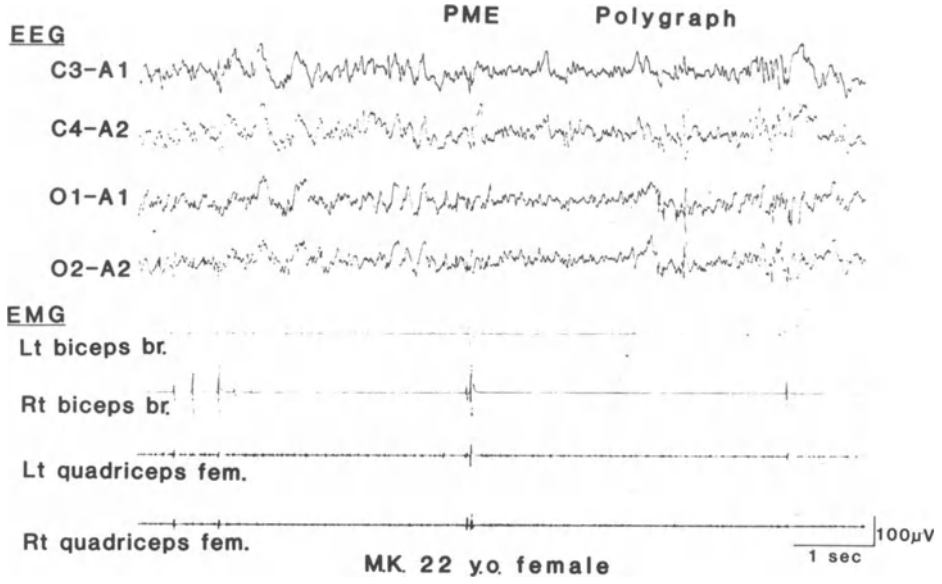

Fig. 9.1. EEGs and EMGs in a 22-year-old female patient with degenerative type PME. There are abundant spikes or multiple spikes and waves in the EEGs, but their association with myoclonic discharges is not constant.

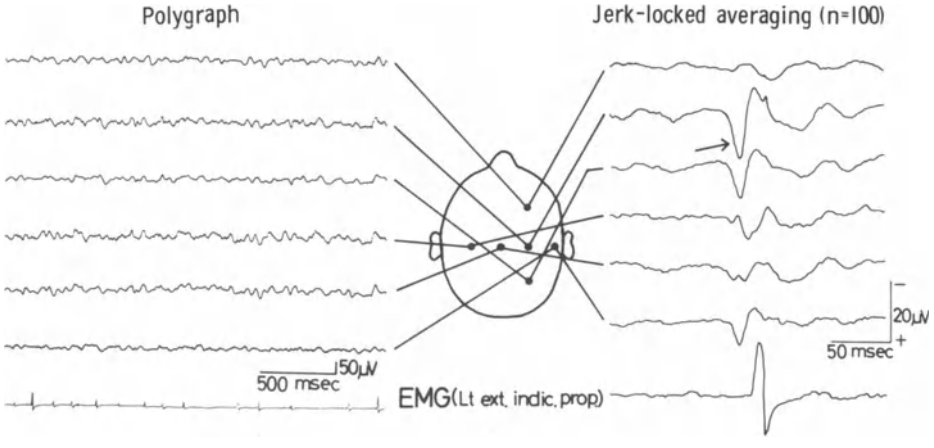

Fig. 9.2. Conventional EEG-EMG polygraph (*left*) and jerk-locked average (*right*) in a 17-year-old male patient with α-neuraminidase deficiency. There is no paroxysmal abnormality in the EEG, but by averaging the EEG with respect to myoclonic EMG discharges, a positive–negative spike (*arrow*) preceding the myoclonus of the left forearm muscle is recognized at the right central region. (Shibasaki and Kuroiwa 1975)

The first report of polygraphic recording of EEG and EMG in patients with PME was by Grinker et al. (1938), who described a short burst of 10- to 15-Hz rhythmic spikes in association with myoclonic jerks. Based on a congruity in time between the spikes and the myoclonic twitchings, they proposed a cortical origin for the myoclonus, which was thought to be a "building-up" process of a true seizure. Dawson (1946) found an accurate correlation between EEG spikes and myoclonic EMG discharges in two patients with PME. In fact, an EEG spike preceded the myoclonic jerk of the quadriceps femoris muscle by 15–40 ms. In another patient with mild myoclonus, however, there was no constant relationship between EEG spikes and myoclonic jerks, and Dawson proposed that these two phenomena were both correlates of some third process. Since then, polygraphic studies of spontaneously occurring myoclonus with simultaneous recording of the EEG have been performed by many investigators (Haguenau et al. 1950; Gastaut and Rémond 1952; Bradshaw 1954; Harriman and Millar 1955; Kreindler et al. 1959; Halliday 1967b; Roger et al. 1967; Hambert and Petersen 1970; Engel et al. 1977). A subcortical origin for both the EEG spikes and the myoclonic EMG discharges was suggested by the lack of a fixed correlation between them or by too short a time interval between them when a constant time relationship was noticed (Haguenau et al. 1950; Gastaut and Rémond 1952; Bradshaw 1954; Harriman and Millar 1955; Kreindler et al. 1959; Roger et al. 1967; Engel et al. 1977).

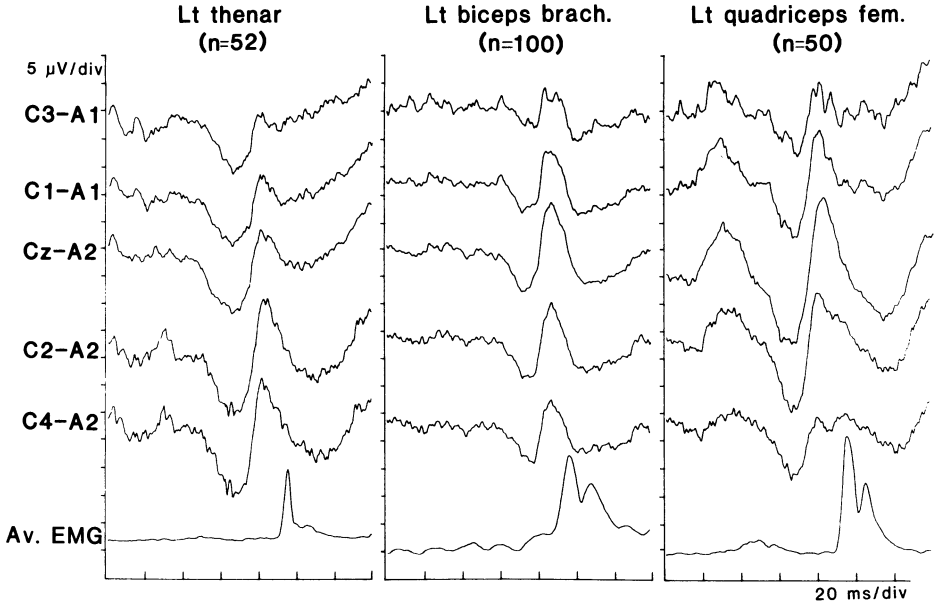

Fig. 9.3. Records of jerk-locked averaging in a 22-year-old female patient with PME (same patient as in Fig. 9.1). The cortical spike time locked to the myoclonus of the left thenar muscle (*left*), the left biceps brachii muscle (*middle*), and the left quadriceps femoris muscle (*right*) is maximal at C2 and C4, Cz and C2, and Cz electrode, respectively. The positive peak of the cortical spike precedes the onset of the myoclonus of each muscle by 22 ms, 14 ms, and 22 ms, respectively. (Shibasaki et al. 1985b)

Halliday (1967b) proposed the term "pyramidal" myoclonus for those myoclonia that follow a cortical spike discharge with a fixed and characteristic latency. In cases of "pyramidal" myoclonus, Halliday (1967b) found four kinds of paroxysmal EEG abnormality: (a) focal cortical spikes in the contralateral rolandic region, (b) diffuse cortical spiking, (c) a bilaterally synchronous spike or burst of spikes followed by a slow wave, and (d) a localized sinusoidal "after-discharge" at about 30 Hz in the rolandic area either unilaterally or bilaterally. This central fast activity seems to be almost characteristic of action myoclonus. Kelly et al. (1978) described movement-activated central fast rhythms at 20–40 Hz which were somatotopically related to the extremity being used.

With the conventional polygraphic technique it has often been difficult to evaluate the relationship between the myoclonic discharge and EEG paroxysms (Fig. 9.1). Shibasaki and Kuroiwa (1975) succeeded in recording the EEG correlates of myoclonus, which were not recognizable on the routine polygraphic recordings, by averaging the EEG time locked to the following myoclonic discharge (Fig. 9.2). This technique of jerk-locked averaging has been useful not only for detecting the EEG correlates of myoclonus which otherwise cannot be recognized, but also for elucidating the temporal as well as the topographical relationship between the EEG and myoclonic jerks (Fig. 9.3) (Chadwick et al. 1977; Hallett et al. 1977; Shibasaki et al. 1978; Hallett et al. 1979; Franceschetti et al. 1980; Janzen 1980; Janzen et al. 1983; Shibasaki et al. 1985a,b).

Enhanced Cortical Response to Stimulation

Dawson (1947) reported a patient in whom myoclonic jerks were elicited by muscle stretch stimulation such as tendon tap. Each evoked muscle jerk was associated with a cerebral potential over the contralateral hemisphere (Fig. 9.4). By presenting electric shocks to a peripheral nerve once every second and by superimposing EEGs with respect to the stimulus, Dawson (1947) demonstrated a large amplitude, positive–negative biphasic potential at the contralateral precentral scalp electrode, its latency being 19 ms after elbow stimulation and 43 ms after ankle stimulation. Some patients were sensitive not only to muscle stretch but also to stimuli of other modalities such as flash and loud sound (Watson and Denny-Brown 1955) or touch and pressure (Sutton 1975).

The extremely large early cortical components of the somatosensory evoked potential (SEP) have been specifically found in patients with PME but not in those with other kinds of myoclonic disorder (Halliday 1967b, 1975; Shibasaki et al. 1985b). In a typical giant SEP (Fig. 9.5), the initial cortical negative response ($\overline{N20}$) is normal, and the following positive ($\overline{P25}$) and negative ($\overline{N33}$) components are as large as 35 and 75 μV, respectively (Shibasaki et al. 1978, 1985b). The component corresponding to $\overline{N62}$ is often absent, and the next negative component ($\overline{N150}$) is usually enhanced.

If the EMG is simultaneously recorded from the thenar muscle of the stimulated side in the median nerve SEP paradigm and is averaged with respect to the stimulus pulse, an EMG response is often recorded at an onset latency of 30–60 ms (Shibasaki et al. 1978, 1985b) (Fig. 9.5). This enhanced long-latency reflex can be recognized as a clinically visible reflex myoclonus and corresponds to the C reflex

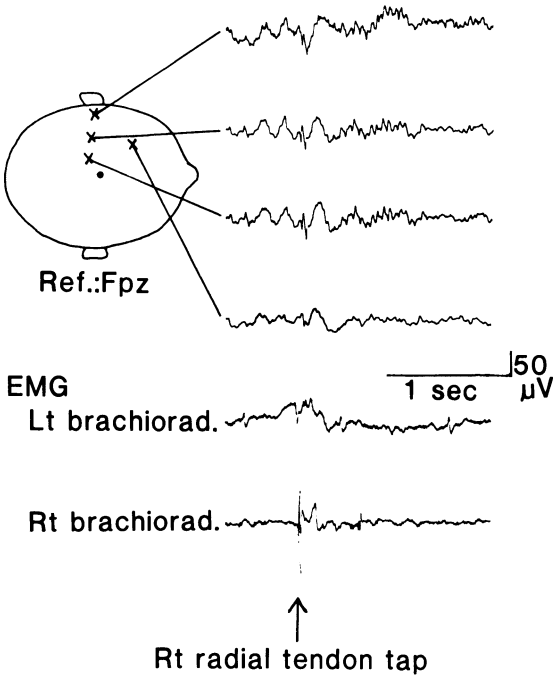

Fig. 9.4. EEGs and EMGs in a 22-year-old female patient with β-galactosidase-neuraminidase deficiency. Tendon tap to the right radial muscle (*arrow*) generates a spike and wave complex at the left central region.

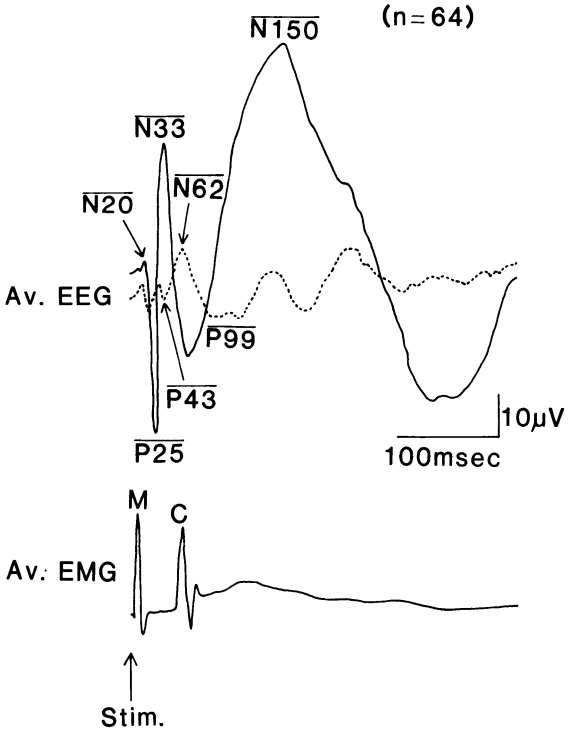

Fig. 9.5. Giant SEP following electrical stimulation of the median nerve at the wrist in a 16-year-old male patient with degenerative type PME. Early cortical components corresponding to P25 and N33, and N150 are markedly enhanced. A long-latency reflex (C) is recorded from the thenar muscle of the stimulated side.

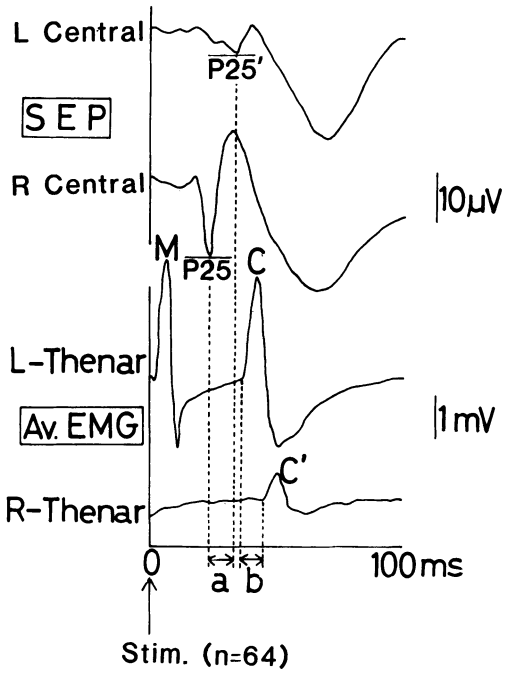

Fig. 9.6. Giant SEPs and long-latency (C) reflex following left median nerve stimulation in a 57-year-old female patient with degenerative type PME. The time interval (*a*) between the $\overline{P25}$ of giant SEP and $\overline{P25}'$ (response ipsilateral to the stimulation) is 10 ms and similar to that (*b*) between the two long-latency reflexes C and C′ (recorded from the nonstimulated hand). (Shibasai et al. 1978)

described by Sutton and Mayer (1974). The EMG response is highly correlated with the occurrence of the giant SEP (Shibasaki et al. 1978; Hallett et al. 1979; Kelly et al. 1981; Shibasaki et al. 1985b). The giant SEP is maximal at the central region corresponding to the stimulus site, and its positive peak ($\overline{P25}$) precedes the onset of the long-latency reflex recorded from an upper extremity muscle by 11–24 ms (Shibasaki et al. 1985b). In some cases the giant SEP is recorded over the hemisphere ipsilateral to the stimulation at a peak latency 10 ms longer than that on the contralateral hemisphere, and a long-latency (C) reflex can also be recorded from the nonstimulated hand, its onset latency being 10 ms longer than that from the stimulated hand (Fig. 9.6). These observations seem to suggest that this long-latency reflex is cortical (Shibasaki et al. 1978; Hallett et al. 1979).

Pathogenesis

Pathology

Pathologically PME can be classified into three groups: Lafora's disease, lipidosis, and a degenerative group. In Lafora's disease, the characteristic amyloid inclusions are seen within the neuronal cytoplasm in various gray matter structures of the central nervous system. Cerebellar dentate nucleus and cerebral cortex are

most strongly affected, and thalamus, globus pallidus, substantia nigra, red nucleus, and medulla oblongata are also involved to a variable degree (Lafora and Glueck 1911; Ostertag 1925; Schou 1925; Roizin and Ferraro 1942). Lafora bodies can also be seen in other organs such as liver, heart, and skeletal muscles (Harriman and Millar 1955; Schwarz and Yanoff 1965). These inclusion bodies are PAS-positive and thought to be relatively insoluble aggregates of unusual polyglucosan (Yokoi et al. 1968; Pedersen et al. 1982), although an underlying metabolic abnormality has not yet been elucidated.

Lipidoses manifesting myoclonic epilepsy are those of the neuronal storage type. In GM_2 gangliosidosis or hexosaminidase deficiency, ballooned neurons are seen throughout the brain, cerebellum, and spinal cord, and electron microscopy shows these neurons to contain membranous cytoplasmic bodies with regularly spaced concentric dark and pale lamellae. In neuronal ceroid lipofuscinosis, storage cystosomes such as lipofuscin–lipid compound bodies, curvilinear or fingerprint bodies, and miniature membranous cytoplasmic bodies are seen in the neurons throughout the central nervous system and the retina, and in peripheral autonomic neurons (Chou and Thompson 1970). These storage cytosomes can also be found in the bone marrow, lymphocytes, and fibroblasts.

Since the original report by Hunt (1921), the dentate nucleus and superior cerebellar peduncle have been shown to be most commonly and strongly affected in dyssynergia cerebellaris myoclonica (Hodskins and Yakovlev 1930; Bird and Shaw 1978), although there are some exceptional cases without a dentate lesion (Bonduelle et al. 1976; Choteau et al. 1980). Dysfunction of the cerebellifugal system is, therefore, believed to play a major role in causing intention (action) myoclonus. Degenerative changes and atrophy of neurons can also be seen in the cerebral cortex to a variable degree. In cases with generalized convulsions and myoclonic jerks, the pathological findings are more diffuse, involving the cerebral cortex and basal ganglia (Hodskins and Yakovlev 1930). Dentatorubropallidoluysian atrophy is similar to dyssynergia cerebellaris myoclonica clinically as well as pathologically, but is unique in terms of an additional involvement of the globus pallidus and subthalamic nucleus (Smith et al. 1958; Naito and Oyanagi 1982).

Cortical Reflex Myoclonus vs Reticular Reflex Myoclonus

Most intention (action) myoclonia belong to the stimulus-sensitive myoclonia (Watson and Denny-Brown 1955). Hallett et al. (1977, 1979) and Chadwick et al. (1977) proposed two major forms of the reflex myoclonus with respect to the reflex center: "reticular reflex" and "cortical reflex." Reticular reflex myoclonus starts in the muscles innervated by lower cranial nerves and spreads upward as well as downward, involves mainly proximal muscles, and is generalized when stimulus evoked. There are spike and wave discharges in the EEG, but they are variably related to myoclonus (Hallett et al. 1977; Chadwick et al. 1977). Cortical SEP is not enhanced. Cortical reflex myoclonus, on the other hand, involves mainly distal muscles, resembling coarse tremor, and is somatotopically localized when stimulus evoked. Cranial nerve muscles are activated in a downward direction. Myoclonus is preceded at a fixed time interval by an EEG spike from the contralateral central cortex, and early cortical SEP components are extremely enhanced in amplitude

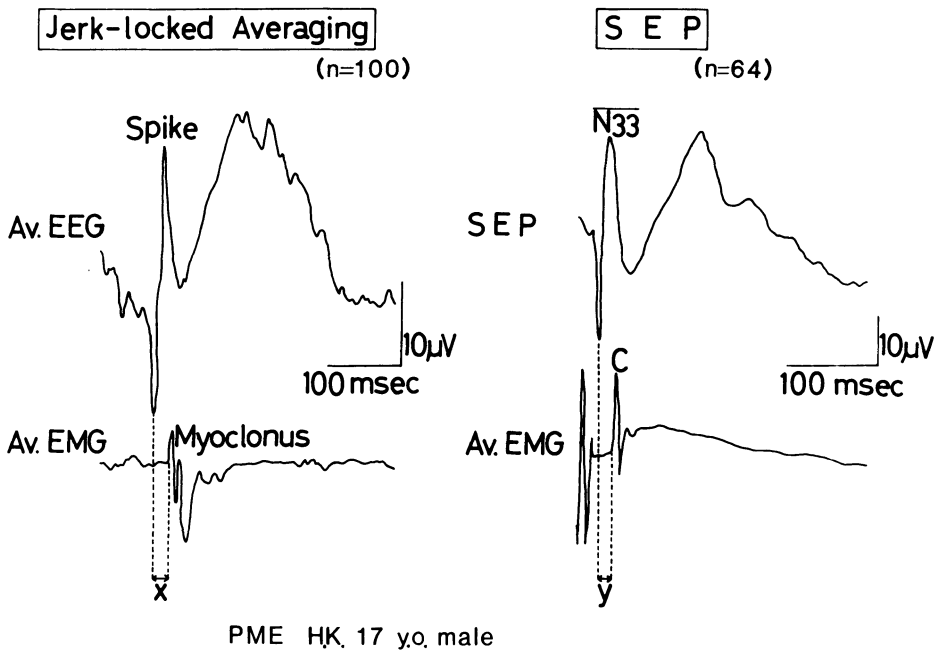

Fig. 9.7. Cortical spike recorded by jerk-locked averaging with respect to myoclonic EMG discharges (*left*) and giant SEP followed by long-latency (C) reflex (*right*) in a 17-year-old male patient with PME. The wave forms of two cortical potentials are similar, and the time interval from the positive peak of cortical spike to the myoclonus onset (x) is similar to that from the positive peak of giant SEP to the onset of C reflex (y). (Shibasaki et al. 1978)

(Chadwick et al. 1977; Hallett et al. 1979). Reticular reflex myoclonus is commonly encountered in cases of posthypoxic myoclonus (Lance and Adams 1963; Chadwick et al. 1977). Cortical reflex myoclonus can occur in any kind of PME and can also be seen in some cases of posthypoxic myoclonus (Chadwick et al. 1977) and in Creutzfeldt-Jakob disease at a certain stage of the illness. A similar condition, but focal in nature, has been reported in patients with focal reflex myoclonus (Sutton and Mayer 1974; Rosén et al. 1977).

In cortical reflex myoclonus, the EEG spike preceding myoclonus and the giant SEP were found to be quite similar in terms of the wave form, scalp topography, and time relationship to either myoclonus or long-latency (C) reflex (Fig. 9.7) (Shibasaki et al. 1978). Furthermore, Shibasaki et al. (1985a,b), by stimulating the peripheral nerve at precisely the time of, or at varying time intervals after, the myoclonus onset and by comparison with the paired stimulation SEP, found a relatively enhanced cortical excitability immediately following both the myoclonus-related cortical spike and the giant SEP. Shibasaki et al. (1985b) found that

antimyoclonus agents such as clonazepam and 5-hydroxytryptophan (5-HTP) reduced all of the myoclonic jerks, the myoclonus-related cortical spikes, and the giant SEP, but Rothwell et al. (1984) found no change or even an increase in the giant SEP despite reduction of spontaneous myoclonus and reflex muscle jerking after administration of lisuride or clonazepam. Myoclonic jerks were suppressed during slow-wave sleep, as was the giant SEP (Shibasaki et al. 1985b). It was therefore postulated that the myoclonus-related cortical spike and the giant SEP are generated, at least in part, by common physiological mechanisms (Shibasaki et al. 1978; Hallett et al. 1979; Shibasaki et al. 1985b). Thus, an apparently spontaneous myoclonus may in fact be an enhanced long-latency reflex in response to some unnoticed stimulus.

Significance of Brain Stem Reticular Formation and Serotonin Metabolism

Adrian and Moruzzi (1939) observed stimulus-sensitive myoclonic jerking involving all limbs and the trunk in cats under chloralose anesthesia. This first experimental myoclonus was shown to involve the motor cortex (Adrian and Moruzzi 1939; Alvord and Fuortes 1954). Another animal model of cortical reflex myoclonus was produced in monkeys by making alumina foci in the primary motor area (Chauvel et al. 1978). Stimulation of the proprioceptive afferents of the corresponding limb evoked cortical spikes quite similar to spontaneous spikes which then appeared to generate an EMG burst at a fixed latency.

In contrast with these experimental myoclonia of cortical reflex type, Cesa-Bianchi et al. (1967) induced stimulus-sensitive myoclonus and EEG changes in cats by injecting cobalt powder into the medullary reticular formation or midline thalamic structures. Zuckermann and Glaser (1972) elicited a myoclonic syndrome in cats by intravenous infusion of urea, and recorded spikes and sharp-wave discharges in the nucleus gigantocellularis of the lower brain stem reticular formation. Angel and Lemon (1973) produced myoclonic jerks in rats by intraperitoneal injection of 1,2-dihydroxybenzene (catechol) and proposed the brain stem reticulospinal inhibitory system as a site of catechol effect. Hwang and Van Woert (1978) induced stimulus-sensitive myoclonic jerks in mice and rats by oral administration of *p,p'*-DDT, and found that serotonergic agents reduced the myoclonus whereas serotonin antagonists aggravated it. Although there are conflicting reports on whether 5-HTP induces myoclonic jumping behavior in guinea pigs and whether dopamine agonists antagonize the effect (Chadwick et al. 1978; Weiner et al. 1979), dysfunction of the serotonergic system of the medullary reticular formation has been postulated to have a causal relationship to stimulus-sensitive myoclonus (Halliday 1975). 5-HTP-induced myoclonus in guinea pigs (Chadwick et al. 1978) was thought to be of reticular reflex type because the myoclonic jerks were bilaterally synchronous, were not preceded by an EEG spike, and persisted in decerebrate animals.

In human patients with posthypoxic myoclonus or PME, 5-hydroxyindoleacetic acid, a metabolite of serotonin, is reduced in the cerebrospinal fluid, suggesting serotonin deficiency in the brain (Van Woert and Sethy 1975; Chadwick et al. 1977; Van Woert et al. 1977).

Prognosis

The prognosis of PME differs significantly depending on the underlying etiology, but in general, myoclonic jerks and generalized convulsive seizures are progressive, resulting in severe disability within several years after onset and death in 10–20 years. Patients with Lafora's disease usually die within 2–10 years after onset (Schwarz and Yanoff 1965; Roger et al. 1967). Patients with various forms of lipidoses, including neuronal ceroid lipofuscinosis, also die within several to 20 years after onset. The prognosis of the degenerative form is also poor in most cases: patients usually die within 10–20 years after onset, although in some the progression is less fast (Diebold et al. 1967; Koskiniemi et al. 1974a; Takahata et al. 1978; Naito and Oyanagi 1982).

Treatment

Although there is no treatment for the underlying diseases, myoclonic jerks and generalized convulsions can be suppressed by medications to some extent. At present the drug of first choice for intention (action) myoclonus and myoclonic seizures may be clonazepam at a daily dose of 2–12 mg in three divided doses. Clonazepam can be used for both PME, including Lafora's disease, and post-hypoxic myoclonus (Goldberg and Dorman 1976; Pedersen et al. 1982). Intention myoclonus seen in cherry-red spot–myoclonus syndrome responds partially to clonazepam (Thomas et al. 1979). According to Chadwick et al. (1977), clonazepam is effective especially in posthypoxic myoclonus of reticular reflex type. Kelly et al. (1981) and Rothwell et al. (1984) have reported that clonazepam is also effective in cortical reflex myoclonus.

Sodium valproate at a daily dose of 600–1200 mg in three divided doses is likewise effective (Koskiniemi and Palo 1978; Nishimura and Barranger 1980; Kelly et al. 1981; Pedersen et al. 1982). In degenerative type PME, Koskiniemi and Palo (1978) reported an increased urinary indican and its decrease along with a reduction in myoclonus after treatment with sodium valproate and clonazepam. Combined administration of clonazepam and sodium valproate is worth trying regardless of the type of myoclonus.

5-HTP, a serotonin precursor, has also been effective in some patients if severe gastrointestinal symptoms, especially nausea and vomiting, can be coped with (Van Woert and Sethy 1975; Growdon et al. 1976; Chadwick et al. 1977; Van Woert et al. 1977; Choteau et al. 1980; Thal et al. 1980; Feit et al. 1983). 5-HTP is effective in intention (action) myoclonus due to any cause (Van Woert et al. 1977; Thal et al. 1980), but it seems to be particularly effective in posthypoxic myoclonus (Van Woert and Sethy 1975; Growdon et al. 1976; Chadwick et al. 1977). 5-HTP can be given by an intravenous infusion of 50–300 mg or orally at a daily dose of 100–1000 mg along with a decarboxylase inhibitor (carbidopa) (Van Woert and Sethy 1975; Chadwick et al. 1977). There are, however, some patients with PME whose myoclonus is rather exaggerated by 5-HTP (Growdon et al. 1976). Although Chadwick et al. (1977) reported that reticular reflex myoclonus without any constant EEG spike–EMG discharge time relationship and without giant SEP

responds better to 5-HTP, Thal et al. (1980) did not find biochemical or electrophysiological tests to be a useful index for predicting drug efficacy.

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Chapter 10

Generalized Status Epilepticus

A. David Rothner and Harold H. Morris III

Introduction

Calmeil clearly defined generalized tonic–clonic status epilepticus (SE) in 1824. He wrote, "There are cases where as soon as one attack is barely over another begins, so that there is a succession of up to as many as 40–60 uninterrupted attacks. That is what the patients amongst themselves call 'etat de mal'. The danger is urgent, many patients die." (Hunter 1959). After his initial description, the frequency of reports concerning SE increased. They paralleled the increasing availability of medications used in the treatment of epilepsy. In 1870, Hughlings Jackson recognized that the sudden withdrawal of anticonvulsant medications, bromides, allowed the previous tendency of convulsions to return and that withdrawing the medication was a causative factor in producing the seizures (Hunter 1959). The present classification of SE was elaborated in Marseilles, France, during the 10th European Conference on Epileptology and Clinical Neurophysiology in 1962. During that conference, SE was redefined as "a condition characterized by an epileptic seizure which is so frequently repeated or so prolonged as to create a fixed and lasting epileptic condition." Implicit in this definition was the existence of as many types of SE as there are types of seizure. This classification was published by Gastaut and officially adopted by the International League Against Epilepsy in 1970 (Gastaut 1970). The duration of the ongoing seizure activity required to constitute SE has varied considerably. Certain patients having seizures as brief as 10 min have been reported as having SE; others do not consider the condition to exist until the seizures have been present for 8–10 h. Most frequently, SE has been defined as seizures lasting 30 min or more, or 1 h or more (Hauser 1983), and includes patients who fail to regain consciousness between repeated convulsions during that period of time.

Seizures have been classified on the basis of their clinical manifestations, anatomical origin, electroencephalographic patterns, presence or absence of convulsive movements, etiology, and the patient's age. SE is classified as either generalized (1° or 2°) or partial. Partial forms of SE will be discussed elsewhere. The forms of generalized SE include tonic–clonic SE, tonic SE, clonic SE, myoclonic SE, and absence SE.

Generalized Tonic–Clonic Status Epilepticus

When Calmeil described SE in 1824, he was referring to the generalized tonic–clonic form. It should be noted that this form of generalized SE includes seizures that are generalized from their onset or secondarily generalized after an initial partial onset. This condition is a medical emergency which requires prompt recognition and immediate treatment. If the treatment is not immediate, permanent neurological sequelae or even death may occur. Exact incidence rates for SE do not exist. It is estimated that anywhere from 1.3% to 16% of patients with epilepsy may at some time develop SE. SE occurs in 9% of those with "symptomatic" epilepsy and in less than 2% of those with "idiopathic" epilepsy (Hauser 1983). SE may occasionally present as the patient's initial seizure. This presentation seems to be more common in children (Aicardi and Chevrie 1970). There is no clear-cut sexual predominance in cases of SE. In adults the most common seizure type preceding SE is a partial seizure which becomes secondarily generalized. In children, primarily generalized seizures are the most predominant preceding seizure type (Aicardi and Chevrie 1970).

Status epilepticus has usually been characterized as either idiopathic or symptomatic. In adult patients with SE, the idiopathic variety occurs in anywhere from 12% to 37% (Hauser 1983; Roger et al. 1974). In children, it occurs more frequently, and Aicardi and Chevrie reported it in 53% of patients (Aicardi and Chevrie 1970). In adults, symptomatic epilepsy may be due to tumor in 3%–35% of patients, trauma in 12%–39%, cerebrovascular disease in 4%–15%, and degenerative disease in a small percentage (Hauser 1983; Roger et al. 1974). In children, symptomatic causes include infection, congenital malformations, and perinatal injuries (Aicardi and Chevrie 1970). A distinction must be made between an acute disorder causing SE and other triggers of SE in previously epileptic patients. In the latter group withdrawal of anticonvulsive medication, alcohol abuse, sleep deprivation, and intercurrent infection associated with fever have been implicated (Lederman 1984).

The prognosis for patients having had SE is dependent upon their preexisting neurological status, the etiology of their SE, the duration of the SE prior to the initiation of treatment, and problems related to the treatment itself (Celesia 1983). Acute mortality in recent times has ranged from 4% to 25%, whereas in earlier years mortalities up to 50% were common. Nonfatal sequelae include intellectual deterioration, hemiparesis, and aphasia. Nonneurological complications include pulmonary edema, compression fractures, aspiration pneumonia, myoglobinuria, and acute renal failure (Celesia 1983). SE may have a poorer prognosis when occurring in an infant or very young child. According to Aicardi and Chevrie, 40% of children with onset of idiopathic SE below 1 year of age experienced subsequent

neurological abnormality, and 27% mental retardation. In those with symptomatic SE, neurological abnormality occurred in 50% and mental retardation in 75% (Aicardi and Chevrie 1970; Lombroso 1983; Aicardi and Chevrie 1983). Data regarding the prognosis for adults who have had SE has not been well tabulated (Celesia 1983).

In generalized tonic–clonic SE, consciousness is immediately lost and coma may persist for a variable time after the convulsive movements have ceased. Neurological signs during and after the seizure are common, and may be asymmetrical. Pupillary change, decreased or increased tone and Babinski signs are most common. Autonomic manifestations may include tachycardia, hypertension, hyperpyrexia, and hypersecretion. Acidosis may develop and there may be increases in the white blood cell count, blood sugar, urea nitrogen, and creatine phosphokinase. Data concerning the metabolic effects of prolonged seizures on the central nervous system in humans are scarce. Posner demonstrated that cerebral metabolism increased markedly during seizure activity and suggested that providing adequate oxygen and glucose to the brain during the seizure could prevent neuronal damage (Posner et al. 1969). Meldrum and co-workers studied the physiology of SE in primates (Meldrum and Horton 1973; Meldrum and Brierley 1973) and were able to divide the effects into those which occurred during the early stages of SE (initial 15–20 min) and those which occurred in the later stages (greater than 25 min). In the early stages there was a rise in the arterial pressure, an increase in cerebral blood flow, an increase in intracranial pressure, a fall in the PO_2 and PCO_2, an increase in cerebral metabolic rate, lactic acidemia and systemic acidosis, and variable blood glucose changes. During the latter phase, hypoglycemia, hyperthermia, hypotension, hypoxemia, hypercalcemia, and cardiovascular collapse occurred. Cerebral hypermetabolism was maintained and neuronal damage seemed to occur during this late phase. They felt that neuronal damage could in part be prevented by paralysis, intubation, and maintenance of metabolic homeostatsis. In neonatal rats, SE inhibited DNA synthesis, delayed behavioral milestones, and reduced the seizure threshold (Wasterlain 1976). Neuropathological findings in patients dying of SE have included changes consistent with the primary underlying condition as well as the changes seen in anoxia. Microscopic abnormalities are most prevalent in the hippocampus, the Purkinje's cell layer of the cerebellum, and the middle neuronal layer of the neocortex (Corsellis and Bruton 1983).

All would agree that the prognosis of SE depends both on the underlying condition and the rapidity with which successful cessation of seizure activity is accomplished. The goal of treatment is prevention of the above-described metabolic abnormalities, pathological changes, and resultant clinical deterioration.

Treatment

As stated above, generalized tonic–clonic SE is an emergency requiring immediate and vigorous treatment (Rothner and Erenberg 1980; Treiman 1983). Other forms of SE do not usually constitute such a medical emergency, and treatment may be delayed until the patient is being monitored with EEG. The management of generalized tonic–clonic SE is best handled by an experienced team so that

evaluation and treatment can be done simultaneously. A general scheme of management is as follows:

1. Ensure adequate respiratory exchange and oxygenation
2. Monitor vital signs
3. Protect from physical harm
4. Perform brief history and baseline physical and neurological examination
5. Draw blood for laboratory tests
6. Secure an intravenous line and begin intravenous infusion
7. Infuse 50% glucose solution
8. Begin treatment with antiepileptic drugs (acute/chronic)
9. Perform further laboratory tests
10. Complete the history and continue close monitoring

Vital Functions

Maintenance of cerebral oxygenation is critical. If an oral airway is sufficient, it should be inserted and oral suction instituted. Oxygen should be given if cyanosis is present. If any question whatsoever exists regarding respiratory exchange, the patient should be intubated. The patient's vital signs should be recorded continuously. Temperature and fluid intake and output must be monitored frequently. The patient should be protected from injury during the convulsive episode and placed on a flat, soft surface with side rails up and padded to avoid injury.

Only after the vital functions have been ensured should the diagnostic evaluation take place. It should be brief but complete. A history is obtained when possible. If the patient has a known seizure disorder, dosages of anticonvulsants being received and compliance with this regimen are recorded. Past and current medical problems such as diabetes, infection, or trauma should be delineated. A brief general physical examination follows, searching for possible infection or injury as well as for any other alteration of the patient's general medical condition. The neurological examination is useful to determine a possible underlying cause and to assay the patient's general neurological state. One should look for signs of increased intracranial pressure, focal deficit, asymmetrical pupil size, or posturing that may indicate a more serious neurological condition which would mandate further neurological studies as soon as the seizures have been stopped. Blood should be drawn for a complete blood count, sugar, magnesium, calcium, BUN, electrolytes, and liver function tests, and an arterial sample should be sent for analysis of blood gases. A urinalysis should be performed; if the patient has not voided, catheterization should be undertaken. Appropriate blood samples should also be obtained for toxicology screening, blood cultures, and anticonvulsant levels. An intravenous line is secured and infusion started, using dextrose in quarter-strength saline.

If the patient is not dehydrated, maintenance intravenous fluids should be administered. Hyperthermia, if present, must be aggressively treated. More active therapy begins with the infusion of 50% dextrose. In a child, 2 mg/kg is infused. In adults, a bolus of 50 ml of 50% glucose is given. There is disagreement about the routine infusion of calcium, and it is our feeling that it should not be used unless

Table 10.1. Drug therapy for SE

Drug	Dose in adults	Dose in children	Rate	Toxic side effects	Remarks
Diazepam	5–10 mg, up to 40 mg	0.3 mg/kg	~5 mg/min	Resp. depression Hypotension	Give more slowly in children Initiate long-term therapy Increased depression when combined with phenobarbital
Lorazepam	2–10 mg	0.05–0.2 mg/kg	~2 mg/min	Resp. depression	Limited experience in younger children
Phenobarbital	10–20 mg/kg	5–10 mg/kg	Over 10–15 min	Sedation Resp. depression	10–20 mg/kg in neonates "Titrate" patient, giving 3–5 mg/kg/15 min to observe effect
Phenytoin	15–20 mg/kg	15–18 mg/kg	< 50 mg/min	Hypotension Cardiac arrhythmia	Provides short- and long-term (24 h) coverage
Paraldehyde	0.1–0.15 mg/kg	0.1–0.15 mg/kg	~10–30 min	Pulmonary edema Renal, cardiac and hepatic toxicity	As a 4% solution in saline

hypocalcemia has been demonstrated. SE induced by calcium deficiency is indeed rare and probably does not cause severe central nervous system damage. If there is any question as to the patient's nutritional state or alcoholism, 50 mg thiamine hydrochloride should be given intravenously (Treiman 1983).

Specific antiepileptic therapy is begun next (Table 10.1). The physician should use a single drug at an appropriate dosage and must be familiar with the possible side effects of the drug. High doses must be used intravenously to quickly produce therapeutic drug levels in the blood and sufficient time allowed for the drug to act before more of the same medication (or other medications) is used. Intramuscular injections are to be avoided as they produce uncertain results. It must be assumed that intravenous medications may lead to side effects such as cardiovascular changes and respiratory depression. It is for this reason that the patient should be managed in a unit where blood pressure, respiration, and cardiac rhythm can be monitored closely and the equipment necessary to provide respiratory assistance is available.

In both adults and children, the most commonly used drugs for the initial treatment of SE are diazepam (Gastaut et al. 1965), phenobarbital (Goldberg and McIntyre 1983), and phenytoin (Wilder et al. 1977). The advantages and disadvantages, doses, rates of injection, possible side effects, as well as onsets of action of these drugs are outlined in Table 10.1. Use of the maximum dosage of a single drug is preferable to the use of smaller dosages of several different medications. If, however, the use of a single drug does not control the seizures, a second agent may be necessary. If the combined effect of several drugs does not suffice, other treatments must be considered, including paraldehyde (Browne 1983), lidocaine (Morris 1979), lorazepam (Walker et al. 1979), thiopental (Orlowski et al. 1984), valproic acid (Vajda 1983), and general anesthesia (Opitz et al. 1983). If SE is not readily controlled, less common causes such as unrecognized metabolic disorders should be sought.

Diazepam

Diazepam is often used as the initial agent to suppress seizure activity. A syringe containing the undiluted solution of 5 mg/ml should be attached directly to the hub of the needle. Injection is best given into a large vein to avoid vascular irritation. In children, the initial dosage is 0.3 mg/kg given over a 2-min period. The maximum dose for a single injection is 10 mg. In adults, a bolus of 5–10 mg is given directly i.v. over a 2-min period. If diazepam is to be given as an infusion, the rate should be no more than 8 mg/h. Side effects include hypotension, respiratory depression, sedation, respiratory arrest, laryngospasm, and cardiac arrest. These side effects may be more frequent in patients who have received phenobarbital. The dosage of diazepam may be repeated in 15–20 min if seizures are not completely controlled; a maximum of 40 mg is suggested. For unknown reasons, some individuals are able to tolerate very high doses without severe side effects, but patients not responding to 40 mg will rarely respond to higher dosages. Diazepam offers relatively short-lived anticonvulsant protection. Although peak brain concentrations occur as quickly as 1 min after injections, low brain concentrations are found within 30 min after infusion due to rapid redistribution. A longer acting anticonvulsant must be given, as soon as the status has been interrupted, in order to ensure long-term seizure control.

Phenobarbital

In children begin with a dosage of 5 mg/kg infused at the rate of not more than 30 mg/min. In adults, 10–20 mg/kg should be given fractionally over 30–90 min, with careful monitoring of vital signs. Phenobarbital for injection is usually available in a concentration of 130 mg/ml, and it may be diluted with normal saline to any concentration desired. The drug is a general depressant and inevitably leads to sedation and respiratory difficulty. Patients receiving phenobarbital and diazepam together have increased difficulties with respiratory function. Peak brain concentrations occur in about 3 min, and clearance from the brain is slow. The patient should receive a total of 15 mg/kg in the first 4 h, even if this amount exceeds that necessary to interrupt the status. This amount will ensure the presence of a therapeutic drug level for 12–24 h. Daily maintenance will be necessary 12–24 h after the loading dose. Drug levels will help determine when this medication should be given and in what amounts.

Phenytoin

Phenytoin has been recognized as an excellent treatment for SE for 20 years. It is generally safe and usually not as sedating as the above-mentioned medications. One can continue to monitor the patient's level of consciousness when giving this medication. A syringe containing the undiluted solution of 50 mg/ml should be attached directly to the intravenous line. Flushing the line will decrease vascular irritation. Both in children and adults, a dose of 18 mg/kg is infused at a rate not to exceed 50 mg/min. Possible side effects include cardiac arrhythmias and hypotension. The latter can be avoided if the infusion rate is slowed. There may be cardiac conduction problems in older patients with pre-existing cardiac difficulties. Peak brain concentrations occur in 3–6 min and a therapeutic drug level will usually be maintained for approximately 12–24 h. Maintenance dosages should be started after 12–18 h.

Paraldehyde

A 4% solution of paraldehyde (4 ml of drug added to 96 ml of normal saline) may be utilized next if diazepam, phenobarbital, and phenytoin have been unsuccessful in stopping seizure activity. Rectal administration is highly unreliable. The rate of infusion is set so that 0.15 ml/kg (3.75 ml/kg of the 4% solution) would be administered over a 1 h period. If seizures stop before this amount is infused, the infusion rate is lowered to the smallest amount which will maintain the seizure-free state. The infusion rate is lowered every few hours until it is possible to discontinue the infusion without the resumption of seizure activity. Side effects include pulmonary edema and cardiac, renal, and hepatic toxicity, although these are rare. Paraldehyde must be administered only from freshly opened, dated vials since this drug deteriorates to acetaldehyde and then acetic acid on exposure to light and air. The bottle and tubing should be protected from light. Paraldehyde is also incompatible with most plastics and should always be contained in glass and administered from a glass syringe. It is important to remember that at least one long-acting anticonvulsant must be continued simultaneously in maintenance dosages.

Other Drugs

Lidocaine has been used on occasion to treat intractable seizure states, even though the drug is epileptogenic in higher dosages (Morris 1979). Few studies have addressed the issue of this drug in the treatment of SE, and it is not currently recommended for use in children. Other drugs that have been utilized include lorazepam (Walker et al. 1979), thiopental (Orlowski et al. 1984), and valproic acid (Vajda 1983) by nasogastric or rectal routes, althesin, and chlormethiazole.

General Anesthesia

On rare occasions, the above drugs may fail to stop generalized SE. A general anesthetic such as thiopental may then be administered by an anesthesiologist. Curarizing agents may be used in conjunction with general anesthesia. It is necessary to monitor the EEG so that the electrical state of the patient can be followed. There are no firm guidelines as to how long general anesthesia should be maintained. Periodic lowering of the anesthetic level with EEG monitoring is necessary to ascertain whether the patient still requires this method of therapy (Opitz et al. 1983).

Further Laboratory Testing

After seizure activity has been controlled, therapy should be modified depending on the results of the previously obtained laboratory tests. Additional laboratory testing may also be necessary. Special consideration must be given to the possible need for a computerized tomography (CT) brain scan or a lumbar puncture. The CT scan should be performed first if there is any thought that the patient may have a mass lesion. If the scan excludes this possibility, a lumbar puncture can then be performed. If a CT brain scan is not readily available, neurosurgical consultation should be obtained prior to the performance of the lumbar puncture, in the event that the patient's condition deteriorates rapidly after the procedure is performed. Agents such as mannitol should be available in case rapid lowering of the intracranial pressure becomes necessary.

Electroencephalography

The EEG changes seen in generalized tonic–clonic SE are basically those seen in individuals with a generalized tonic–clonic seizure. The seizure begins with a few seconds of generalized attentuation of background activity, which in turn may be followed by generalized, low-voltage fast activity. The fast activity grows in amplitude and forms an epileptic recruiting rhythm of approximately 10 Hz (Gastaut and Tassinari 1975). Over the next few seconds the epileptiform recruiting rhythm increases in amplitude and slows in frequency. This initial EEG

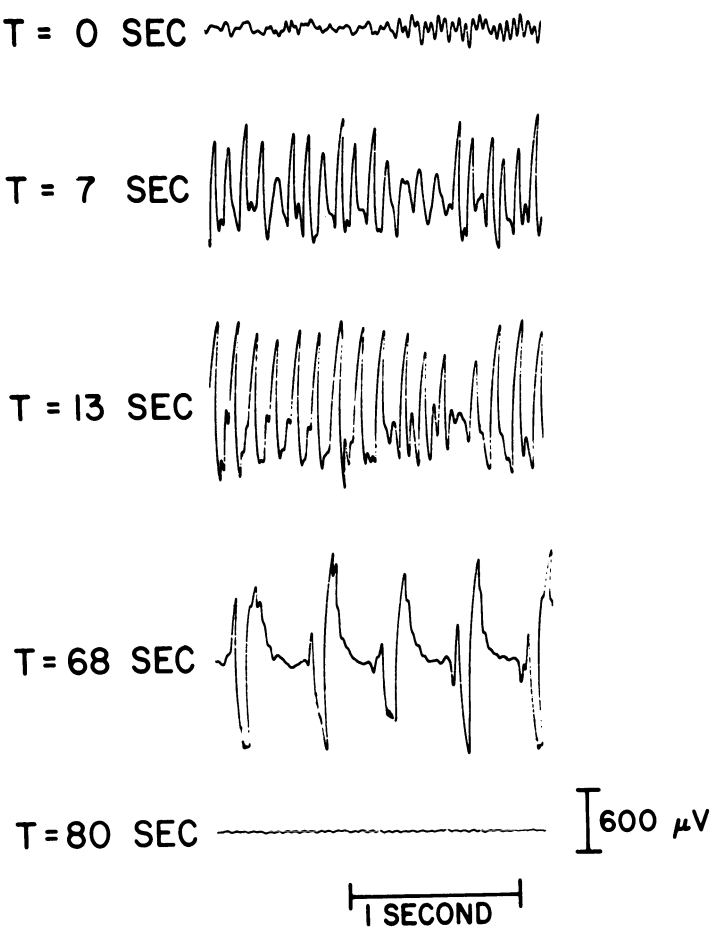

Fig. 10.1. The sequence shows the electrographic evolution of a tonic–clonic seizure. The recording is from subdural electrodes in a patient being evaluated for surgery for epilepsy. Recording directly from the cortex allows identification of waveforms invariably obscured with scalp recordings during a grand mal seizure. The first sequence demonstrates low-voltage fast activity; the second an "epileptic recruiting rhythm," which correlates with the tonic phase of the seizure; the third shows evolution of the epileptic recruiting rhythm into repetitive sharp waves; the fourth shows 2- to 3-Hz sharp-wave complexes which correlate with the clonic phase of the seizure; the fifth reveals profound cortical depression immediately postictally.

period lasting anywhere from approximately 15 to 30 s is followed by generalized polyspike and slow-wave discharges with a repetition rate which gradually slows from 4 Hz to 1 Hz or less and then ceases (Fig. 10.1). Electromyographic artifact associated with the tonic phase of the seizure frequently obscures the initial attenuation phase of the EEG and the epileptic recruiting rhythm is usually difficult or impossible to see. The clonic jerks are associated with the polyspike phase of the spike and slow-wave complexes.

Between individual seizures, the EEG shows diffuse slowing of variable degree; however, characteristically the background is in the delta frequency. Immediately after the seizures there is diffuse depression of background activity lasting from several seconds to 1–2 min, followed by a gradual increase in voltage and

frequency of rhythms. If the patient's seizures are prolonged and frequent, there may be marked depression of background activity for the entire period between the seizures. Intermittent generalized paroxysms of spike and wave activity may occur without clinical symptoms. Occasionally, depending on the associated circumstances and whether or not there is a superimposed hypoxic or metabolic encephalopathy, a burst suppression pattern may be seen interictally.

The EEG changes of secondarily generalized tonic–clonic SE may show a focal onset of epileptiform activity over one or the other hemisphere. On other occasions either an asymmetry of the fast activity, of the epileptic recruiting rhythm, or of the sharp- and slow-wave complexes may be found, with this activity being higher over the hemisphere from which the seizures originate. Following cessation of the individual seizure, the postictal slow activity may be more marked in the hemisphere from which the seizure originated.

Generalized Tonic Status Epilepticus

Tonic SE was described by Gastaut et al. in 1963. This seizure type is more common in children and adolescents who have chronic epilepsy and are mentally retarded, such as in the Lennox-Gastaut syndrome. The disorder consists of a rapid succession of tonic seizures associated with autonomic disturbances. The seizure may consist of contractions of the neck muscles, facial muscles, and thoracic and abdominal musculature, as well as the arm and leg muscles (the lower limbs are usually involved to a lesser extent). The patient may become opisthotonic. Seizures may be fully expressed or only partially expressed and may be associated with sweating, excessive secretions, tachycardia, hypertension, and cyanosis. On rare occasions the seizures are subclinical, at which time the only abnormality is confusion coupled with the abnormalities seen on the EEG. Most tonic seizures last 10–20 s and may occur 10–20 times per hour. The prognosis is related to the primary neurological state and usually the patient remains with a chronic seizure disorder. In some cases, intellectual deterioration occurs following the seizures. Tonic seizures can be the result of secondarily generalized tonic–clonic SE, although some authors recommend avoidance of benzodiazepines as they have been reported to precipitate tonic SE (Tassinari et al. 1972).

The EEG changes in tonic SE are the same as those found in records of individual tonic seizures and consist of three main types: (a) a generalized electrodecremental response or diffuse desynchronization; (b) paroxysmal fast activity of low voltage which progressively slows in frequency and grows in amplitude; and (c) a generalized epileptic recruiting rhythm of approximately 10 Hz (Fig. 10.2) (Gastaut and Tassinari 1975; Gastaut et al. 1963; Tassinari et al. 1972; Roger et al. 1974). Each seizure lasts approximately 5–20 s and they tend to occur more often during non-REM sleep than at other times.

Polygraphic recording of electromyographic activity may be of value during the EEG as it may detect tonic muscle spasms of low amplitude that are clinically inapparent (Roger et al. 1974).

Interictally, the EEG frequently shows background slow activity, multifocal sharp waves, or a slow spike–wave pattern if the patient has the Lennox-Gastaut syndrome, as many do.

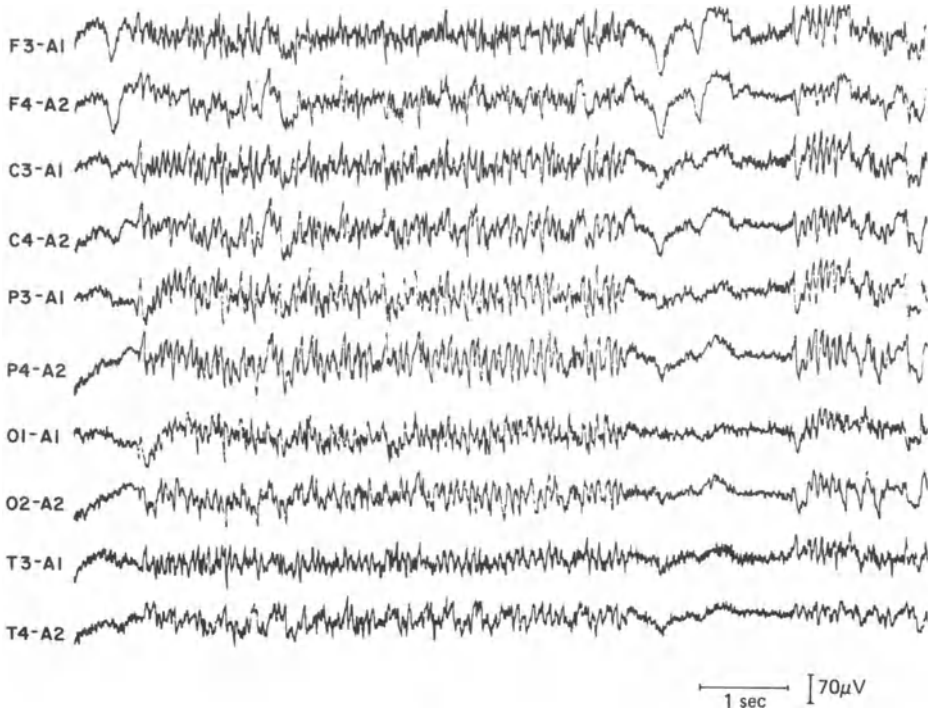

Fig. 10.2. EEG from a 42-year-old mentally retarded male hospitalized because of frequent tonic seizures. The 6-s paroxysm of generalized 11-Hz activity is mixed with EMG artifact from the tonic seizure.

Generalized Clonic Status Epilepticus

Clonic SE appears to be a condition seen more frequently in infants and young children. Its etiology is idiopathic in approximately 50% of the cases. In an additional 25% it is the symptom of an acute encephalopathic event, and in another 25% it occurs in children who have a chronic neurological deficit. Fever seems to provoke this disorder. The condition consists of low amplitude jerks which are usually bilateral but may be asymmetrical. They recur in a rhythmic or arrhythmic fashion and are associated with EEG changes. The prognosis in this condition is related to the primary neurological disorder. The condition may be treated in the same way as generalized tonic–clonic SE. The administration of benzodiazepines does not appear to affect this condition adversely (Aicardi and Chevrie 1970; Congdon and Forsythe 1980).

The EEG findings in clonic SE show generalized and synchronous high amplitude slow waves mixed with bursts of spikes or polyspikes or an epileptic recruiting rhythm (Gastaut 1983).

Generalized Myoclonic Status Epilepticus

Myoclonic SE is an unusual condition which may be seen in two clinical settings:

1. In association with a variety of degenerative, metabolic, and toxic encephalopathies, such as post-anoxic encephalopathy, uremic encephalopathy, progressive myoclonus epilepsy, the Ramsay Hunt syndrome, and various lipidoses. The EEG findings are those of a slow background rhythm with bursts of generalized spike or polyspike and slow-wave complexes and differ according to the basic underlying condition responsible for the illness. They will not be discussed further in this chapter.
2. In patients with a history of generalized epilepsy. It is then characterized by recurrent, generalized, more or less pronounced myoclonic jerks with preservation of consciousness. The EEG shows bursts of generalized polyspike activity in association with the myoclonic jerks. Interictally, the background activity is relatively normal (Gastaut and Tassinari 1975).

Marked myoclonus has rarely been mentioned as being a feature of absence SE (Terzano et al. 1978; Storm Van Leeuwen et al. 1969). In this entity the patient is confused and mentally dulled as in other cases of absence status but in addition prominent myoclonic jerks are present. The EEG correlate of the myoclonic jerks are bursts of generalized polyspikes.

Myoclonic SE is not a life-threatening situation. Judicious use of intravenous benzodiazepines is the treatment of choice.

Generalized Absence Status

In 1945 Lennox described a condition of a prolonged confusional state in children associated with generalized spike-and-slow-wave discharges (Lennox 1945). He termed this illness petit mal status. Since the initial report many case reports and several reviews of absence status (petit mal status) have appeared (Brenner 1980; Andermann and Robb 1972; Porter and Penry 1983).

Many names have been used for this entity, including petit mal status, prolonged petit mal automatism, epilepsy minorus continual, spike–wave stupor, epileptic twilight state, spaced-out status, and transient ictal psychosis (Brenner 1980; Andermann and Robb 1972). Of all forms of nonconvulsive SE, generalized absence status is the most commonly encountered (Porter and Penry 1983).

Clinically, the degree of impairment of sensorium varies from a mild degree of mental clouding all the way to extreme stupor. Different degrees of impairment may be seen in the same patient in different bouts of absence status. In addition to the clouding of consciousness, frequent myoclonic twitches of the eyelids, facial muscles or extremities may be seen. Occasionally an episode of absence status may terminate with a generalized tonic–clonic convulsion.

Absence status may be seen in patients of any age but most commonly occurs in children. The majority of patients are neurologically normal except for having a history of generalized epilepsy and are either currently under treatment or have

been treated in the past. Many of these patients have had typical absence seizures, but they may have had myoclonic and generalized tonic–clonic seizures as well. Occasionally, absence status may appear de novo in older patients who have had no history of epilepsy (Schwartz and Scott 1971; Ellis and Lee 1978; Van Zandycke et al. 1980). The incidence of absence status in patients with absence epilepsy is between 2% and 10% (Roger et al. 1974).

The differential diagnosis of absence status includes complex partial SE, psychiatric disturbances, toxic or metabolic encephalopathies, and transient global amnesia.

The EEG demonstrates generalized and bilaterally synchronous spike and slow-wave complexes of a variable frequency. Usually one to four complexes per second are present (Fig. 10.3). Only occasionally is the classic three per second spike and wave complex typical of petit mal epilepsy observed. These EEG findings are of great help in separating the condition from various encephalopathies in which only slowing of background activity should be seen or from complex partial SE, in which focal epileptiform activity should be seen in the temporal leads.

Niedermeyer et al. (1979) and Morris (1983, personal communication) have each observed cases of absence status which were apparently secondarily generalized. Clinically, these patients were indistinguishable from those with primarily generalized absence status, but the EEG showed spike and slow-wave complexes which

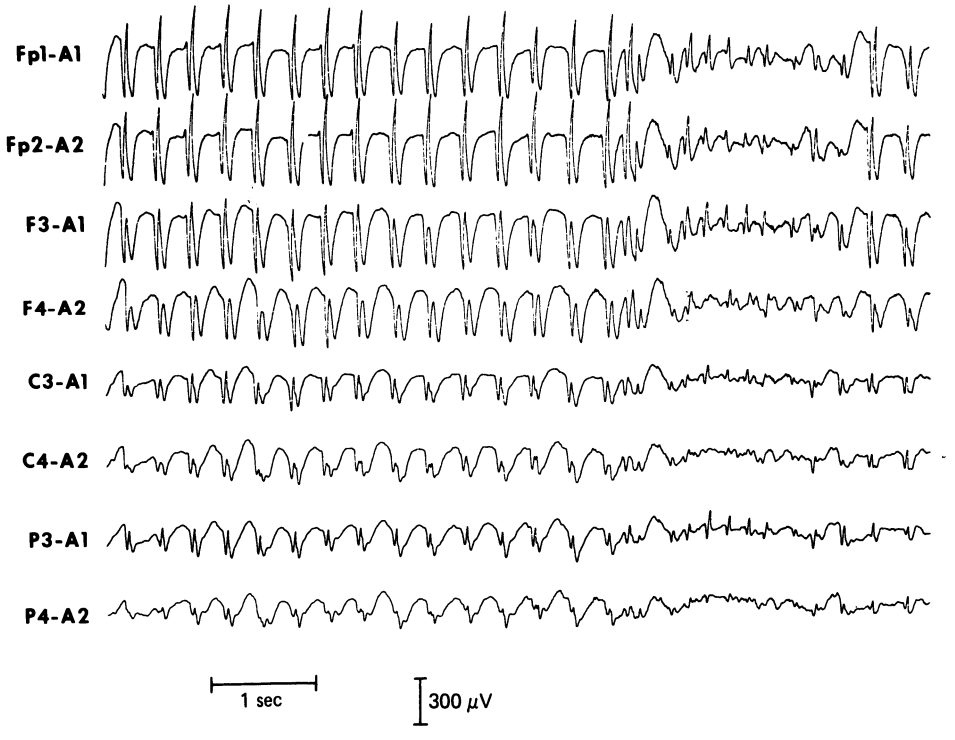

Fig. 10.3. Generalized high-amplitude 3-Hz spike and wave complexes with occasional runs of lower amplitude fast frequency spike–wave complexes were found in a 15-year-old patient during a prolonged confusional episode.

were higher in amplitude over one hemisphere. In Morris' case, the generalized spike and wave complexes were aborted abruptly following injection of 50 mg amobarbital into the right carotid artery (discharges were maximal over the right hemisphere). There was no significant change in a subsequent bout of absence status when 50 mg phenobarbital was injected into the left internal carotid artery (Fig. 10.4) (Rovit et al. 1961).

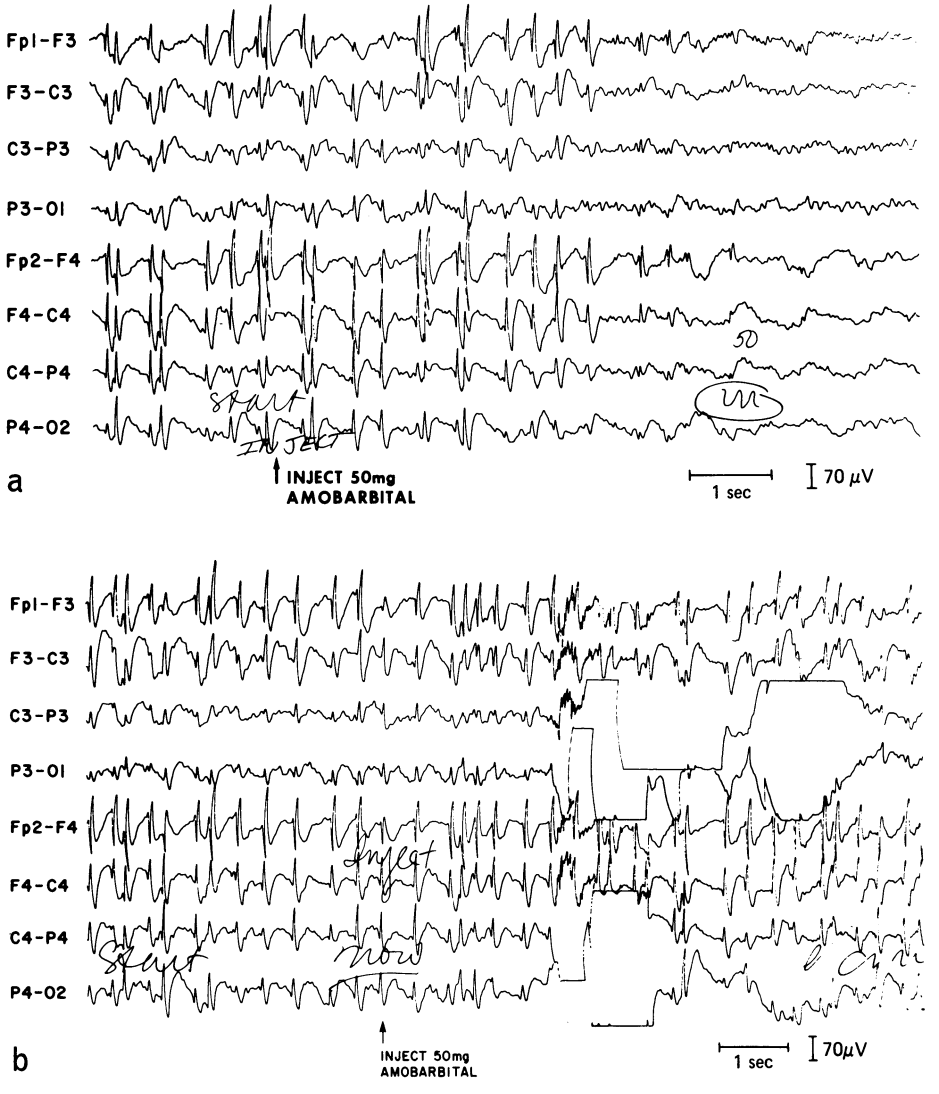

Fig. 10.4a,b. EEGs recorded from a 41-year-old woman with recurrent episodes of absence status. The sharp waves are higher in amplitude over the right hemisphere, suggesting secondary generalization. Following injection of amobarbital into the right carotid artery, all epileptiform activity is quickly abolished (**a**) but there was no effect with left carotid injection (**b**). This finding supports the impression of secondarily generalized epilepsy of right hemisphere origin.

No systematic study of the treatment of absence status has been published; however, most authors remark that the entity is remarkably sensitive to intravenous diazepam and our own experience has also revealed this to be the case. As absence status is not as life threatening as is generalized tonic–clonic SE, the illness should not be treated as vigorously as the latter. There is no agreement on which drug to use for prevention of future episodes of absence status. If the patient has generalized tonic–clonic seizures in addition to absence seizures, it would seem reasonable to use either valproic acid as a single agent or ethosuximide combined with phenobarbital, phenytoin, or carbamazepine. Success in preventing future episodes of absence status using either phenytoin or phenobarbital has been reported in adults with no previous history of epilepsy (Ellis and Lee 1978). Presumably the pathophysiology underlying absence status is different from that underlying classic petit mal as these drugs are not efficacious in that illness.

The prognosis of petit mal status is excellent as the patients invariably are neurologically unchanged after the episode of absence status has ended.

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Chapter 11

Simple Partial Seizures

Ronald P. Lesser, Hans Lüders, Dudley S. Dinner, and Harold H. Morris III

Introduction

It is over a century since Fritsch and Hitzig, Ferrier, and Jackson laid down the experimental and clinical basis for functional localization in persons both with and without seizure disorders, and it is over 50 years since Foerster, Penfield, and their collaborators began applying these insights systematically to the surgical treatment of intractable seizures.

Despite this experience, localization is still very much an "alive" subject for investigation, and the increasing use of implanted electrodes and the accumulating experience with metabolic studies of cortical function are likely to enhance our understanding of the anatomical underpinnings of focal seizure disorders. These new techniques will be most beneficial, however, if we have a clear understanding of the insights gained by our predecessors. This review was undertaken, therefore, first to collect and summarize the previously reported experience regarding the symptoms and signs of partial seizures and, second, to review related issues regarding the etiology and treatment of these seizures.

Synonyms

Partial seizures are seizures which begin in a circumscribed area of the brain. Although they have been recognized since antiquity, the linkage between a partial seizure and a localized cerebral discharge is linked historically with the name of Hughlings Jackson, and it was Charcot (Holmes 1927) who first proposed the term jacksonian epilepsy for the focal motor seizures which Jackson described. Many authors, including Jackson, have recognized, however, that "hemiplegic epilepsy"

was first actually described by Bravais, in 1827 (Holmes 1927; Parker 1929); this has led some to use the term Bravais-Jacksonian seizures for seizures manifested by a "march" of symptoms, indicating progressive spread of the seizure from its point of origin (Cotte-Rittaud and Courjon 1962). The term jacksonian seizures may also be applied to focal sensory seizures (Lennox and Lennox 1960). Elementary (simple) partial (focal) seizures, using the current international classification (Dreifuss 1981), are those which begin in a circumscribed region and do not alter consciousness, regardless of the number or complexity of symptoms which may occur. It should be recognized, however, that a seizure may remain localized and nonetheless alter consciousness. This is implicitly recognized in the International Classification, and cases exemplifying this have been reported (Ludwig et al. 1975; Gloor et al. 1980). It should be realized that, whether the term focal or partial is used, the term itself implies no specific assumptions about how large the epileptogenic area might be, and there is evidence that the size may vary considerably among patients with focal seizures (Ludwig et al. 1975; Babb et al. 1984a,b).

There are terms which are used for seizures of focal origin which refer to specific types of partial seizure or to specific syndromes. For example, the term "aura" has been used since Galen's time to imply a "warning" that a seizure is about to occur. In actuality, however, the aura is usually a focal seizure. The term HHE syndrome has been used for patients with hemiconvulsions, hemiplegia, and epilepsy; the hemiconvulsions represent seizures which are restricted to the motor strip or are more widespread, up to and including the entire hemisphere. Rasmussen's syndrome (Rasmussen and McCann 1968) is a subacute epileptogenic inflammatory disturbance affecting varying percentages of the brain; the seizures which occur in this syndrome most likely originate in and around the localized area of inflammation and thus are, by definition, seizures of partial origin.

Finally, a Todd's paralysis is a postictal impairment of function within a discrete region or regions of the brain. Although patients with Todd's paralyses may have had seizures which generalized, others have had seizures which have remained relatively localized, with resultant postictal impairment. It is important to note that the impaired region is not necessarily the region of seizure onset.

Classification

The International Classification of Epileptic Seizures (Dreifuss 1981) divides simple partial seizures into four major categories: (a) those with motor signs, (b) those with somatosensory or special sensory symptoms, (c) those with autonomic symptoms or signs, and (d) those with psychic symptoms. The clinical manifestations of seizures of focal origin will be discussed within this general framework. It should be understood, however, that many reports, especially in the older literature, do not distinguish between seizures which remain discretely localized and those which spread to involve other areas of the brain. Indeed, an area of interest for future research would be a comparison of the tendency for spread from different regions of the brain. A second problem is that the site of seizure origin may not be the generator of a specific phenomenon. For example, Gastaut (1958) described ictal elementary visual phosphenes, of presumed occipital origin, but due to spread of epileptiform activity from the temporal lobe. Similarly, Schneider et

al. (1961) and Gloor et al. (1982) described cases in which experiential phenomena were evoked by spontaneous seizures or by brain stimulation only when limbic (as opposed to lateral neocortical) structures were involved, regardless of the site of seizure onset or of stimulation (see also Halgren et al. 1978). Gloor et al. discussed whether the limbic system was needed for the origin, or for the sense of immediacy, of the phenomena they reported. A third problem is that the same sign or symptom might be generated from more than one brain region. For example, although automatisms and autonomic signs are frequent in temporal lobe epilepsy (Penfield and Kristiansen 1951; Currie et al. 1971), patients with frontal lobe epilepsy manifest these as well (Ludwig et al. 1975; Geier et al. 1977b; Rasmussen 1983) and

Table 11.1. Initial signs of seizure onset in 222 candidates for surgery at the Montreal Neurological Institute (adapted from Penfield and Kristiansen 1951)

Sign at seizure onset	No. of patients	Location of seizure focus					
Motor							
Focal motor with march	20		11 RF 2 RP		7 ? V		
Adversive, unconscious	16	13 F				3 T	
conscious	7	6 F					1 TP
Vocalization	2	2 FI					
Arrest of vocalization	6	2 FB			1 V		3 TP
Sensory							
Somatosensory	55	2 FI	24 RP 18 R 7 RF			1 ? T	3 P
Visual	11						11 O
Auditory	3					3 T	
Olfactory	1					1 T	
Gustatory	2					2 T	
Autonomic							
Mastication	3		1 R			2 T	
Epigastric/abdominal	8	3 FI		5 SS			
Epigastric, rising sensation	8			4 S	4 V		
Thoracic	3			3 S			
Cardiac	8	1 F		3 S	3 V		1 TPO
Misc. body sensations	9	4 FI		1 S		3 T	1 P
Misc. cephalic sensations	16	6 FI	3 RP/P		1 VS, 2 ? 1 V	5 T	
Yawning	1	1 FA					
Psychic symptoms							
Forced thinking	2	2 FS					
Fear	3	1 FI		1 S		1 T	
Perceptual illusions	13	4 F				9 T	
Hallucinations	5					3 T	2 TPO
Generalized convulsion	10	8 F				1 T	1 TPO
Loss of consciousness	1	1 FT					

Abbreviations: F, frontal; FA, anterior frontal; FI, intermediate frontal; FB, Broca's area; FS, superior frontal; FT, frontotemporal; O, occipital; P, parietal; R, rolandic; RF, prerolandic fissure; RP, postrolandic fissure; S, sylvian; SS, suprasylvian; T, temporal; TP, temporoparietal; TPO, temporoparieto-occipital; V, vertex/midline; VS, supplementary motor area.

Table 11.2. Percentage of patients with various symptoms and signs of epilepsy in five studies[a]

Study	Temporal			Frontal			Extratemporal, other
	A	B	D	C	D	E	D
Total number of patients in study	52	666	270	22	46	40	184
Motor, not specified		14		77		27[c]	
Motor, tonic			51		83		47
Motor, clonic			34		43		64
Motor, atonic				82			
Adversive		0.5	61	86	70	8	50
Speech alterations		22					
Somatosensory		2	19		17	18	32
Visual	10	18	7	22	0		35
Auditory		16	3		2		2
Olfactory	12	12	13		0		
Gustatory	8	3					
Nose, throat burn	4						
Vertiginous		19					
Autonomic, not specified		40	41	59	17		17
Masticatory	35	10					
Epigastric	15						
Gastrointestinal	21[b]						
Palpitations	13						
Respiratory	8						
Sweating	12						
Pallor	25						
Flushing	8						
Piloerection	2						
Psychic, not specified		19	52		48	14	27
Memory disturbances	25	17					
Cognitive changes	10	27					
Fear	48						
Other unpleasant emotion	27						
Pleasure	23						
Depression	10						
Perceptual illusions	8						
Formed visual hallucinations	8						
Formed auditory hallucinations	4						
Automatisms, not specified		95			61	30	39
simple				73			
complex				32			
Loss of contact				100			

[a] Direct comparison of each symptom or sign is not possible for each study due to the differing intents and definitions of each report. "Temporal," "Frontal" and "Extratemporal, other" indicate that the site of seizure onset was thought to be temporal, frontal, or elsewhere. Study A is Daly 1958[a]. Study B is Currie et al. 1971. Study C is Geier et al. 1977[b]. Study D is King and Ajmone-Marsan 1977. Study E is Rasmussen 1983. In the study by Daly, the majority but not all were thought to have temporal lobe epilepsy.

[b] This is the total of: borborygmi, belching (2%); miscellaneous abdominal (15%); and defecation, urge to defecate (4%).

[c] Unspecified sensorimotor signs/symptoms.

there are close functional relationships between a number of temporal and frontal regions (Reep 1984).

These considerations support the conclusion made by many authors that it often will not be a specific symptom or sign but rather the set of clinical and electroencephalographic data which finally may indicate the site of seizure origin (Tables 11.1, 11.2). As experience increases regarding the results of video-EEG monitoring, using implanted electrodes, our understanding of the cortical origins of many of the manifestations of epilepsy may improve. However, as will be seen, current knowledge only occasionally allows the localization of a symptom or sign to a single region of the brain and it is quite likely that this may reflect the underlying organization of the brain, with parallel processing of data by more than one brain region in some cases and sequential processing in others, with symptomatology producible at any point along the pathway.

Particularly in the case of unusual symptoms and signs (see below) it is often the weight of multiple observations from multiple institutions which makes it convincing that these descriptions are indeed of epileptic events. The next section of this chapter therefore will review phenomena reported in simple partial seizures, comparing the available reports in the literature. It should be understood that the separation of various seizure manifestations, as in this chapter, is often artificial, since actual seizures often are characterized by many "different" signs and symptoms. For example, in Daly's (1958a) review of ictal affect, many patients were found also to have ictal autonomic signs and symptoms (also see Daly 1975).

Clinical Manifestations

Simple Partial Seizures with Motor Signs

Motor Seizures Without March

Motor seizures may be either tonic or clonic. Fincher and Dowman (1931) described the motor manifestations as jerking, twitching, quivering, drawing, or stiffening. The majority of focal motor seizures affect the face, arm, or leg, but any body part may potentially be affected. For example, Matsuo (1984) has reported seizures of the truncal musculature and Klass and Dyck (1984) have recently described a patient with muscular clonus in the genitoanal area and foot during seizures, without any sensory, eliminative, or erogenous symptoms. In the series of Fincher and Dowman, 84 of 130 patients had only motor symptoms, 17 motor and sensory symptoms, and, interestingly, only 9 solely sensory symptoms. In nine cases motor symptoms were followed by sensory and in 20, sensory followed by motor symptoms. Thus, in this series of patients with seizures originating in the rolandic region, the majority had motor seizures without spread beyond the motor region; the authors did not discuss the frequency of spread within the motor region. Loiseau et al. (1977) reviewed 200 cases of partial seizures and reported that 61 had partial motor symptoms alone. Of the 8938 epileptic patients studied

Table 11.3. Types of focal seizure found among patients with epilepsy admitted to the University Hospital of Lyon between 1965 and 1975 (adapted from Mauguiere and Courjon 1978)[a]

	No.	%
Focal motor without march	1158	12.9
Focal motor with march	199	2.2
Hemiconvulsions	582	6.5
Adversive	461	5.2
Somatosensory	127	1.4
Other sensory (visual, auditory, olfactory, gustatory)	262	2.9
Complex partial	449	5.0
Brief complex partial with elementary gesticulation[b]	293	3.3

[a] A total of 8938 patients with focal and/or generalized seizures had been admitted.
[b] The last category is separated from the seventh as possibly indicative of mesial frontal, rather than temporal, origin (Mauguiere, personal communication 1985).

by Mauguiere and Courjon (1978), 1158 had focal tonic or clonic seizures, 582 hemitonic or clonic seizures, and 199 jacksonian seizures (Table 11.3).

In discussing his cases of truncal seizures, Matsuo (1984) reviewed the evidence that the truncal muscles have a relatively small cortical representation and also the evidence (French et al. 1956) that this region might have a higher threshold before stimulation would produce signs or symptoms. Another issue of interest in this report was the postulated parietal location of the ictal focus; Matsuo cited the evidence (Foerster 1936; Woolsey 1978) supporting the occurrence of motor contractions in response to postcentral stimulation, although acknowledging the possibility of spread anterior to the rolandic sulcus as well as the possibility of sensory symptoms unreported by the patient. A related possibility is that the ictal discharges may indeed have had a postrolandic onset, but in an area with a relatively high threshold for functional alterations (as discussed on p. 234). The seizure could then have spread anteriorly, into an area with a lower threshold. However, Russell and Whitty (1953) found that sensory phenomena were more likely to precede than to follow motor phenomena in their patients with focal seizures. This implies that sensory thresholds were not necessarily higher than motor thresholds in their patients. Also, it should be noted that somatomotor manifestations can be due to extrarolandic as well as rolandic foci (Bossi et al. 1984). In any case, it is clear that a seizure which clinically may not have a march might actually have one if electrocorticography were performed.

It should be noted that several authors have reported focal tonic symptoms as manifestations of spinal cord pathology, including multiple sclerosis (Matthews 1975) and cord meningiomas (Harrington and Bone 1981; Plant 1981). Therefore, in selected cases, tonic or dystonic spasms could be the result of subcortical pathology and therefore not epileptic in origin. In addition, benign focal epilepsy of childhood frequently manifests itself as a focal motor seizure; this entity is discussed elsewhere in this volume.

Motor Seizures with Ocular Manifestations. Nystagmus with a fast phase in one direction and a slow phase in the other has been frequently described, but pendular nystagmus also occurs. At least as common as these, if not more so, is forced eye deviation to one side. Gastaut and Roger (1954), White (1971), Huott et al. (1974),

Dalla Bernardina et al. (1977), Beun et al. (1984), Ramani (1985) and Thurston et al. (1985) described patients with posterior quadrant epileptiform discharges opposite to the fast phase of ictal nystagmus; however, Gastaut and Roger (1954) and Gastaut (1960) have described epileptic nystagmus with the slow phase opposite a posterior quadrant focus. Of the two reports of epileptic pendular nystagmus, one was due to a posterior quadrant and the other to a posterior frontal focus (Trevisan and Belsasso 1961; Trevisan and Dettori 1967).

Of 300 cases with adversive seizures reviewed by Cotte-Rittaud and Courjon (1962), the seizures in two were manifested by eye deviation alone. Smith and Kellaway (1964) reviewed 452 children with occipital epileptogenic foci and reported eye, or head and eye, turning to accompany the seizures in 24% of cases. The question of lateralization was not discussed (also see pp. 230–231).

Motor Seizures Manifested by Motor Inhibition. Gowers (1885), Jackson (1890), Collier (1928), Penfield and Jasper (1954), and Globus et al. (1982) have all described the occurrence of such episodes. Holmes (1927) referred to them as negative seizures, noted that Jackson had described a patient with ictal loss of motor power in the face and hand, and added a case of loss of hand movement which he had seen. Penfield and Jasper described ictal paralysis of eye, arm, and leg movement.

Holmes and Penfield and Erickson (1941) presumed the seizures to be due to primary inhibition of the rolandic motor cortex, but Penfield and Welch (1951) listed motor inhibition as one of the symptoms of supplementary motor seizures, Penfield and Kristiansen (1951) described unilateral ictal weakness due to an orbital frontal lesion, and a case reported by Kofman and Tasker (1967) had ipsilateral weakness and sensory manifestations due to a meningioma in the second somatosensory area. In support of these reports are the observations that electrical stimulation of the extrarolandic motor areas can produce motor inhibition (Penfield and Jasper 1954; Lesser et al. 1984e, Lüders et al. 1985a). Thus, seizures in at least three cortical regions may produce ictal weakness (also see pp. 230–231).

Motor Seizures with March

Motor seizures without march often bear Jackson's name and are manifested by a progressive spread of ictal motor symptoms from one part of the body to another. Holmes (1927) alluded to the possibility of a relatively slow spread in some patients, an issue also discussed by Russell and Whitty (1953). As described earlier, Fincher and Dowman (1931) reported motor followed by sensory symptoms in nine and sensory followed by motor symptoms in 20 of 130 patients with focal seizures. Loiseau et al. (1977) found that 10 of 71 patients with focal motor seizures manifested a march. Of 60 jacksonian seizures in infancy and childhood reported by Holowach et al. (1958), 25 began in the face (8 of these around the eye and 5 around the mouth). Seventeen patients' seizures began in the hand, 7 in the arm, 2 in the shoulder, 6 in the leg, and 3 in the foot. It is possible that these distributions reflect the actual area within the motor strip pertaining to each of the body parts. Also to be mentioned are unilateral seizures or hemiconvulsions, as described by Gastaut et al. (1957, 1959–60, 1962). Many of the reported patients had jacksonian spread of their seizures, including some with onset around the eye. In some

patients, hemiconvulsions are associated with infantile hemiplegia (Freud 1897; Aicardi et al. 1969; Gastaut et al. 1959–60; Gold and Carter 1976).

Some seizures spread slowly, others relatively rapidly. One might expect the spread of a seizure to follow a homuncular pattern, as did case 1 of Foerster and Penfield (1930), for example. There are, however, many examples of alternative patterns of spread (Hallen 1952). For example, in the cases of Russell and Whitty (1953), case 29 exhibited spread from the leg to the abdomen, case 33 exhibited spread from the foot to the leg to the shoulder to the sternocleidomastoid to the triceps, and case 66 exhibited spread from the right hand directly to the right foot. In many cases this is probably because the convolutions of the cortex of an individual patient are such that adjacent areas of cortex may at times represent nonadjacent areas of the body (cf. Rasmussen and Penfield 1947). It is also possible that a seizure could spread into an area with a relatively high threshold for manifesting clinical changes, an issue discussed in greater detail on p. 234.

Versive Seizures

Versive seizures were classically described by Foerster and Penfield in 1930 to be manifested by turning of the head, eyes, and at times the trunk, to one side, and similar cases were described by David et al. (1944), Penfield and Welch (1951), Russell and Whitty (1953), Zee et al. (1974), Loiseau et al. (1977), and Pedley et al. (1981). Typically patients do not lose consciousness during episodes. Cotte-Rittaud and Courjon (1962) and R. Ochs et al. (1984) both concluded that "forced" turning could be to either side. However, Wyllie et al. (1986) have recently reassessed the issue of forced version. In this study, the video recording was evaluated without knowledge of the EEG data and forced turning was invariably away from the side of the focus and was a reliable lateralizing sign regardless of the lobe of ictal onset and regardless of whether version occurred at ictal onset or later during the seizure. This latter study used real time, whereas the earlier studies used no, or time-lapse, video recording. In agreement with the data of Wyllie et al., Revol et al. (1972) found the first motor manifestations of experimental epileptogenic cingulate foci always to be contralateral to the foci. Penfield and Jasper (1954) had described a patient whose mouth was drawn in a forced manner to one side, but whose eyes were deviated to the other. However, they concluded that the eye deviation was due to inhibition of oculomotor activity. Thus the lateralizing signs in this patient were consistent with one another. Also, Rasmussen and Penfield (1947) reported that not only contralateral but also ipsilateral eye deviation (as well as occasional upward deviation and convergence) could occur when stimulating "the precentral gyrus immediately anterior to the central fissure," whereas stimulation of more anterior sites always resulted in contraversion. Thus, in theory, forced eye deviation could be contralateral to forced head deviation during at least a portion of a seizure.

Versive seizures have been associated with supplementary motor, superior frontal, parietal, and occipital lesions and a variety of other signs and symptoms have been associated with ictal version. Often the clustering of findings in a given patient has appeared to have some localizing significance. For this reason associated findings and site of origin will be discussed together. Signs other than version attributed to the supplementary motor area have included motor inhibition, vocalization or speech arrest, alterations in heart rate or pupillary diameter

(Penfield and Welch 1951; Kennedy 1959; Rasmussen 1974; Green et al. 1980; Pedley et al. 1981) including unilateral (ipsilateral) pupillary changes (Zee et al. 1974), and ipsilateral nonversive motor signs. Automatisms have been reported (Ajmone-Marsan and Ralston 1957). Jackson's (1882) patient had seizures which at times would affect both sides of the body without loss of consciousness secondary to a superior frontal glioma. Kofman and Tasker (1967) described clonic movements of the right arm and hand associated with inability to move the head, secondary to a meningioma affecting the right supplementary motor area, and seizures with ipsilateral signs were also described by Dechaume et al. (1961), Arseni and Maretsis (1979), and Ahuja and Tharakan (1982). Many of these patients had mass lesions and several reports pointed out the possibility of a compressive effect upon the contralateral supplementary motor area or motor strip in patients with tumors.

Kennedy (1959) reviewed the clinical manifestations of seven cases of seizures in the superior–medial aspect of the hemispheres and noted the occurrence of visceral, genital, and anal sensations, as well as tonic postures and sensations involving the leg. Clearly, some lesions may have been restricted to the supplementary motor area, some lesions were restricted to the primary motor or sensory strip, some may have involved more than one of these regions, and still others may have involved spread to other areas of the brain (Ajmone-Marsan and Ralston 1957). Most of these patients lost consciousness in the course of their episodes but Kennedy noted that Jackson had described in 1882 a patient with bilateral motor signs and inability to speak without loss of consciousness during seizures secondary to a superior frontal glioma. Ludwig et al. (1975) reviewed the literature on seizures originating in the orbital frontal cortex; several patients had contralateral version in the course of their episodes. Foerster and Penfield (1930) described adversive seizures of parietal lobe origin as well as a patient with seizures of occipital origin which began with unformed and then formed visual hallucinations followed by adversion and then hemiclonic activity.

Postural Seizures

Seizures within the supplementary motor area can, in addition to the symptoms described above, present with prominent posturing which is not versive. For example, Geier et al. (1977a) noted the occurrence of tonic postural changes of the arm in association with parietal lobe discharges and noted the similarity of this to the "larval M2e" seizures described by Ajmone-Marsan and Ralston (1957) and also by Feindel and Penfield (1954). They discussed the role of spread of the discharge into areas adjacent to the primary focus, as reviewed above (Penfield and Welsh 1951; Rasmussen 1974; Green et al. 1980).

Seizures Manifested by Vocalization, or by Arrest of Vocalization

The language-related manifestations of epileptic seizures have been extensively reviewed by Hecaen and Angelergues (1960). These authors reviewed the distinctions between expressive and receptive aphasias, as they might pertain to the epilepsies, and also differentiated interferences with speech from alterations of perception per se and from alterations affecting the primary sensorimotor strip.

They found 142 patients with speech arrest, of whom 96 had this as an isolated symptom, and also found five patients with agraphia, in each case in association with other signs. These were patients with rolandic, prerolandic, temporal, or temporo-parieto-occipital junction origins for their seizures. The possibility of vocalization with supplementary motor area seizures has just been alluded to. In addition, Robinson and Watt (1947) described vocalization and right face twitching among the secondary manifestations of a seizure of left occipital onset. Dreifuss (1983) has suggested that vocalization or repetitive utterances may be associated with nondominant hemisphere lesions, speech arrest with dominant hemisphere lesions, and unintelligible dysarthric utterances of the muscles of the mouth, pharynx, or jaw. He related to these episodes of epileptic coughing ("Charcot's laryngeal epilepsy," Charcot 1876; Janz 1969), which he was careful to distinguish from cough syncope. Other ictal disturbances in language are discussed on pp. 241–242.

Simple Partial Seizures with Sensory Signs

Somatosensory Seizures

Holmes (1927) had described tingling, deadness, or a sense of movement as occurring in patients with seizures of the somatosensory area. The last of these could represent a patient's description of an unfamiliar sensation, but could also represent a sensory illusion (see p. 245) or actual muscle contractions not readily observed clinically. Other descriptive terms used have included prickling, tingling, burning, needle-like (Fincher and Dowman 1931), pain, heat (Head and Holmes 1911; Penfield and Kristiansen 1951; Russell and Whitty 1953; Mauguiere and Courjon 1978), electrical (Arseni et al. 1957; Talbert and Clark 1968), and tickling or cramping (Kennedy 1959). Penfield and Boldrey (1939) described that the hand of their case 8 "went to sleep" in response to electrical stimulation. Penfield and Kristiansen (1951) listed numbness in nine, numbness and tingling in eight, pins and needles in four, a sensation of movement in two, pain in two, a sense of tightness in two, and a throbbing in two patients. One patient each described crawling, quivering, buzzing, water running down the arm, a feeling that the hand was increasing in size, awkwardness followed by a high frequency vibration, and a sick feeling in the throat (interpreted by the authors to be sensory, not autonomic). Of 127 patients reported by Mauguiere and Courjon (1978), 114 described ictal paresthesia, 30 pain, 14 a warm or cold sensation, and 13 a somatognostic illusion (see p. 245). The descriptions of numbness cited above could represent patient descriptions of paresthetic phenomena which were hard for the patient to characterize otherwise, but also could represent ictal sensory inhibition.

Both Penfield and Jasper (1954) and Daly (1975) were struck by the absence of formed somatosensory hallucinations, "for example . . . the sensation of feeling an apple or coin" (Penfield and Jasper 1954). Daly (1975) noted that this was particularly surprising in view of the relative frequency of somatosensory illusions.

Ipsilateral Sensory Seizures

Patients generally have ictal sensations contralateral to the epileptogenic focus but occasional patients describe symptoms which are ipsilateral or bilateral in distribution and which are identical in character to those occurring only contralaterally (Penfield and Jasper 1954). Penfield and Jasper postulated origin in the second sensory area at the base of the motor strip in the frontoparietal operculum. Additional cases have been reported by Dechaume et al. (1961), Kofman and Tasker (1967), Herskowitz and Swerdlow (1972), Ahuja and Tharakan (1982), and Lesser et al. (1983). The second of these reports was of a patient with ipsilateral hand and perioral sensations secondary to a parasagittal meningioma. The authors postulated spread to the second sensory area. However, another possibility would be an ictal focus in a parasagittal region with bilateral body representation, i.e., a supplementary sensory area (Penfield and Jasper 1954). Similarly, Rossi et al. (1978) reported a patient with paresthesiae in the left arm followed by elevation and turning of the head to the left; they localized the ictal focus to area 7 in the right parietal lobe. Mauguiere and Courjon (1978) described a patient with bilateral paresthestic sensations, but attributed these to spread via the corpus callosum, the site in this patient of a reticulum cell sarcoma. A patient described by Pedley et al. (1981) had unilateral sensory phenomena, followed by adversion of the head and arm associated with a vertex epileptogenic focus. Rasmussen and Penfield (1947) noted bilateral as well as ipsilateral sensory responses referrable to the eyes or face, on stimulation of the appropriate portion of the sensory homunculus of the postrolandic cortex.

Sensory Seizures with March

Lende and Popp (1976) reviewed the clinical manifestations of sensory jacksonian seizures after observing patterns of ictal spread not easily accounted for by standard maps of the motor and sensory representations in the human perirolandic cortex. In particular they suggested that the patterns of spread better fit the maps in other primates, as described by Woolsey and his collaborators, than they fit the maps proposed by Penfield and his collaborators. They also raised the possibility that the somatosensory cortex might be organized into three functional subunits, the leg, arm, and face, for which some support is available from the primate data of Jones and Powell (1969). Without specifically validating or invalidating their suggestion, one should also consider the possibility that the precise manner in which the various representations of the body relate to one another might vary due to interindividual differences in the interdigitations of subareas of the cortex with one another. Thus, for example, in one individual the eye, or nose, sensory region might be closer, or farther away from, the representation of the mouth or hand.

Mauguiere and Courjon (1978) noted that seizures beginning in the leg tended to spread throughout the ipsilateral half of the body. By comparison, 40% of sensory seizures beginning in the hand or fingers tended to remain restricted to the arm, 24% involved only the hands and perioral regions, and 24% only the arm and face. It is possible that the likelihood of spread to other areas of the body in part reflects the size of the sensory representation on the cortex of these other areas, but there could also be intrinsic mechanisms inhibiting the spread of the ictal discharge, as, for example, occurs in benign focal epilepsy of childhood (see elsewhere in this

volume). In addition, Penfield and Boldrey (1939) described patients in which "even the most easily elicitable responses fail ... quite independent of obvious clinical seizure." We have found (Lesser et al. 1984c) that the thresholds for afterdischarge in response to electrical stimulation of the cortex differ from point to point and also differ at each point from the thresholds for cortical response, e.g., sensory or motor responses. Moreover, afterdischarges may occur at a given site without the occurrence of cortical responses, although these may occur at later testing when higher intensities can be used without the production of afterdischarges. If one is willing to accept afterdischarge as being at least of "paraepileptic" significance, one can conclude that epileptiform activity could spread into a region without the production of sensory symptoms or motor signs.

Table 11.3 lists the frequency of various types of seizure in the study of Mauguiere and Courjon (1978). Confirming the relative rarity of pure sensory seizures, Krejcova et al. (1965) found 32 cases of sensory, 29 of sensory–motor, and 75 of motor seizures among 136 patients with jacksonian epilepsy.

Sensory Seizures with Visual Symptoms

Holmes (1927) described seizures manifested by moving multicolored spheres, by twinkling lights, by the appearance of shell bursts or balls of fire, by bright lights of all colors, or by a dull black patch followed by flashes of lightning. Foerster and Penfield (1930) described a patient with a visual aura which was followed by nystagmus to one side. Penfield and Kristiansen (1951) reported a total of 11 patients with visual symptoms at ictal onset, described as gross sensations of light, darkness, or color and in all cases originating in the occipital lobe. Browne and Erba (1983) have reported visual obscuration ("fading vision") during seizures in patients with Sturge-Weber disease, and Barry et al. (1984) have reported ictal blindness. Newton and Aicardi (1983) reported 16 patients with occipital spikes suppressed by eye opening. Four had transient loss of vision, two saw brightly colored circles and one experienced visual distortion at seizure onset; in all, seizures progressed to obscure consciousness. Russell and Whitty (1955) had divided visual ictal patterns into those originating in (a) calcarine cortex, manifested by weaving patterns, zigzags, sparks, or colored lights, (b) optic radiations and adjacent superior occipital–parietal lobe, manifested by interrupted flickering, visual hallucinations, distortions, or alterations in field, (c) higher visual cortex, manifested by negative visual phenomena, i.e., loss of visual field, and (d) temporal-posterior parietal cortex, manifested by hallucinations. In agreement with this classification is the report by Gastaut et al. (1956) of colored phosphenes in association with an occipital focus and the reports by Smith and Kellaway (1964) and Camfield et al. (1978) of an aura of blindness and flashing lights with posterior quadrant foci. Daly (1958a) suggested that hallucinations would change from unformed to formed as the focus shifted from primary visual to association cortex. However, Potzl and Schober (1958) reported sensations of color with a parietal focus.

A large variety of formed hallucinations have been reported. Fay and Scott (1939) described ictal formed visuo-auditory hallucinations of a group of people singing, associated with a midline parietal meningioma. A patient with a pterional (sylvian point) meningioma (case 161 of Cushing and Eisenhardt 1938) reported colored flowers, persons in costume, and a man carrying a cane and walking a dog.

In addition this patient experienced complex auditory hallucinations, gustatory hallucinations, and quivering sensations in the hypogastrium. A patient of Robinson and Watt (1947) saw pictures of past experiences, appearing as flat, uncolored miniatures. The ictal visual hallucination of a double of oneself was reviewed by Lhermitte (1951). A patient of Daly (1958a) experienced a vision of herself and her mother, seated on a couch, as a part of a complicated scene. Lance (1976) described patients with formed hallucinations, associated with metamorphopsia in one case and palinopsia in two cases with lesions of the parieto-occipital region. Schneider et al. (1961) and Ludwig et al. (1975) reported cases of formed visual hallucinations due to orbital frontal lesions. Jacome and Gumnit (1979) reported a patient with audiovisual ictal synesthesias associated with focal pain, and Gastaut and Zifkin (1984) reported patients with ictal hallucinations of numerals.

Sensory Seizures with Auditory Symptoms

Holmes (1927) reported a patient who heard a bell. Penfield and Kristiansen (1951) described three patients with auditory sensations at the onset of attacks originating in the superior temporal gyrus and characterized by "a roaring in the ears" or the sound of "a plane going by." The authors specifically noted that none had associated dizziness. Mulder and Daly (1952) reported two patients with sounds described as a bell, ringing, or buzzing during temporal lobe seizures. Penfield and Jasper (1954) reported ictal hallucinations of a name being called, and of singing. Holowach et al. (1958) described patients with hyperacusis. Dreifuss (1983) and Browne and Erba (1983) described rushing, hissing, buzzing, whistling, knocking, crescendo noises, musical tunes, or even the sound of a crowd shouting the name of a horse. The general topic of visual and auditory hallucinations has recently been reviewed by Trimble (1981).

Sensory Seizures with Olfactory Symptoms

Sensory seizures with olfactory symptoms have long been recognized (Jackson 1873; Holmes 1927) and are often associated with the term uncinate seizures (Jackson 1899). Interestingly, only 1/222 patients of Penfield and Kristiansen (1951) reported a smell (like burning oil) at seizure onset. Daly (1958b) reported one patient who smelled peaches, another who smelled lemons (Daly 1975), a third who reported a seizure with an odor like blood (Daly 1958a), and a fourth who had a burning and tingling in the nose; this could have been either somatosensory (see Daly 1958b) or olfactory. Most authors (Holmes 1927; Penfield and Kristiansen 1951; Daly 1958a; Wieser et al. 1985) agree that this phenomenon is associated with seizures of temporal lobe origin, but the impression that uncinate seizures might be associated with a higher likelihood of tumors was not confirmed by a recent report (Howe and Gibson 1982). King and Ajmone-Marsan (1977) reported four patients with occipital or central foci, versus 13 with temporal foci, who had ictal olfactory or gustatory symptoms.

Sensory Seizures with Gustatory Symptoms

Gustatory symptoms have likewise long been reported and are associated with temporal lobe epilepsy (Jackson 1880; Gowers 1901; Holmes 1927; Daly 1958a; Wieser et al. 1985). However, Jackson thought this symptom to be rare, and Penfield and Kristiansen (1951) reported only two patients with a taste sensation at ictal onset. One described a peculiar and the other a rotten taste. In both, seizures progressed to alteration of consciousness. Daly (1975) concluded that sensations usually parallel the basic sensations of taste—acid, bitter, or salty—although the term "metallic taste" is also used. Sweet tastes apparently occur less commonly, although Daly (1958b) reported the ictal combination of a sweet taste and a pungent odor. Bornstein (1939–40) postulated localization of taste in the parietal operculum, and Penfield and Jasper (1954), localization in or near the insula.

Sensory Seizures with Vertiginous Sensations

Ictal vertigo was reported in 9 of 222 patients by Penfield and Kristiansen (1951) and they noted that Gowers' patients commonly described a sense of turning at seizure onset. It appears that in most cases, seizures would evolve into complex partial seizures or would secondarily generalize. However, many of the cases of Smith (1960) appeared to have had simple partial seizures. Penfield and Kristiansen distinguished between dizziness in the sense of lightheadedness (Kogeorgos et al. 1981) and dizziness in the sense of rotation ("tornado epilepsy," Dreifuss 1983), falling, or floating and said that the latter was rare. Penfield and Erickson (1941) had suggested that auditory and vertiginous sensations would frequently be associated, but this was not found commonly in the review of Penfield and Kristiansen. Jackson (1874–76) believed that ictal vertigo was actually a manifestation of a discharge of motor cortex, i.e., in the frontal lobe, even if no movement was observed clinically. However, in Penfield and Kristiansen's series, the epileptogenic lesion was generally at the temporal–parietal–occipital junction, although one patient's lesion was near Heschl's gyrus and another's was superior parietal. Eviatar and Eviatar (1977) described two patients with right frontal foci (others had temporal or generalized epileptiform activity). Smith localized phenomena associated with vertigo to the insular, perirolandic, and perisylvian regions, or, in particular, to the temporo-parieto-occipital region.

Sensory Seizures Associated with Erotic Sensations

Sensory seizures in association with erotic sensations occur occasionally (Erickson 1945; Gastaut and Collomb 1954; Daly 1958a; Freemon and Nevis 1969; Currier et al. 1971). Mulder et al. (1954) reported one patient who experienced vaginal sensations similar to those during orgasm as well as a second who experienced tingling in the testes, scrotal region, and thighs, followed by piloerection and, at times, unconsciousness. Mullan and Penfield (1959) described a patient who experienced vaginal tingling. Stoffels et al. (1980) reported a patient with lateralized scrotal paresthesiae in association with an ictal focus in the paracentral region. region. These authors, as well as Erickson (1945), also described patients who would experience ictal orgasms or erections, which could also be considered

autonomic or affective signs. We have evaluated a patient (#S308) who experienced ictal vibratory sensations in the pelvis, fingers, and toes which she described as being "miniorgasmic." These were often associated with visual or auditory hallucinations and with slight, but not prominent, dulling of alertness. A recorded episode documented left temporal ictal epileptiform discharges. Seizures appeared to be of mesial temporal origin in a number of previous studies. However, Spencer et al. (1983) reviewed reports localizing ictal genital sensations to the parietal lobe (York et al. 1979; Ruff 1980) and the sexual aura to the temporal lobe, and contributed four patients with ictal sexual automatisms, all with frontal lobe pathology (as was the case for Erickson's patient). In the study of Remillard et al. (1983) there appeared to be an increased incidence of ictal sexual arousal or orgasm in women; however, three of Spencer et al.'s four patients were men.

Seizures with Autonomic Symptoms or Signs

The various types of autonomic manifestation will be discussed in turn. In some cases presumed anatomical correlates will be discussed with each subsection, with the overall issue of the origin of autonomic symptoms discussed at the end of the section.

Ictal Salivation

Ictal salivation was noted by Mulder et al. (1954), Williams (1956), and Daly (1958a). Salivation was localized by Rasmussen and Penfield (1947) to the lower postcentral gyrus, on the basis of cortical stimulation.

Ictal Mastication

Ictal mastication was described by Magnus et al. (1952), Holowach et al. (1958), and Van Buren (1963). In many cases it might be difficult to distinguish between mastication as an autonomic sign and mastication as an automatism, an area reviewed below. In the cases of Magnus et al. (1952), the seizures of four began in the insula, of two in the uncus, of four in the base or tip of the temporal lobe, of one in the lateral temporal lobe, of five in the posterior aspect of the first temporal convolution, of one in the lower central region, and of two in the frontal lobe. Hecker et al. (1972) described spitting automatisms, not associated with other oral or gustatory phenomena; they concluded that this behavior was similar in genesis to mastication. Usually these occurred during a period of unconsciousness (hence the term automatism). One patient, however, had postictal recall of this behavior, raising the possibility that it had not become "complex." Their patients had temporal lobe epilepsy, but they reviewed the evidence of Rasmussen and Penfield (1947) that spitting had a postcentral localization on the basis of stimulation. Talairach et al. (1973) described a variety of primitive movements, including sucking, nibbling, or palpation, which were executed with lips, tongue, or fingers and induced by electrical stimulation of the anterior cingulate gyrus. At times these

movements were associated with euphoria or autonomic changes (including mydriasis, reddening of the face, tachycardia, and tachypnea). The authors stated speaking and comprehension were never affected. Remillard et al. (1981) and Wieser et al. (1985) have reported ictal water drinking. In the former report, this was sometimes the sole manifestation of stereotactically demonstrated temporal lobe seizures.

Seizures with Epigastric Sensations

Seizures with epigastric sensations are commonly reported (Jackson 1874; Holmes 1927; Penfield and Welch 1951; Penfield and Kristiansen 1951; Magnus et al. 1952; Williams 1956; Gupta et al. 1983). Specific descriptive terms include an empty feeling, a feeling of weakness, a sinking feeling, a sinking feeling associated with testicular tingling, epigastric pain (Penfield and Kristiansen 1951; Young and Blume 1983), a queer feeling in the epigastrium (Russell and Whitty 1953), a rising sensation (Mulder et al. 1954), a homesick feeling, nausea, and hollowness associated with distress in the thorax (Daly 1958a), although sensations may at times be pleasurable. Van Buren (1963) reviewed the sensations described in 100 patients. Twenty could not describe the sensation; 16 reported fear, nervousness or guilt; 14 nausea; 9 a tenseness, a knot, a weight, or squeezing; 9 rolling, turning, or whirling in the abdomen; 9 ticking, tingling, or shock-like sensations; 8 pain; 8 vibration, fluttering, or butterflies; 6 "gas" or pressure; 6 an empty or hungry feeling; 5 warmth; 5 a sense like descending in an elevator; 2 burning or heartburn; and 1 each abdominal noise, cold, or sad feelings. Rasmussen and Penfield (1947) and Penfield and Kristiansen (1951) felt that patients with simple (not rising) epigastric sensation generally had their ictal focus in the upper bank of the sylvian fissure. Patients with a rising sensation had seizures of intermediate frontal origin. These authors proposed that accompanying symptoms such as tingling in the roof of the mouth, thirst, salivation, or altered taste subsequent to the epigastric sensation helped to localize the seizure to the perisylvian region, whereas adversive phenomena helped to localize the seizure to the upper prerolandic area. Of 100 patients with abdominal aura collected by Van Buren, 69 had temporal lobe foci, 4 diffuse left hemisphere, 2 supplementary motor, 2 left frontoparietal, and 1 each bifrontotemporal, left occipital, left central, and right frontotemporal foci. Three had petit mal seizures. In 16 the seizures could not be localized. Tharp (1972) described two children with abdominal sensations due to orbitofrontal seizures. One complained of "butterflies in the stomach," the other appeared to be experiencing abdominal pain. Thus epigastric sensations are predominantly but not uniquely of perisylvian or temporal origin.

Seizures with Other Gastrointestinal Manifestations

Other described symptoms and signs include borborygmi, belching, vomiting, or flatus (Penfield and Kristiansen 1951; Mulder et al. 1954; Williams 1956; Mitchell et al. 1983) and defecation or the desire to defecate (Penfield and Kristiansen 1951; Mulder et al. 1954; Daly 1958a, Van Buren 1963). A temporal focus is usually presumed. In addition, Penfield and Kristiansen suggested foci deep within the sylvian fissure or in the frontal lobe in some cases, especially in the supplementary

motor area, a conclusion supported by Jacome and FitzGerald (1982). Penfield and Faulk (1955) produced vomiting by stimulating the insula.

Seizures with Thoracic Sensations

Sensations of thoracic distress or pain were reported by David et al. (1944), Penfield and Kristiansen (1951), and Mulder et al. (1954). Penfield and Kristiansen's patients had seizures of sylvian, upper central, or mesial–supracingulate origin.

Seizures with Cardiac Symptoms

Cardioacceleration, slowing, and palpitations have all been described (Penfield and Kristiansen 1951; Mulder et al. 1954; Williams 1956; Daly 1958a; Mullan and Penfield 1959; Talbert and Clark 1968; Green et al. 1980; Coulter 1984). One of Penfield and Kristiansen's cases had a medial anterior frontal focus, another a posterior temporal focus. The patient of Green et al. had supplementary motor area seizures.

Respiratory Changes During Seizures

Hyperventilation was described by Mulder et al. (1954), Williams (1956), and Talbert and Clark (1968). Van Buren described labored respiration and Marossero et al. (1980) a sense of suffocation. Jackson (1899) described ictal apnea and Coulter (1984) reported an infant with ictal apnea and bradycardia, preceded by left temporal epileptiform activity.

Seizures with Genitourinary Manifestations

Ictal urination was described by Temkin (1945), Penfield and Kristiansen (1951), Mulder et al. (1954), and Williams (1956). This could occur without loss of consciousness. Penfield and Kristiansen emphasized that this was a rare symptom, and differentiated it from the more common problems of (a) involuntary urination during the course of a generalized seizure which might be accompanied by hypertonus, and (b) postictal urination.

Seizures with Sweating

Seizures with sweating were observed by Penfield and Kristiansen (1951), Mulder et al. (1954), Williams (1956), Daly (1958a), and Van Buren (1963). Penfield and Kristiansen commented that two of their patients had sweating in association with focal sensory and one with focal motor seizures; in all three the area of sweating was identical to the area of sensory or motor involvement.

Seizures with Pallor

Ictal pallor was described by Mulder et al. (1954), Williams (1956), Daly (1958a), and Van Buren (1963).

Seizures with Flushing

Seizures with flushing were reported by Mulder et al. (1954), Daly (1958a), and Van Buren (1963).

Seizures with Piloerection

Seizures with piloerection, characterized by gooseflesh or goosebumps at times in association with a cold feeling, have been described by Penfield and Kristiansen (1951), Landau (1953), Mulder et al. (1954), Williams (1956), Brody et al. (1960), Tharp (1972), Green (1984), Andermann and Gloor (1984), and Lesser et al. (1985a). It is possible that these do not have a mesial temporal origin. Penfield and Kristiansen postulated a rolandic focus and Brody et al. raised the possibility of hypothalamic involvement with these. The patient of Lesser et al. (1985a) initially had complex partial seizures accompanied by bilateral piloerection; ictal piloerection without other signs or symptoms continued after removal of lateral and mesial, but only limited removal of basal, temporal structures (due to the location of a basal speech area; Lüders et al. 1985b). In this patient there was no evidence for suprasylvian involvement. Finally, Tharp (1972) described piloerection in seizures of orbital frontal origin.

Seizures with Pupillary Changes

Pupillary changes, including unilateral pupillary changes, have been reported by Zee et al. (1974), Lance (1976), Green et al. (1980), and Gadoth et al. (1981). The patient of Zee et al. was described as having an adversive and the patient of Green et al. a supplementary motor area seizure (see pp. 230–231).

Ictal Pain

Gowers (1885) reported a variety of cephalic sensations at seizure onset in 90 of 2013 patients, including pounding, jerking, full, empty, heavy, and strange feelings. He noted frank pain but Penfield and Kristiansen (1951) found this to be only rarely a true aura. Laplante et al. (1983) described ictal headaches due to temporal lobe epilepsy. Mauguiere and Courjon (1978) found 30 of 8938 epileptic patients (30 of 127 with somatosensory epilepsy) to have ictal pain. Only two had ictal pain alone. Ictal pain was found in 24 of 858 epileptic patients by Young and Blume (1983). Ten had unilateral face, arm, leg, or trunk pain, 11 head pain, and 3 abdominal pain. They concluded that in the first group pain reflected involvement in the rolandic area, that in the second group pain was not localizing, and that in the third group pain was of temporal lobe origin. In the second group, cases 15 and

17 had head pain ipsilateral to the epileptogenic focus; one possible explanation for this would be activation of trigeminal and other sensory fibers accompanying the overlying pia-arachnoidal vessels (Lesser et al. 1985c).

Localization of the Epileptogenic Focus in Patients with Autonomic Signs

Penfield and Kristiansen's (1951) cases had temporal, perisylvian, perirolandic, or superior–mesial frontal epileptogenic areas. In the study of visceral epilepsy by Mulder et al. (1954), 75 had temporal lobe foci, 5 anterior parasagittal foci, and 1 each a frontal, occipital, or parietal focus. They subdivided the generators of ictal autonomic symptoms into (a) the frontotemporal region, including the posterior orbital cortex, the insula, and the anteromesial temporal lobe, and (b) the mesial parasagittal frontal lobes. In a similar study by Van Buren (1963), 69 had temporal lobe seizures, 4 seizures of diffuse left hemispheric origin, 2 a supplementary motor focus, 2 a frontoparietal focus, and 1 each bifrontal and bitemporal, occipital, central, or frontotemporal foci. Three had petit mal epilepsy; in another 16 the focus could not be localized. Similarly, King and Ajmone-Marsan (1977) found autonomic symptoms associated with ictal foci throughout the brain. Thus, although autonomic symptoms are predominantly of temporal, perisylvian, or superior–medial frontal origin, in individual patients other ictal foci must be postulated. However, one cannot exclude the possibility that patterns of ictal spread might be such that seizures starting elsewhere would rapidly spread into the temporal, perisylvian, or superior–medial frontal regions. Finally, one must always consider the possibility that an autonomic sign might occur not because of the occurrence of epileptogenic activity in a particular region but rather as a manifestation of a psychological or physiological reaction to the occurrence of a seizure.

Seizures Manifested by Psychic Symptoms

Seizures with Disturbances of Speech

Aphasic seizures were described by Gowers (1901) and Holmes (1927) as well as by other authors in the late nineteenth and early twentieth centuries. Alajouanine (1955) suggested dividing these between primary sensorimotor disturbances and disorders of higher cortical function. Hecaen and Angelergues (1960) collected 208 patients of whom 142 had speech arrest, 52 word deafness, 35 verbal amnesia, 21 paraphasia, 11 alexia, and 5 agraphia. These would occur as the only sign in 96, 6, 6, 0, 1, and 0 patients in each group. An additional 32 patients had verbal automatisms. In this study speech arrest, word deafness, and verbal amnesia could occur with lesions in the frontal, parietal, or temporal lobes, including the opercular region and the temporal–parietal–occipital (TPO) junction. Paraphasia and alexia could occur with opercular, temporal, parietal, or TPO lesions. Penfield and Kristiansen (1951) had reported patients with foci in Broca's area, along the precentral gyrus near the midline, and at the TPO junction. Hamilton and

Matthews (1979), Racy et al. (1980) and Dinner et al. (1981) reported patients who presented monosymptomatically with aphasic status. EEGs demonstrated left frontal, left temporal, and left frontotemporal ictal patterns. Peled et al. (1984) demonstrated ictal speech arrest of likely left supplementary motor origin. Gilmore and Heilman (1981) demonstrated that altered speech comprehension occurred in a patient with ictal speech arrest associated with left centrotemporal paroxysmal discharges. These considerations suggest that ictal speech changes are relatively nonspecific from the point of view of localization. However, some of this apparent nonspecificity could be due to ictal spread of epileptiform activity. Also, it is possible that detailed clinical testing together with precise localization of the ictal focus might demonstrate correlations analogous to those due to cerebrovascular accidents or mass lesions.

Seizures Manifested by Memory Disturbances

An alteration of memory function may occur in isolation, but more often occurs in association with a revery, a flashback, or even the forced recollection of a past event or series of events (Dreifuss 1983). This implies that although elements of memory, of cognition, and of affect can be separated for descriptive purposes, they often coexist during clinical seizures. Jackson (1880) described reminiscences and other experiences, including déjà vu, a sense that something seen which is not familiar is familiar, jamais vu, a sense that something seen which should be familiar is not familiar, and the equivalent terms for auditory experiences, déjà entendu and jamais entendu. Daly (1958) reported 6 patients with déjà vu and 7 with jamais vu, of a series of 52 patients with ictal psychic symptoms.

Mullan and Penfield (1959) reported that, in their series, illusions of familiarity were more likely to be associated with right temporal lobe foci, a conclusion extended to a variety of experential responses by Penfield and Perot (1963).

The study of Gloor et al. (1982) considered a wide variety of dysmnesic, cognitive, illusional, and emotional phenomena occurring during seizures or in response to electrical stimulation. These were usually associated with limbic or limbic and temporal neocortical discharges. In this study right and left temporal stimulation were about equally likely to result in experiential responses, whereas 12 of 18 patients with experiential phenomena during seizures had predominantly right-sided ictal foci. These authors noted that only four of six patients with left-sided seizure onset were left dominant for speech. In a series of 290 patients, Gupta et al. (1983) found dysmnesic symptoms in 11 patients with right, 2 with left, and 1 with bilateral temporal lobe EEG abnormalities. These authors again suggested that autonomic and psychic symptoms in general were more associated with right temporal foci. The other possibility, however, is that experiences go unreported during seizures of the language dominant hemisphere owing to the occurrence of ictal language disturbances. Indirect support for this possibility comes from the relatively equal division between the two hemispheres of stimulus-evoked experiential phenomena in the study by Gloor et al. (1982).

King and Ajmone-Marsan (1977) tried to determine whether a wide variety of subjective sensory, autonomic, or psychic symptoms could be reliably related by EEG criteria to the anterior or posterior temporal lobe. Auditory experiences, vertigo, and nausea were always associated with anterior temporal foci; no such

relationship was found for the other symptoms reported. Moreover, such symptoms could also be associated with extratemporal foci (see also pp. 245–246).

Seizures Manifested by Cognitive Changes

Seizures manifested by cognitive changes have also long been described. Jackson (1879) and Holmes (1927) referred to the occurrence of a dreamy state and Wilson (1930) described pleasant dreams, or dreams of delight in some patients. Such descriptions suggest overlap with seizures manifested by pleasurable affect, or by hallucinations, subtopics reviewed elsewhere in this chapter. Moreover, whether sensations of familiarity or unfamiliarity, or reality or unreality, are cognitive, recollective or illusional in nature may be a matter for definition in each case. Ictal "forced thinking" or ictal alterations are more clearly categorized here. Penfield and Kristiansen (1951) describe a feeling of being out of the world, or of unreality, or of being a spectator to an event which one is participating in. They localized these phenomena to the temporal lobe in three and to the frontal lobe in one of four cases. Clearly, again, many of these symptoms interrelate with the other categories discussed in this section.

Seizures with Affective Symptoms or Signs

Ictal Fear. Affective signs and symptoms of focal seizures have been described in many patients. These will be described separately, but it should be understood that many, if not most, patients have described several phenomena occurring together, rather than a single phenomenon in isolation. Ictal affect need not be accompanied by loss of consciousness. Weil (1955) and Daly (1958a) have discussed the reasons for postulating that these symptoms and signs originate in the limbic system. Fear or terror is the most commonly described emotion (Jackson 1874, 1880; Gowers 1901; Macrae 1954a,b; Williams 1956; Daly 1958a; Holowach et al. 1958; Mullan and Penfield 1959; Lennox and Lennox 1960; Van Buren 1963; Talbert and Clark 1968; Iemolo and Menendez 1981; Strauss et al. 1982), and was the only symptom in one documented case (McLachlan and Blume 1980). Jackson had suggested that fear and terror occurred as the result of "slight discharges of very complex nervous arrangements," and drew attention to the association of these with epigastric sensations. This association was not prominent in Gower's series, however, and Penfield and Kristiansen (1951) pointed out that there may be an association between fear and epigastric sensations in nonepileptics. Williams (1956) suggested an anterior temporal lobe focus for fear and a posterior temporal location for pleasure and "unpleasure." Daly questioned this, however, and, while most of Mullan and Penfield's (1959) cases with ictal fear were found to have anterior temporal foci, individual cases had posterior temporal, parietal, or sagittal localizations. Although some qualitative differences were noted, ictal fear was found with equal frequency in patients with left and right temporal lobe epilepsy by Strauss et al. (1982). Fear was the emotion of 61 of 100 of Williams' patients with ictal affective changes and was a prominent symptom in 12 of 446 epileptic patients reported by Fiol et al. (1984). In addition to fear per se, Daly (1958) noted that anxiety and other unpleasant emotions were described by some patients.

Ictal Pleasure. This is less commonly described (Wilson 1930; Subirana 1953; Williams 1956; Daly 1958a, 1975; Cirignotta et al. 1980) although, due to the descriptions of Dostoyevsky, they are well known (cf. Alajouanine 1963). Descriptions of the emotion include elation, pleasure, serenity, satisfaction, relaxation, gladness, ecstasy, quietude, and confidence. An emotion of pleasure can be followed by one of depression. Pleasant emotions occurred in 9 of 100 patients studied by Williams. Temporal lobe foci appeared to be present in reported cases.

Ictal Depression. Ictal depression, sadness, or sorrow occurred in six patients described by Weil (1955), in 21 of Williams' (1956) patients, and in five patients of Daly (1958a). Other cases have been reported by MacLean (1952) and Penfield and Jasper (1954). Weil and Daly localized these symptoms to the temporal lobe. Williams found two with anterior temporal, seven with midtemporal, and nine with posterior temporal foci.

Other Ictal Emotions. Seventeen of Williams' (1956) patients demonstrated ictal aggression and some investigators have postulated a relationship between temporal lobe epilepsy and violence (Ervin et al. 1969; Bear and Fedio 1977; Goldstein 1974; Pincus 1980). However, Daly (1958a) concluded that ictal anger was rare, Mullan and Penfield (1959) commented that they had never encountered a case of ictal rage, and Rodin (1973) found no such behavior among 150 monitored patients. Ramani and Gumnit (1981) intensively monitored 19 epileptic patients with episodic aggression and found that none demonstrated this ictally. An international panel has confirmed the extreme rarity of ictal directed aggression (Delgado-Escueta et al. 1981). In Williams' (1956) series epileptogenic lesions were anterior temporal or inferior frontal.

Seizures manifested by laughter ("gelastic epilepsy") have been described by many authors, including Trousseau (1873), Fere (1898), Daly and Mulder (1957), Druckman and Chao (1957), Lehtinen and Kivalo (1965), Gumpert et al. (1970), Gascon and Lombroso (1971), and Chen and Forster (1973). The last of these found laughter or running ("cursive epilepsy") in 16 of 5000 cases. Eight had laughing alone, 6 running alone, and 2 both. Sethi and Rao (1976) described a patient with episodes, variously, of laughter, crying, or running and who was found to have a temporal lobe tumor.

Patients reported by Daly and Mulder (1957) and Markand and DeMeyer (1984) had temporal foci. Chen and Forster localized pathology to the limbic system, particularly in the temporal lobe. Gumpert et al. postulated a hypothalamic lesion; however, their patient had no EEG changes during episodes of laughter and EEG discharges that did occur were generalized. In the series of Druckman and Chao and of Gascon and Lombroso, many patients demonstrated generalized discharges as well as temporal, central, or parieto-occipital foci. Ludwig et al. (1975) described a patient with ictal laughter due to orbital frontal seizures. We have studied a patient who demonstrated a hollow, semihysterical ictal laughter and who had an ictal EEG focus just anterior to the motor strip. These reports suggest, therefore, that ictal laughter may have more than one anatomical substrate, a conclusion also reached by Loiseau et al. (1971).

Strauss et al. (1983) found a variety of facial expressions at the onset of pentylenetetrazole–bemegride activated seizures, including sadness, fear, surprise,

and happiness, with no clear relationship between side of seizure onset and facial expression.

Seizures with Illusions

Daly (1975) defined illusions as "distortions of ongoing sensory experiences." Mullan and Penfield (1959) divided illusions into four major groups: auditory illusions (sounds louder, clearer, fainter, more distinct, nearer, farther), visual illusions (things clearer or blurred, larger, smaller, fatter, thinner), illusions of recognition (sense of déjà vu, jamais vu, strangeness, unreality), and illusional emotions (fear, loneliness, sorrow, or disgust). Alterations in time perception (faster, slower) may also occur (Daly 1975). Many of these subclassifications are discussed elsewhere in this review. Moreover, often these are associated with other classes of psychic symptoms. Arseni et al. (1957) reported a patient with jacksonian seizures which evolved to include a sense of enlargement of the left face. Mullan and Penfield (1952) suggested that visual illusions and illusions of familiarity originated predominantly in the nondominant hemisphere whereas auditory illusions and illusions of fear could originate on either side. They summarized literature dating back to Gower and Wilson supporting such a view. Arseni et al.'s patient had a right frontoparietotemporal oligodendroglioma. Penfield and Kristiansen (1951) had noted several patients with illusions of movement who had frontal lobe lesions but postulated a close functional relationship of the frontal, temporal, and insular lobes to account for the discrepancy of localization. The comments on pp. 242–243 are also pertinent to the localization issues pertaining to ictal illusion.

Seizures with Somatic Illusions. Riddoch (1941) described seizures during which a patient would have the sense of having two sets of toes or arms, or would have the sense that the forearm had disappeared. Go (1961) described a patient with a similar ictal sense of an additional arm. Russell and Whitty (1953) described agnosia of the hand, as well as phantom limb, and phantom movement of the fingers, followed by tonic, then clonic movements. Critchley (1953) reported a sensation "as if the limb were moving," as well as shortening or telescoping of a limb. He noted that the hand was the most frequently involved body part and attributed this to the hand's large cortical representation. Castaigne et al. (1952), Gastaut et al. (1956), Williams (1956), Arseni et al. (1957), Daly (1958b), and Mauguiere and Courjon (1978) all described ictal alterations in body schema or body image, including a sense that the teeth, tongue, face, or hand were swelling or, in one case, shrinking. A sense of telescoping of the hand was described by Arseni et al. (1957), a sense of levitation by Mauguiere and Courjon (1978), and a sense of flying, a "growing heart," and of suffocation by Marossero et al. (1980). These have not had a consistent cortical origin in the reported cases.

Seizures with Visual or Auditory Illusions. Robinson and Watt (1947) described a patient with periodic palinopsia as well as episodes of formed or unformed visual hallucinations associated with speech difficulties, due to a lesion at the TPO junction. Russell and Whitty (1955) described visual distortions in association with

lesions of the optic radiations. Mullan and Penfield (1959) described an illusion that objects were tilted to one side. Interesting additional phenomena described by these authors included an illusion that the speed of movement was slowed (also see pp. 234 and 235).

Seizures with Olfactory Illusions. Gastaut et al. (1955) described a patient during whose seizures cigarette smoke smelled like that of a locomotive. Case 4 of Daly (1958b) experienced an intensification of food odors.

Partial Seizures Occurring Secondary to Stimuli

Musicogenic Epilepsy

Critchley (1937) was the first to delineate extensively the syndrome of musicogenic epilepsy, and cases of focal seizures induced by music have been added by other workers subsequently (Teglbjaerg 1949; Fujinawa et al. 1977; Forster 1977; Newman and Saunders 1980). Some reported stimuli were quite specific, including pieces by Beethoven, Chopin's A major prelude (Teglbjaerg 1949), dance band music (Daly and Barry 1957), hymns (Dearman and Smith 1965), or other musical sounds with particular rhythmic and melodic characteristics (Poskanzer et al. 1962; Newman and Saunders 1980; Sutherling et al. 1980), including voice (Forster 1977; Daly 1975; Tsuzuki and Kasuga 1978). Daly and Barry (1957) extensively reviewed the literature regarding this. In many cases patients are unconscious during their seizures, but cases 3, and possibly 10, of Critchley (1937) and case 1 of Teglbjaerg (1949) appear to have had simple partial seizures. Critchley pointed out that some patients appear able to inhibit the occurrence of an attack, despite the presence of the precipitating music. He divided precipitating causes as follows: startle responses to auditory stimuli, intolerance to particular musical sounds, and epileptic reactions to monotonous sounds. The first two subcategories are in accord with the idea that both emotionally related and purely sound-related stimuli might be epileptogenic; an alternative explanation for the third would be seizure occurrence due to the onset of drowsiness.

The available literature suggests a temporal focus for these seizures.

Vestibulogenic Epilepsy

Stauder (1934) described a patient with a left temporal focus whose seizures were induced by contralateral caloric stimulation, and Behrman and Wyke (1958) described secondarily generalized seizures provoked by cold water caloric testing in the right ear. Similar phenomena were described by Molnar et al. (1959) and by Cantor (1971). Behrman and Wyke (1958) distinguished between vestibular seizures, i.e., seizures characterized by vertigo (p. 236), and vestibulogenic seizures, i.e., seizures brought on by stimulating the end-organ of the vestibular apparatus.

Sensorimotor Reflex Epilepsy

Strauss (1940), Penfield and Welch (1951), Falconer et al. (1963) and Aquino and Gabor (1980) described patients whose focal seizures occurred when stretching or performing particular movements; the last of these reports described such seizures in patients with nonketotic hyperglycemia. Lishman et al. (1962) and Lishman and Whitty (1965) emphasized the occurrence of a sudden movement. A patient studied by Gabor (1974) continued to have movement-induced seizures after peripheral sensory anesthetic block, and a patient described by Reder and Wright (1982) had these only when using the hand to eat. Related to these is the patient of Lee et al. (1980) who had focal motor seizures of the right face, jaw, and neck muscles, induced by reading aloud or writing but not by nonlinguistic movements or intellectual activities.

Penfield and Welch (1951), Falconer et al. (1963), and Lance (1983) suggested supplementary motor area origins for these episodes; Reder and Wright (1982) postulated that their patient had a focus adjacent to but not in this area. Vignaendra (1978) reported a patient with a right posterior quadrant epileptiform paroxysms induced by ocular convergence.

In the presence of such episodes one must consider the possibility of nonepileptic attacks, such as movement-induced dystonia (Newmark 1983), paroxysmal choreoathetosis (Mount and Reback 1940), or syndromes such as the Jumping Frenchman of Maine (Beard 1880; Newmark 1983). Similarly, patients with orthostatic hypotension or cough syncope (Whitty 1943) have at times mistakenly been considered to have epilepsy.

Sensory Reflex Epilepsy

Cases of sensory reflex epilepsy were reported by Jackson (1886), Gowers (1901), and Wilson (1930). Jackson (1886) described a patient whose seizures began when the head or face was touched, and Wilson and Denny-Brown (Denny-Brown 1929–30; Wilson 1930) a patient whose seizures began when the right ear was touched. Initially the latter patient's seizures consisted of ictal motor–sensory symptoms in the right face. Later, similar episodes occurred in response to stimulation of the right foot; these evolved into unconsciousness. Goldie and Green (1959) found that seizures with sensory and versive components and maintained consciousness could occur if their patient rubbed, or imagined to rub, the face. Additional, similar cases have been contributed by Denny-Brown and Robertson (1934), Rothova and Roth (1963), Scollo-Lavizzari and Hess (1967), Forster and Cleeland (1969), Mani et al. (1974), and Santanelli et al. (1985). In some cases there has been evidence for pararolandic or supplementary motor foci. Lugaresi et al. (1984) reported occipital lobe seizures induced by obscuring central vision.

The reported cases of simple partial seizures related to meals or presentation of food, where movements of the mouth, jaw, or hands are not the precipitating factors, may also be classified here (Robertson and Fariello 1979; Ahuja et al. 1980). Both frontal and temporal foci have been described.

A number of patients have been reported to have partial seizures induced by reading per se (Newmark and Penry 1979). Ramani (1983) reviewed the literature on this and described a patient with focal motor manifestations and unilateral

EEG discharges in association with both silent and aloud reading and not precipitated by jaw or eye movements per se. Robertson and Fariello (1979) reported a patient with focal sensorimotor seizures induced only by chewing food or holding liquids in the mouth, and Holmes et al. (1982) a patient with focal motor seizures induced by brushing the teeth.

Psychological Reflex Epilepsy

The reflex epilepsies often appear to represent, in a sense, an accentuation of a sensory-evoked response. However, Daly and Barry (1957) reviewed the literature on musicogenic epilepsy, including their own cases, and pointed out that it is often difficult to know whether the music itself had precipitated the seizure, or if music had engendered a mood change which in turn resulted in the attack. A similar point was made by Goldie and Green (1959) for sensory reflex epilepsy and either psychological or circadian factors could be postulated as important in the case of Falconer et al. (1963): it was stretching on arising in the morning which was epileptogenic, but many patients have their seizures on awakening in any case (Denny-Brown and Robertson 1934). Similarly, case 2 of Ludwig et al. (1975) had orbital frontal seizures precipitated by "extensive reading and emotional stress." Although the mechanism underlying the relationship is not understood, the role of stress, startle, or excitement in producing seizures is well known (Jackson 1886; Gowers 1901; Wilson 1930; Denny-Brown and Robertson 1934; Wabayashi et al. 1962; Bancaud et al. 1967; Nakamura et al. 1975; Forster 1977; Tsuzuki and Kasuga 1978; Kelly 1979; Newmark 1983). Although many described seizures have been of temporal lobe origin, others have not. Gastaut's (1954), Kennedy's (1959), and Bancaud et al.'s (1967) patients had supplementary motor area foci. Saenz-Lope et al. (1984) and Aguglia et al. (1984) have reported a series of patients with structural brain damage, hemiparesis, and startle-induced seizures involving the hemiparetic side.

Finally, one must always consider the possibility of psychogenic pseudoepilepsy in the differential diagnosis of such episodes, especially when ictal epileptiform EEG correlates are not present (Newmark 1983).

Electroencephalographic Manifestations

Since the electroencephalographic hallmark of a seizure disorder of focal origin should be a focal epileptiform discharge, the EEG can be of great value in the evaluation of partial seizures (Engel 1984; Ajmone-Marsan 1984). Several basic principles need to be kept in mind, however. First, only definite epileptiform activity confirms a diagnosis of epilepsy. Second, a random EEG may not demonstrate such activity. Third, special techniques are sometimes necessary to demonstrate epileptiform activity in patients with focal seizures.

1. In the evaluation of patients with possible focal seizures, one must always exclude from the record nonepileptiform transients such as psychomotor variant, "six-per-second spike and wave," small sharp spikes or benign epileptiform

transients of sleep, 14- and 6-per-second positive spikes, wicket spikes, slow-wave transients of the elderly, temporal–parietal rhythmic discharges of adults, hyperventilation responses, hypnogogic or hypnopompic hypersynchrony, and limbic spindles. These all can occur in persons without epilepsy and are of no value in the diagnosis or localization of focal seizures (Rodin et al. 1962; Bennett et al. 1969; Reiher et al. 1977; Reiher and Lebel 1977; White et al. 1977; Engel et al. 1978; Kellaway 1979; Pedley 1980; Westmoreland and Klass 1981; Klass and Westmoreland 1985). In addition, significant EEG changes, such as continuous focal slow activity, can occur in the EEG due to a variety of underlying causes. While these are of definite clinical significance, they are not specific for epilepsy per se. Finally, one must be aware of the varying electrographic presentations of focal seizures (Blume et al. 1984).

2. Because a single random EEG need not demonstrate epileptiform activity, a variety of techniques are often utilized in the evaluation of seizure disorders. Sleep, for example, has been repeatedly demonstrated to increase the occurrence of epileptiform activity on the EEG (Gibbs and Gibbs 1947; Bagchi and Jones 1951; Gloor et al. 1957, 1958; Silverman and Morisaki 1958; White et al. 1962; Mattson et al. 1965; Niedermeyer and Rocca 1972; Klass 1975; Dinner et al. 1984; Martins da Silva et al. 1984; Rossi et al. 1984). Although at times the increase in yield was only 5%–10% (Gloor et al. 1957), in other studies the yield increased up to severalfold. Sleep deprivation (Ellingson et al. 1984) was similarly useful in activating epileptiform activity on the EEG in 47 of 114 patients studied by Pratt et al. (1968) and 31 of 42 studied by Scollo-Lavizzari et al. (1977). Although hyperventilation is most useful in activating 3-Hz spike and slow-wave complexes, this technique can activate focal epileptiform discharges in some patients [6% in the study of Gabor and Ajmone-Marsan (1969)]. These techniques increase the diagnostic yield of the EEG with minimal risk to the patient, and we utilize them routinely in our laboratory. In addition, Sperling (1984) has successfully used hypoglycemia to activate epileptiform discharges.

When methods such as those just described are not successful in demonstrating epileptiform activity one must next consider whether this could be due to a sampling problem. The routine EEG records activity during a brief segment of a patient's life, a segment when the patient's cortex may not be generating epileptiform activity recordable at the scalp. For example, Pratt et al. (1968) had 33 patients with normal routine recordings return for a second study; 6 then became abnormal. Similar considerations are likely to apply to recordings during electrocorticography (Engel et al. 1975).

Despite the usefulness of repeated EEGs diagnostically, reports differ on the value of recordings (Brazier et al. 1975; Theodore et al. 1984) in predicting treatment outcomes. It should be realized, however, that the purpose of these studies differed. Brazier et al. reported a surgical series; in this group EEG recording was obtained subsequent to surgical resections performed for the control of seizures intractable to medication. The other report pertained to diagnostic studies in patients not primarily assessed as candidates for surgical resections. As Theodore et al. noted, their study would be subject to the spontaneous variability in the occurrence of epileptiform discharges discussed above. Also, many patients with partial seizures do not respond to anticonvulsant drugs alone (Elwes et al. 1984), especially those evaluated in tertiary care centers, and the Theodore et al. study would be expected to reflect this.

A recent report stressed the role of midline spikes in the genesis of some focal seizures (Pedley et al. 1981). Rarely, surface positive spikes can occur, often due either to the presence of a skull defect or to the occurrence of a dipole at the scalp (Matsuo and Knott 1977; Lesser et al. 1985d). Ludwig et al. (1975) emphasized the demonstration by depth recordings of orbital frontal onset of seizures thought previously to be of temporal lobe origin. However, these authors emphasized that surface EEG often had demonstrated bifrontal or frontopolar discharges. Thus, careful analysis of surface recordings can often be helpful in predicting the results which would be found with depth electrodes (Morris et al. 1986; also see below).

3. Because routine scalp electrodes may not be ideally placed for the recording of epileptiform activity, many laboratories utilize nasopharyngeal (Gloor et al. 1957; Rovit et al. 1961), sphenoidal (Pampiglione and Kerridge 1956; Rovit et al. 1961), ethmoidal, anterior temporal (Silverman 1960; Sperling and Engel 1985), or other added scalp electrodes (Chatrian et al. 1985; Lueders et al. 1982; Morris et al. 1983; Lesser et al. 1984a; Morris et al. 1986) in the assessment of patients with intractable seizures. The purpose of these is to increase the diagnostic yield in a noninvasive, or relatively noninvasive manner, especially when one is interested in activity from basal–mesial cortical regions or from the frontal pole. The question of which added electrodes are most useful is currently an area of active investigation (Jones et al. 1984; Marcus et al. 1984; Starkey et al. 1984; Sperling and Engel 1985; Morris et al. 1986). Second, in selected patients, withdrawal of anticonvulsants can increase the occurrence of epileptiform activity (Ramani et al. 1980). Although there is a possibility that this might activate areas not previously epileptogenic, or of marginal clinical significance (Engel and Crandall 1983), Spencer et al. (1981) found that the results after abrupt withdrawal were consistent with those prior to withdrawal in 25 patients. In our laboratory we withdraw medication more slowly, but our experience is similar to that of Spencer et al. Finally, several groups have been interested in assessing the value of power spectra, time relationships between discharges, and discharge frequency in the localization of focal epileptiform discharges (Gotman and Gloor 1976; Lieb et al. 1978, 1980. 1981a,b; Gotman et al. 1979; Gotman 1980, 1982, 1983; Rossi et al. 1982; Lange et al. 1983; Guedes de Oliviera et al. 1983; Gotman and Marciani 1985).

Although the scalp EEG, with or without the above techniques, may be sufficient for initial assessment of patients with focal seizures, additional data are often needed in patients whose seizures are refractory to medication and who become candidates for surgical approaches to their epilepsy. Prolonged (Ives et al. 1976) and/or video-EEG monitoring (Porter et al. 1977; Sutula et al. 1981) can be useful in such patients since it can help to ascertain that the clinical events are preceded by focal ictal epileptiform activity, the presumption being that if such a pattern precedes the ictal event, and if the pattern is focal, the location of this pattern is likely to be the location of seizure onset (Bancaud et al. 1969; Talairach and Bancaud 1974; Bancaud et al. 1975; Wieser et al. 1979). Some authors feel that ictal behavior at times may be of benefit in determining prognosis. In comparing patients with temporal and frontal foci, Munari et al. (1981) found oroalimentary activities and epigastric sensations characteristic of the former and indicated that impaired consciousness was uncommon unless extratemporal involvement occurred. Gestural activities and impaired consciousness characterized frontal lobe seizures. Another group has studied the relationship of a motionless stare at ictal onset to temporal lobe epileptogenic foci (Walsh and Delgado-Escueta 1984;

Maldonado et al. 1985), but the localizing value of a motionless stare in regard to temporal lobe seizure onset has not been confirmed (Holmes et al. 1985).

Scalp EEG may not record ictal patterns during auras or other circumscribed episodes and, for this reason, many centers employ implanted electrodes to establish further the site of seizure onset (Lieb et al. 1976). Stereotactically placed depth electrodes are the most frequently utilized (Bickford et al. 1953a,b; Talairach et al. 1958, 1967; Bancaud et al. 1965; Talairach and Bancaud 1973; Milner 1975; Delgado-Escueta et al. 1979; Engel et al. 1981; Spencer 1981; Wieser 1981; Spencer et al. 1982), but a number of centers, including our own, employ subdural electrode strips or plates for this purpose (Penfield and Jasper 1954; Goldring 1978; Lueders et al. 1982; Blume et al. 1985; Goldring and Gregorie 1984; Laxer et al. 1984; Schomer et al. 1984; Wyler et al. 1984). As with scalp recordings, video-EEG is currently used in most centers to document the site of seizure origin (Geier and Bancaud 1973; Geier et al. 1974, 1975; Delgado-Escueta et al. 1979; Engel et al. 1981; Lesser et al. 1984a). As with scalp recordings, it is possible that errors in localization could occur due to small differences in electrode placement (Mars and Lopes da Silva 1983), due to the montage utilized (Engel et al. 1981), or due to the precise manner of seizure propagation in a specific patient.

Other Diagnostic Measures

In addition to radiological techniques such as specialized analysis of pre- and/or postcontrast enhancement computerized tomographic (CT) scans (Oakley et al. 1979; Wyler and Bolender 1983), of particular interest are reports of transient focal hypodensity in association with focal seizures (Rumack et al. 1980; Rougiez et al. 1984; Zegers de Beyl et al. 1985). More recently, magnetic resonance imaging has been utilized in epileptic patients in an effort to improve the sensitivity of imaging in detecting alterations in brain structure (Abou-Khalil et al. 1984; Sussman et al. 1984; Riela et al. 1984; Spencer et al. 1984b; Baker et al. 1985; Jabbari et al. 1985; Lesser et al. 1986; Navia et al. 1985; Theodore et al. 1985a). Metabolic studies such as ^{133}Xe regional cerebral blood flow (Hougaard et al. 1976; Oikawa 1976; Lavy et al. 1977; Sakai et al. 1978; Wilson 1980), positron emission tomography (Kuhl et al. 1980; Engel et al. 1982a–d; Bernardi et al. 1983), and single photon emission computed tomography (Bonte et al. 1983) have also been employed in an effort to localize areas of abnormal metabolic activity which may correspond with, or be adjacent to, areas of abnormal neuronal firing.

Pathogenesis

Holmes (1927) credited Jackson with first relating the signs and symptoms of focal seizures to the anatomical pattern of ictal spread in the opposite hemisphere, a "fulminate which explodes." He recognized that the precise lesion was not in itself important, and that a slowly enlarging lesion might be more epileptogenic than a

stable lesion. He also recognized that a lesion might be in proximity to the area which actually caused the seizures without destroying that area. Jackson's contemporaries Fritsch and Hitzig (1870) and Ferrier (1873) demonstrated that electrical stimulation of the motor cortex resulted in focal motor seizures. Thus current concepts of functional localization and of focal seizures developed together. The literature regarding this can be most conveniently approached by considering first reports of structural lesions or other medical illnesses which result in epileptic seizures in susceptible patients and second, the concepts which have developed regarding the pathophysiology of the seizure focus itself.

Between one-seventh and one-third of patients with focal seizures are found to have a discrete definable etiology for these (Hauser and Kurland 1975; Mathieson 1975; Spencer et al. 1984a), and a further group have more diffuse disturbances which may be related to their seizures. Although percentages vary according to the series, the overall conclusions regarding the occurrence of underlying causative lesions are similar. Table 11.4 summarizes the pathological findings in some three dozen reports from the literature. It should be understood, however, that in many cases the authors proceeded from the known existence of a seizure disorder to presuming that a coincident condition was its antecedent. There are conditions such as astrocytomas (Gonzales and Elvidge 1962; Rasmussen 1969) which have a high predilection for epileptogenesis. However, in other circumstances, such as premature birth or similar perinatal factors, epileptogenesis must be considered presumed, not proven. Many of these studies were general reviews and did not necessarily look into why seizures might have been related to a specific underlying condition. For example, hydrocephalus is a reported condition underlying focal seizures, but the data from Finney and Arlant (1977) and Ines and Markand (1977) point out that the seizures are probably related to infection, bleeding, or a foreign body reaction to the shunt. In any case, as can be seen, although disease was found in many patients, there remains a group of patients in which no antecedent mishap and no gross or microscopic lesions could be found. Of particular interest in this regard are patients who have had focal seizures in association with metabolic alterations, but without evident structural lesions, and originating in various portions of the brain [for example seizures of presumed supplementary motor area origin have occurred in association with nonketotic hyperglycemia (Venna and Sabin 1981)]. It appears that metabolic changes can be epileptogenic in areas which would be apparently normal on routine pathological assessment. Moreover, experimental temporal lobe epileptogenic lesions can produce epileptiform activity in portions of the affected lobe which are distant from the original focus (Mayanagi and Walker 1974).

These considerations imply again that the pathological lesion is not necessarily synonymous with the epileptogenic focus, and support Jackson's observations that abnormal tissues, as defined pathologically, are not necessarily epileptogenic. Therefore, epilepsy can best be viewed as the result of a variety of insults, with the disorder being produced only if the insult produces the appropriate physiological alterations. Whether or not they are actually epileptogenic, the type of lesions accompanying epilepsy are likely to be group specific. For example, in the young one would expect to find a higher incidence of congenital defects or perinatal trauma, and in the old a higher incidence of vascular disease (Lesser et al. 1985b). In individual cases, however, whether a coexisting condition is causative or coincident is often difficult to determine. One problem in defining febrile seizures as a cause for partial seizures, for example, is the frequency with which partial

Table 11.4. Etiologies of seizures in five reports with more than 500 patients each, plus a summarization of etiologies in 32 other studies with fewer patients[a]

Source of patients	Gibbs and Gibbs (1952), modified by Lennox and Lennox (1960) EEG laboratory				Rasmussen (1969) Surgical series	Hauser and Kurland (1975) Epidemiologic study	Bergamini et al. (1977) Epilepsy clinic, no tumour patients			Pazzaglia et al. (1982) Epilepsy clinic				32 series Varied
Total no. of patients in study	678	578	479	1735	1450	516	227	397	624	102	332	108	542	1342
	Complex partial	Jacksonian	Focal, other	Total focal			Simple partial	Complex partial	Total	Simple partial	Conplex partial	Partial, secondarily generalized		
Tumor	0.4	6	3	3	20	4								15
Astrocytoma					15									5
Vascular	2	5	4	4		5								15
Angioma/telangiectasia														2
Perinatal factors	4	17	18	12	26	6	19	13	15	29	20	22	22	15
Trauma of later life	11	17	12	13	20	5	19	8	12	8	7	15	9	10
Atrophy, cyst, hydrocephalus, malformation							11	8	9	6	7	6	6	7 17
Infectious, inflammatory	6	13	15	11	12	3								0.2
Rasmussen's syndrome														0.6
Calcification														0.6
Metabolic										7	4	4	4	6
Miscellaneous	0.1	0.7	0.2	0.3	6	0.6	51	72	64	50	62	53	59	15

[a] The numbers indicate the percentage of patients with specific etiologies for their seizures, as indicated on the left. Where the percentages do not add up to 100%, the balance did not have an etiology established. In the epidemiological study by Hauser and Kurland, about 75% of cases with known etiologies had partial seizures. The studies in the table plus Dreifuss (1983) include the following among the less common etiologies for focal seizures: Inborn errors of metabolism include maple syrup urine disease, phenylketonuria, galactosemia, hyperglycinemia, neuronal storage diseases, and leukodystrophies. Metabolic causes include hypocalcemia, hyponatremia, and hypernatremia. Infectious causes include encephalitis, meningitis, postinfectious encephalomyelitis, postimmunization encephalomyelitis, rubella, syphilis, cysticercosis, and echinococcosis. In addition, herpes simplex virus DNA has recently been found in temporal lobectomy specimens (Gannicliffe et al. 1985). Vascular causes include lupus erythematosus, Sturge-Weber disease, fibromuscular hyperplasia, and moya-moya disease. Miscellaneous causes include lead encephalopathy, burn encephalopathy, chlorambucil therapy, drug withdrawal, tuberous sclerosis, hamartomas, and iodophendylate myelography.

The 32 reports summarized are: Fincher and Dowman 1931, Vizioli and Morocutti 1957, Holowach et al. 1958, Fischer 1959, Hedenstrom and Schorsch 1962, Sumi and Teasdall 1963, Krejcova et al. 1965, Stepién et al. 1969, Biemond 1971, Ring and Waddington 1972, Vermess et al. 1972, Ring and Waddington 1972, Remillard 1974, Yarnell et al. 1974, Isch-Treussard et al. 1977, Roger et al. 1977, Loiseau et al. 1977, Mauguiere and Courjon 1978, Rasmussen 1978, Wroblewski and Korzeniowska 1978, Crosley and Binet 1978, Ogunmekan 1979, Naysmith and Robson 1979, Greenberg and Vance 1980, Lagenstein et al. 1980, Capizzi et al. 1981, Gradzki et al. 1980, Scarpa and Carassini 1982, Landi et al. 1983, J. Ochs et al. 1984, Rich et al. 1985, Mackworth-Young and Hughes 1985.

seizures occur in a young age group (Mathieson 1975). One does not know, in this setting, whether the febrile seizure is causative, or whether the fever simply precipitated a seizure in an already predisposed substrate (also, see below).

Foerster and Penfield (1930) tried to relate the epileptogenic area to the presence of neovascularization, collagen formation, gliosis, or cicatricial contraction, and, echoing these efforts, later workers have observed the presence of a variety of ultrastructural changes within excised epileptogenic tissue, especially mesial temporal sclerosis (Earle et al. 1953; Gastaut 1957; Falconer et al. 1964; Lieb et al. 1981b; Turner and Wyler 1981), but also atrophy, microgyri (Penfield and Paine 1955), proliferation of recurrent axon collaterals (Purpura and Housepian 1961), and dendritic changes (Purpura 1964; Scheibel et al. 1974; Schwartzkroin and Prince 1977).

In some cases, the question has been raised whether the changes observed precede or follow the patients' seizures. For example, Meldrum et al. (1974) demonstrated hippocampal ischemic changes following prolonged allylglycine-induced seizures associated with hypoglycemia and hyperpyrexia. They suggested that this tended to support the hypothesis that febrile seizures could result in temporal lobe epilepsy (Falconer 1970, 1971, 1972a). Moreover, a high incidence of febrile seizures has been reported in other series of patients with epilepsy (e.g., Roger et al. 1981; Dinner et al. 1984). However, although Rasmussen (1979) found febrile convulsions to precede focal seizures in 206 of 1572 patients, in most the febrile convulsions appeared to be secondary to infection or related to pre-existing structural changes. Similarly, Russell and Whitty (1952), noting the stable incidence of post-traumatic seizures despite improvements in wound care and surgical technique, concluded that progressive scarring or gliosis per se could not account for epileptogenesis. Recent pathological and experimental studies have provided evidence both for the presence of pathological changes which precede, and correlate in extent with, the area demonstrated electrically to be epileptogenic (Babb et al. 1984a,b) and for the occurrence of cellular alterations which are secondary to recurrent seizures (Dam et al. 1984).

In a population of patients with seizures of focal onset, some will have only simple partial seizures, some complex partial seizures, some secondarily generalized (tonic–clonic) seizures, and some a combination, with one or another type occurring at a particular time. A number of factors may account for this variability. First, many authors (Prince and Wilder 1967; Dichter and Spencer 1969; Collins and Caston 1979; Schwartzkroin and Wyler 1980) have explored the mechanisms of inhibition in restricting the area of active neuronal firing in experimental models of focal epilepsy. Second, it is possible that the spread of epileptiform activity is, in part, a function of the strength of the seizure focus (Lueders et al. 1980; Bustamante et al. 1980). Third, a number of authors have demonstrated that cortico-subcortical interactions are likely to modify experimental electrographic and clinical seizure phenomena (Woodruff et al. 1973; Collins et al. 1976; Hosokawa et al. 1980; Velasco et al. 1983, 1984; McNamara et al. 1984; Gale 1984). Finally, Buser and Bancaud (1983) have produced hippocampal responses to amygdalar stimulation in both epileptic and nonepileptic patients with depth electrodes, whereas amygdalar responses to hippocampal stimulation only occurred in epileptics, which supports the idea that one result of an epileptogenic focus may be the development of abnormal pathways of propagation. Of clinical interest in this regard are the cases of Babb et al. (1981) and Olivier et al. (1982). In the first report seizures were demonstrated to be both of temporal

and of occipital onset; in the second all were occipital onset. Seizures spread to the temporal lobe prior to alteration of consciousness. These cases illustrate that specific patterns of spread, and specific anatomical substrates, may be needed for seizures to be expressed clinically in some cases, as demonstrated by the good seizure control obtained in the second report by temporal lobectomy alone.

Experimental evidence has emphasized that a variety of factors influence, or are altered by, and within, an epileptogenic focus, including intrinsic burst activity, inhibition, disinhibition, kindling, excitatory coupling, and recurrent excitation (Goddard et al. 1969; Ayala and Vasconetto 1972; Dichter et al. 1973a,b; Racine 1975; Babb and Crandall 1976; Chkhenkeli et al. 1977; Goldensohn et al. 1977; Ayala and Johnston 1977; Ferrendelli and Kinscherf 1977; Anderson and Rutledge 1979; Schwartzkroin and Pedley 1979; Menini et al. 1980; Traub and Wong 1982; Elger and Speckmann 1983; Johnston and Browne 1984; Meldrum 1984; Prince and Connors 1984). These in turn may be the result of, or may be accompanied by, a variety of transmitter-related, ionic, focal metabolic or membrane-related alterations (Macon and King 1979a,b; Tenny et al. 1980; Collins et al. 1983; Delgado-Escueta et al. 1984; Sherwin et al. 1984). Thus a variety of factors can result in limitation, or spread, of epileptiform activity. The brain is presumably more able to limit the spread of abnormal neuronal firing when seizures remain simple partial in type. The development of techniques employing in vitro slice preparations of mammalian tissue (Yamamoto 1972; Kato et al. 1973; Schwartzkroin and Prince 1977; Pedley 1978; Traub and Wong 1982) appears particularly likely to improve our understanding of the factors which promote or retard the spread of ictal events.

Prognosis

In the population study performed in Rochester, Minnesota (Hauser and Kurland 1975; Annegers et al. 1979), no more than 65% of patients with focal seizures were seizure free for 5 years or more. In line with the considerations mentioned in the previous section, Loiseau et al. (1983) concluded that patients with simple partial seizures may have a better prognosis than those with complex partial seizures, owing to "isolation" of the focus and, conversely, patients with seizures with a tendency to generalize may have a worse prognosis. However, in the study by Elwes et al. (1984), 97% of patients with only tonic–clonic seizures, 73% with only partial seizures, and 89% with both types experienced at least 1 year of seizure control at 5-year follow up. Patients with more frequent seizures initially did more poorly at follow up. The different percentages may be the result, in part, of differing definitions of seizure control in these two studies.

Patients with focal seizures due to acute insults, and often associated with paroxysmal lateralized epileptiform discharges (PLEDs), often do not go on to have a chronic seizure disorder (Chatrian et al. 1964; Louis and McDowell 1967; Schwartz et al. 1973; Lesser et al. 1985b), most likely because the acute disturbance did not result in permanent physiological changes. Similar considerations would apply to the relative rarity of epilepsy after electroconvulsive therapy or after uncomplicated febrile convulsions.

Elwes et al. (1984) and Shorvon (1984) have concluded that patients controlled

soon after seizure onset have a better prognosis than those not controlled. This could simply mean that the controlled patients have a more benign disease, but could also support the idea that vigorous attempts at control should be attempted as soon as seizures begin.

Treatment

In the era prior to medication, Jackson (1869) reported a patient who could abort the spread of a seizure by tying a ligature on the arm proximal to the area where the seizures first manifested themselves. Analogous to this is, for example, the more recent report (Efron 1961) of a patient who could abort a sensory seizure by stimulating the arm with a stiff brush, and it is not unusual for patients with partial seizures to report that they can abort episodes by such maneuvers or even by "talking themselves out of it." Conversely, some patients will report an increase of seizure frequency in response to specific factors. In some cases, these reports may simply reflect the natural variations of the disorder, with a patient attributing the lack of generalization, or lack of occurrence, of a focal seizure to a particular maneuver, rather than to fluctuation in the strength of propagation of the epileptogenic focus. However, the likely validity of some of these maneuvers in some patients is supported by the report of Sterman and Friar (1972) of a patient with medically intractable seizures whose episodes were controlled using biofeedback. Nevertheless, in the majority of patients, the mainstay of treatment is anticonvulsant medication.

Most epileptologists have preferred carbamazepine, phenytoin, or, less commonly, primidone or phenobarbital as first-line drugs for the treatment of seizures of focal origin (Daly 1957; Millichap 1972; Rodin et al. 1974; Troupin 1975; Jeavons 1977; Troupin et al. 1977; Livingston and Pruce 1978; Reynolds 1978; Drugs for epilepsy 1979). If seizures continue, clorazepate (Browne 1976; Troupin et al. 1979; Berchou et al. 1981; Wilensky et al. 1981), clonazepam (Fazio et al. 1975; Bang et al. 1976; Mikkelsen et al. 1981) or other benzodiazepines (Walker et al. 1984; Gastaut and Low 1979), sodium valproate or valproic acid (Jeavons and Clark 1974; Simon and Penry 1975; Adams et al. 1978; Mattson et al. 1978; Browne 1980; Dodson and Tasch 1981), or methsuximide (Wilder and Buchanan 1981; Browne et al. 1983) can be employed, although only a minority of patients may benefit (Schmidt 1982, 1983). There has been little evidence clearly demonstrating that any one of the first-line drugs is superior to the others (Troupin et al. 1977; Kosteljanetz et al. 1979a,b), and patients with evidence for structural lesions may have seizures which are particularly difficult to control (Cazzullo et al. 1981). However, a recent cooperative study (Mattson et al. 1985) found that carbamazepine produced control in significantly ($P < 0.05$) more patients (65%) with partial seizures than did phenobarbital (33%), phenytoin (34%), or primidone (26%). Some authors have found the second-line drugs to be as effective as the primary drugs. Mikkelsen et al. (1981), for example, found clonazepam to be equivalent to carbamazepine in controlling complex partial seizures. Often, preferences for particular drugs are based, at least in part, on relative likelihoods of drug toxicity, particularly sedation and/or altered mental status (Theodore and Porter 1983).

Whichever drug one uses, there are principles which can improve seizure control and reduce toxicity:

1. Whenever possible, only one anticonvulsant should be employed. This, first, has the advantage of simplicity. Second, when monotherapy is employed, patients frequently tolerate higher drug levels, with fewer side effects, than would have been anticipated from data based on polypharmacy (Sato et al. 1979; Shorvon and Reynolds 1979; Shorvon et al. 1979; Gannaway and Mawer 1981; Reynolds and Shorvon 1981; Thompson and Trimble 1981; Schmidt 1983; Lesser et al. 1984b,d; Schmidt and Haenel 1984), and the higher levels which can be employed often result in improvements in seizure control.

2. It has been clearly demonstrated that clinical efficacy correlates with drug concentration (Rowan et al. 1975; Reynolds et al. 1976), although one study found this correlation for secondarily generalized tonic–clonic, but not partial seizures (Turnbull et al. 1984). Thus, whichever drug is chosen it should be used in sufficient amount. Drug plasma levels can be used to determine that medication is present in a satisfactory minimum concentration and then are helpful in monitoring the changes in drug level which result from dosage increments and in assessing toxicity. Some authors caution, however, that with very high levels, an increased seizure frequency may occur (Troupin and Ojemann 1975). Also, a recent study indicated that skin eruptions were more likely to occur with high initial anticonvulsant levels, suggesting that final concentrations should be approached gradually (Chadwick et al. 1984).

3. The physician must be aware of the variations in compliance, absorption, protein binding, metabolism, and excretion which can modify plasma drug levels and thus alter both seizure control and toxicity (Eadie 1976; Penry and Newmark 1979; Pippenger 1980; Johannessen 1981). There appears to be a good correlation between plasma levels and brain levels of at least some anticonvulsants (Sherwin et al. 1973). Free drug levels may be of added benefit in monitoring therapy in some, but not all, cases (Lesser et al. 1984b; Theodore et al. 1985b).

4. The physician must be aware of the possibility of laboratory errors in reported blood levels, and should assure that the laboratory performing the assessment has an adequate quality assurance program (Pippenger et al. 1976).

In patients whose seizures remain intractable to medical therapy, surgical excisions of the epileptogenic area have been utilized for the past half century. Although some results (Fincher and Dowman 1931; Meyers 1954) can be taken as questioning the validity of cortical excisions, the weight of opinion from many centers attests to the utility of the technique in properly selected patients. The most extensive experience comes from the series collected at the Montreal Neurological Institute, where, over a 36-year period, nearly two-thirds of patients experienced an elimination or marked reduction of seizure frequency following cortical excisions (Bengzon et al. 1968; Rasmussen 1969), with no operative deaths in the last 700 cases. This success rate dropped to 24% in patients with independent bitemporal foci (Bloom et al. 1959–60). Although the efficacy of epilepsy surgery was challenged by Meyers (1954), good results also have been reported in many other series (Taylor and Falconer 1968; Stepien et al. 1969; Talairach and Bancaud 1973; Zotov 1977; Fode et al. 1978; Rossi et al. 1978; Glaser 1980; Spencer 1981; Engel et al. 1981; Paillas et al. 1983; Polkey 1983; Augustine et al. 1984; Cahan et

al. 1984). Rasmussen (Rasmussen and McCann 1968; Rasmussen 1978) has reported the use of surgical excisions not only in presumably stable lesions but also in cases of chronic, and often progressive, encephalitis, so-called Rasmussen's syndrome, although he commented that surgery should be performed late in the course of the disease, when the disease has stabilized. On the other hand, Gastaut et al. (1962) advised against surgery for a different entity, the HHE syndrome (see above). Finally, Silfvenius et al. (1964) demonstrated that removal of the insula does not improve seizure control and markedly increases morbidity in patients receiving temporal lobectomies.

There has been considerable discussion regarding the timing of surgical ablations and there is considerable evidence suggesting that early surgical intervention, including during childhood, may improve long-term prognosis in patients with drug-resistant temporal lobe epilepsy, perhaps especially in those with mesial temporal sclerosis (Falconer 1972b; Davidson and Falconer 1975). Brown (1973) has suggested that patients with changes in the horn of Ammon or with hamartomas may, in general, respond more favorably to temporal lobectomies.

Although cortical resections are the most frequently utilized techniques for treatment of focal seizures, other methods have been reported by some workers. Wilson et al. (1978) divided the corpus callosum. Morrell and Hanbery (1969) and Morrell and Whisler (1982) have employed multiple subpial transections within nonresectable areas, severing horizontal fibers at 5-mm intervals. They reported that functional impairment was not produced and seizure control improved. Several workers (Mullan et al. 1967; Kusske et al. 1972; Zemskaja et al. 1976; Mori et al. 1982) have employed ventral–anterior thalamotomies or other subcortical lesions in selected patients. Selective amygdalo-hippocampal lesions have been utilized (Wieser and Yasargil 1982), also with reported improvement in seizure control. This report was of interest because of the suggestion (plus that in the study by Ojemann and Dodrill 1985) that lateral cortical resections might in certain instances produce postoperative deficits in verbal memory. Meyers (1954) pointed out that craniotomies had been performed in some reported patients without resecting any epileptogenic tissue but with seizure control. Ribaric and Janicijevic (1979) removed pathological lesions adjacent to an epileptogenic area without removing the area itself but again with seizure control. Case definition may have accounted for the findings summarized by the first of these reports. In the second, patients had hemangiomas in two cases and osteitis and pachymeningitis in one. It is possible in the latter cases that the pathological lesion had produced ischemic, inflammatory, or other metabolic changes in the adjacent epileptogenic area with these changes being reversible upon removal of the primary lesion. The considerations here would be analogous to those mentioned in connection with PLEDs.

As alluded to above, some success has been reported with operant conditioning in patients with intractable epilepsy (Efron 1957; Sterman and Friar 1972; Sterman et al. 1974; Sterman and Shouse 1980; Lubar et al. 1981), although this success has not been confirmed by others (Kaplan 1975; Gastaut 1975; Wyler et al. 1979). Since stress increases seizure frequency in some patients (Temkin and Davis 1984), it is likely that relaxation training would be beneficial in selected cases.

Other suggested techniques for the control of seizures have less clinical verification at this time. These include antiestrogen treatment (Check et al. 1982), localized irradiation (Wieser 1939; Baudouin et al. 1951) or ultrasound (Manlapaz et al. 1964; Elomaa 1980), dentate stimulation (Godlevskii and Shandra 1983), and cerebellar stimulation (Cooper and Gilman 1973; Cooper et al. 1974, 1976;

Rajjoub et al. 1976), a technique which may result in ultrastructural cerebellar changes (Gilman et al. 1975) and whose utility could not be confirmed (Lockard et al. 1979; Levy and Auchterlonie 1979; Strain et al. 1979; Ebner et al. 1980), including in a double-blind study (Wright et al. 1984). Psatta (1983) reported that feedback stimulation via the caudate was more effective than stimulation in other areas such as the mesencephalic reticular formation, thalamus, or hypothalamus in controlling experimental seizures.

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Chapter 12

Complex Partial Seizures

Frank W. Sharbrough

Definition, Related Terms, and Nosology

Most modern classifications divide seizures into major groups based first on differences in the distribution of the electrographic seizure discharge (e.g., partial versus generalized) and then on differences in the clinical manifestations during the seizures (e.g., convulsive versus nonconvulsive). In general, the purpose of any such classification is to furnish a broad framework which should facilitate the identification, description, and categorization of epileptic seizures so as to allow for early detection and appropriate management of different seizure types as well as to facilitate epidemiologic studies and communication among physicans. Secondly, such classifications, based on the more general aspects of seizures, should allow for a more detailed description of individual seizures.

From 1969 to 1981, the most widely used classification was the First International Classification of seizures (Gastaut 1970; Gastaut 1973). However, there were perceived inadequacies, and after much deliberation a second commission published a revised International Classification in 1981 (Commission on Classification and Terminology of the International League Against Epilepsy 1981). The revised system departs from the original in two major areas.

The *first change* emphasizes the need to describe the evolution of seizures sequentially through their different phases. For instance, it is not uncommon for a generalized seizure to begin with a nonconvulsive behavioral arrest (an absence phase) and then proceed to a convulsive phase of tonic–clonic type (commonly designated as a grand mal seizure). The revised classification encourages recognition of this sequential evolution by describing such a seizure as a nonconvulsive to a convulsive generalized seizure. This is in contrast to the original system, which tended to arbitrarily force the seizure into one category or the other. Usually the more dramatic category was chosen and, in the case under consideration, the seizure simply would have been called a "convulsive generalized seizure."

The *second change* is in the criteria for dividing different phases of partial (a synonym for focal) seizures into two major categories so that this decision is now based solely on whether the phase occurs without ($\bar{s}$) impaired consciousness (defined as a *s*imple phase) or with ($\bar{c}$) impaired consciousness (defined as a *c*omplex phase). There are logical, theoretical, and practical reasons for changing the criteria to identify different phases of partial seizures. Regrettably, after changing the criteria, the second commission elected to retain the original names of "simple" and "complex" but to define them differently from their commonly understood meanings. Apparently this was done in an attempt to avoid being accused of making revolutionary changes in a system that already had wide acceptance.

In order to minimize the amount of confusion that can result when making the transition from the original to a revised definition of simple and complex, it is instructive to compare and contrast how both systems apply to the classification of different phases of partial seizures that already have been descriptively divided into major subgroups based on whether or not the patient was later amnestic for that phase of the seizure (Table 12.1).

Table 12.1. Comparison of the original with the revised classification of partial seizures

Original			Revised
Simple		*Nonamnestic*	
	A.	Convulsive and equally uncomplicated autonomic or sensory symptoms	Simple
	B.	More complicated sensory, psychic, or motor symptoms	
Complex		*Amnestic*	
	A.	$\bar{s}$[a] impaired consciousness because observed $\bar{s}$ impaired responsiveness	
	B.	$\bar{c}$[b] impaired consciousness because observed $\bar{c}$ impaired responsiveness	Complex

[a] $\bar{s}$, without.
[b] $\bar{c}$, with.

Prior to the revision, "complex" partial referred to any focal seizure producing complicated clinical manifestations, with or without amnesia. As such, it included all focal seizures previously described as "psychomotor." This latter term was introduced in 1948 (Gibbs et al. 1948) to describe both the nonamnestic but complicated sensory, psychic, or motor phenomena and amnestic semiautomatic behavior.

The revised definition of "complex" partial does not include any nonamnestic focal seizure phases, even if they produce the most complicated psychic symptoms. Such nonamnestic phases of focal seizures currently have to be designated by the word "simple," which, of course, is antithetical to the commonly understood meaning of "simple" (i.e., uncomplicated). This invites confusion that can only be minimized by knowing whether "complex" partial refers to the original or the revised definition of this term.

Regardless of whether the original or revised definition of "complex" partial seizures is used, it is important to recognize that these terms are not equivalent to

either the term "psychomotor" or "temporal lobe" seizures. This is true because some psychomotor manifestations, especially amnestic semiautomatic behavior, can occur as part of generalized, nonconvulsive absence seizures. Therefore, the psychomotor ictal phase need not be a partial seizure. Further, whether the original or revised definition is used, a small percentage of "complex" phases of partial seizures arise outside the temporal lobe, and temporal lobe seizures may have simple phases. Therefore, although all of these terms deal with a similar overlapping group of seizures, none are exactly synonymous.

In addition to facilitating comparisons between the original and revised terminology for complex partial seizures, Table 12.1 emphasizes another important fact: Identifying *c*omplex phases $\bar{c}$ impaired consciousness is dependent on, but more difficult than, identifying amnestic phases because the former depends on the latter plus observed documentation that the amnestic phase was associated $\bar{c}$ impaired responsiveness. Recognition of this fact suggests a method for using the nonamnestic and amnestic divisions as building blocks when classifying partial seizure phases into the revised categories of simple and complex.

Nonamnestic phases of partial seizures can be immediately classified into the *nonamnestic* simple category because being $\bar{s}$ amnesia indicates the phase is $\bar{s}$ impaired consciousness, regardless of the intricacy of the recall symptoms and independent of whether responsiveness was impaired during the nonamnestic phase.

Amnestic phases of partial seizures require additional information from other observers in order to correctly classify them either into the more common *amnestic* *c*omplex category $\bar{c}$ impaired responsiveness or into the less common *amnestic* *s*imple category $\bar{s}$ impaired responsiveness. This latter category accounts for less than 5% of all amnestic phases of focal seizures.

An additional advantage of dividing the seizures into nonamnestic and amnestic categories, based on comparing the patient's history with that given by a third party, is that these divisions not only form the foundation of the current designations for the simple and complex phases of partial seizures, but they also can be designated by terms whose commonly understood definitions have not been recently changed. As such, this approach is similar to that used to divide generalized seizures into clearly defined categories that can be designated by commonly understood terms such as "convulsive" versus "nonconvulsive." Further, because the terms "nonamnestic" and "amnestic" are primarily descriptive, with definitions that remain unchanged whether used to describe phases of partial or generalized seizures, they can be used to emphasize that remarkably similar clinical manifestations occur during both partial and generalized nonconvulsive seizures. This fact is often obscured by the present terminology, which appears to use antithetical terms to designate the same clinical manifestations, depending on whether these manifestations occurred during a partial or a generalized electrographic seizure. An example of this is when the same clinical manifestation of amnestic nonconvulsive behavioral arrest is called complex (partial) or simple (absence), depending on whether the manifestation occurred during a partial or a generalized electrographic seizure.

In summary, *c*omplex partial seizure phases, as currently defined, are the amnestic phases of focal seizures $\bar{c}$ impaired responsiveness. This revised definition of the complex partial phases of focal seizures excludes the nonamnestic phases of focal seizures that were originally designated as complex and that were roughly equivalent to the nonamnestic phases of psychomotor seizures of focal origin.

Further, complex partial seizures (regardless of whether the original or revised definition is used) are usually, but not always, temporal lobe seizures, and temporal lobe seizures usually, but not always, produce complex phases.

Clinical Manifestations

Based on current definitions, the complex phase of partial seizure (amnestic phase with impaired responsiveness) may be the only phase of the partial seizure or may be preceded by a simple phase, which usually is a preamnestic phase previously designated as an aura (because it is a less intense phase of the seizure that serves as a warning that a more intense amnestic phase may be about to follow). Depending on the patient group studied, at least 50% of subjects may have a simple phase preceding the complex phase of their partial seizures (Feldman 1983). For example, in a series of 100 temporal lobectomies for complex partial seizures performed at the Mayo Clinic from 1972 to 1980, 66 patients had simple phases preceding the majority of their complex partial seizures. In most of these 66 patients, the simple phases (the aura) at times occurred in isolation without proceeding into a complex phase. Of the remaining 34 patients, 15 never had and 19 rarely had a simple phase preceding their complex partial seizures.

Simple Ictal Phase

The manifestations of a simple phase progressing into a complex partial seizure are the manifestations that can be seen in any simple partial seizure and can include focal, tonic, or convulsive motor manifestations as well as equally uncomplicated autonomic or sensory symptoms (Table 12.1). This latter group includes the common epigastric aura as well as the motor–sensory symptoms involving the face and extremities, with or without a jacksonian march. It is important to recognize that crude dysesthetic sensations may occur during the simple phase of a partial seizure of temporal lobe origin and can involve one, two, three, or four limbs simultaneously; such an atypical distribution does not mean that the symptoms are functional.

Autonomic manifestations can occur during the simple or complex phase of the seizure. The range of these symptoms includes pallor, sweating, flushing, piloerection, pupillary dilatation, and increased heart rate (Fig. 12.1). Ictal tachycardia, however, is much more common during the complex phase of the seizure (Marshall et al. 1983).

In addition to the more disorganized motor or sensory symptoms mentioned above, simple seizures can produce more complicated psychic symptoms with illusions or hallucinations involving any sensory system as well as symptoms that may be classified as: (a) dysphasic; (b) dysmnesic (e.g., *déjà vu*, *jamais vu*, and flashbacks); (c) cognitive (e.g., forced thinking and dreamy states); and (d) affective (e.g., dysphasia, euphoria, fear, and anger) (Commission on Classification and Terminology of the International League Against Epilepsy 1981).

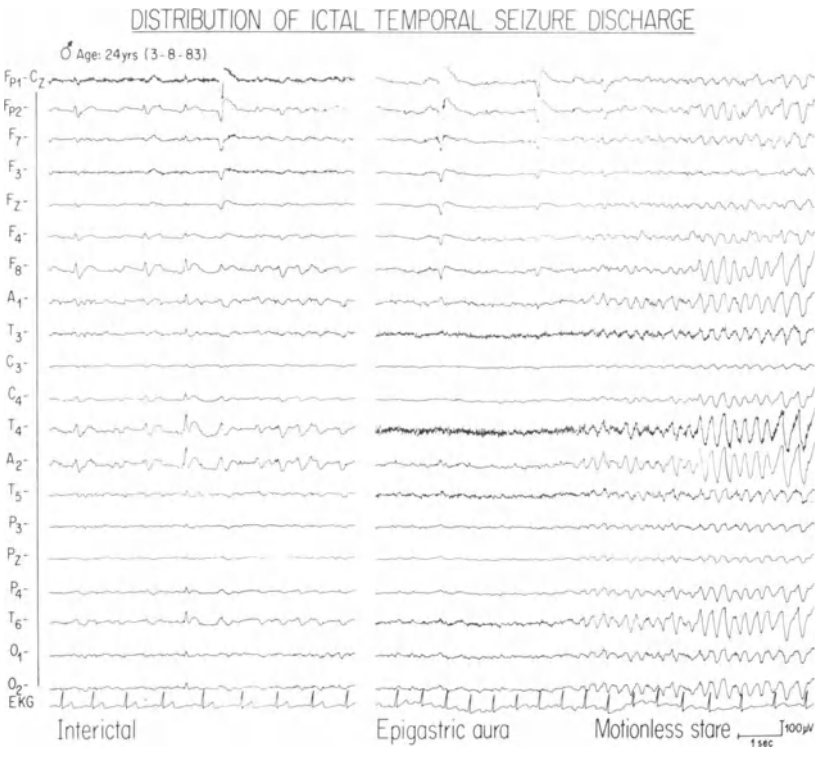


Fig. 12.1 This patient's interictal EEG shows almost continuous semirhythmic slow-wave activity in the right temporal area that at times was clearly a portion of a sharp and slow-wave complex but at other times appeared without obvious sharp wave (*left*). Attenuation of this interictal pattern was the initial electrographic accompaniment of the simple phase of this patient's right temporal lobe seizure, clinically expressed as an epigastric sensation and accompanied by an increase in heart rate from a baseline of 80 to 120 beats/min. With the appearance of a theta-range seizure discharge on the right with reflection in the contralateral temporal lobe, the patient developed behavioral arrest with a blank stare, and the heart rate decreased from 120 to 90 beats/min. The electrographic and clinical evolution of this seizure is further demonstrated in Figs. 12.4 and 12.5.

The preceding classification of sensory and psychic symptoms can be best seen as an attempt to categorize the various simple phases which have vaguely defined boundaries that make it difficult to rigidly assign some symptoms to one category and not the other. For instance, in discussion of these categories, most authors have difficulty in deciding whether temporal disorientation or dreamy states should be classified as dysmnesic or cognitive symptoms and whether some speech distortion should be considered dysphasic or an articulatory disorder. Therefore, the broad categories should be best considered as a mnemonic framework to organize the various manifestations, and the fact that one manifestation might not be strictly confined to one category should not be surprising.

In the past much effort has been devoted to assigning a particular symptom occurring during a simple partial ictal phase to a particular location within the brain. Within broad limits this is possible for certain symptoms, such as the sensory or motor symptoms (or both) with a jacksonian march, that commonly are

associated with a spreading discharge in the contralateral sensorimotor strip. Further, the rare symptom of ictal blindness is usually related to a seizure discharge in the occipital lobe. However, almost any symptom at one time or another can give a misleading localization and, taken in isolation, most do not lend themselves to a simple anatomical localization.

Automatisms (Simple or Complex)

Complicated ictal automatic behavior usually is associated with a sufficiently confused and amnestic mental state (confusional automatism) that it is appropriately classified as the complex phase of a partial seizure. The most commonly used definition of an epileptic automatism is the one adopted from the first sentence of Gastaut's definition of the phenomenon (Gastaut 1973): "More or less coordinated and adapted (eupractic or dyspractic) involuntary motor activity [usually] occurring during a state of clouding of consciousness either in the course of or after an *epileptic seizure*, and usually followed by amnesia for the event." I have added the extra "usually" to the definition because it emphasizes the following important point that Gastaut brought out in his more complete discussion. This type of automatic behavior "usually represent[s] the release of automatic behaviour under the influence of the clouding of consciousness that accompanies a generalized or partial epileptic seizure (*confusional automatisms*)," but it can occur as a result of direct stimulation of certain motor centers during a partial seizure, suggesting that an automatism can occur with a relatively clear consciousness, as indicated by the fact that the patient subsequently is not amnestic for the event. Therefore, although the great majority of ictal automatisms are amnestic automatisms and properly classified as "*complex*," there are a small minority of nonamnestic ictal automatisms that have been classified as "*simple*." In our experience, these rare, nonamnestic ictal automatisms include laughter, exploratory movements of the hands, complicated cycling movements of the feet, and other automatic actions over which the patient has little control in spite of being aware of their occurrence. Most of the "simple" nonamnestic automatisms that we have observed were produced by partial seizures arising in the frontal lobe, although some have been documented to arise from the temporal lobe as well.

Complex Ictal Phase

The complex phase of a partial seizure is usually divided into major groups depending on whether there is simply arrest of ongoing behavior or a confusional automatism, or a sequential combination of both manifestations (Commission on Classification and Terminology of the International League Against Epilepsy 1981). With the behavioral arrest, the patient simply stops what he is doing and then often stares blankly ahead. This may be the only manifestation of the complex partial seizure and, if so, it could be easily mistaken for an absence seizure. The

differentiation usually can be determined based on the presence or absence of a preceding simple phase or a postictal phase or both, but EEG documentation may be required for accurate distinction.

The more commonly recognized manifestation of complex partial seizures is a confusional automatism (see definition above) which may or may not be preceded by a behavioral arrest. It needs to be emphasized that not all confusional automatisms are ictal because such automatisms can occur during postictal as well as during any nonepileptic confusional state.

The range of automatic behavior that can occur during the complex phase of a partial seizure is as broad as the range of complicated psychosensory symptoms that can occur during the simple phase of a partial seizure. Again, any attempt to categorize this range of automatic behavior should be looked on as simply a broad mnemonic framework; individual automatisms will at times not fit into any single, predetermined category. With these limitations in mind, the following categories are frequently distinguished: (a) alimentary (smacking, licking, chewing, swallowing); (b) mimicry (facial expression suggesting an emotional state, often fear); (c) gestural (fumbling or exploratory movements with the hand directed toward the subject or his environment); (d) ambulatory; and (e) verbal. The automatism can be simply a continuation of activity that was occurring when the seizure began (perseverative automatism) or it can be an entirely new activity that may habitually occur in association with a seizure (de novo automatism).

Recently, some investigators have attempted to classify complex partial seizures into two basic types based on the sequence of events that occurred during the amnestic period (Delgado-Escueta et al. 1983). These authors define a type-1 complex partial seizure as beginning with an initial brief stage of motionless stare with behavioral arrest followed by a second stage of stereotyped alimentary automatism (with chewing, smacking, and swallowing), during which the patient is relatively unresponsive, and a final stage of less intense confusion with quasipurposeful automatisms, reactive to environmental stimuli (Delgado-Escueta and Walsh 1985). The type-2 complex partial seizures begin without the behavioral arrest, going immediately into tonic versive posturing or complicated quasipurposeful automatism. It was the opinion of these authors that the partial seizures with type-2 complex phases usually do not arise from the medial temporal structures but more likely arise from more widespread cortical distributions, including the frontal area (Walsh and Delgado-Escueta 1984). Although this generally agrees with our experience, there are clear exceptions to the rule and, as previously emphasized, one should be cautious about always assigning clinical manifestations to a specific anatomical source. More reliable localization can be arrived at only by combining the entire clinical and electrographic picture.

In our surgical series, the additional clinical features that tend to suggest a frontal rather than temporal origin for complex partial seizures are as follows: high-frequency clusters of brief seizures (generally lasting less than 30 s) beginning abruptly, often without aura, and usually ending without postictal state. Such seizures may be associated with a highly complicated hyperkinetic automatism and may be repeated every 2–5 min for 30 min up to several hours. Rarely, these complicated automatisms of frontal origin prove to be "simple automatisms" because of lack of significant impairment of consciousness or amnesia. However, once again the clinical features must be correlated with electrographic features (to be discussed later) by using video EEG techniques in order to determine with confidence the exact origin of the seizures.

Differential Diagnosis and Interictal Manifestations

Complex partial epileptic seizures must be differentiated from nonepileptic episodic behavior, which may be organic or psychogenic in origin (Feldman 1983; Karnes and Sharbrough 1983). An important area of differentiation is from violent or criminal behavior that may be claimed as "epileptic violence" during a court trial. In reviewing video EEG data, detailed studies of this possibility suggest that this rarely, if ever, occurs and for such a claim to be substantiated, it must fulfill a number of rigid criteria (Treiman and Delgado-Escueta 1983).

Over the years there has been much discussion of an epileptic personality and even a specific personality associated with temporal lobe epilepsy (Waxman and Geschwind 1975; Bear and Fedio 1977), including cases that are currently classified as complex partial seizures. However, the simplistic view that there is one characteristic psychopathological feature associated with all patients who have complex partial seizures must be rejected (Rodin and Schmaltz 1984). Any attempt to explain the development of psychopathological features in patients with complex partial seizures must consider the elaborate interaction between the patient's environmental experiences and interictal and ictal abnormalties affecting the patient's brain (Trimble 1983).

Electrographic Manifestations

Although most partial seizures with complex phases arise from the temporal lobe, they also can arise from extratemporal structures, including the frontal as well as more posterior regions of the brain. Because the most common origin of these seizures is in the temporal regions, the electrographic manifestations of seizures arising from the temporal lobes will be discussed first and later compared with the electrographic manifestations of seizures arising outside the temporal regions.

Interictal Manifestations

Gibbs et al. (1948) found that spikes arising from the anterior temporal regions constituted the principal interictal pattern in patients who now would be considered as having complex partial seizures. Further, approximately 90% of patients with an interictal spike focus in the temporal area had a history suggestive of seizures with complex partial phases.

Many subsequent reports have consistently demonstrated that in patients with complex partial seizures, the most common abnormality is an interictal temporal spike focus. This abnormality was identified in 73% of cases studied by Gibbs and Gibbs in 1952, but that study also demonstrated spikes located in the frontal regions as well as the occipital regions in a small percentage of cases. In 1953, Gastaut found interictal spikes located outside the temporal regions in 8% of his patients. Extratemporal pathology, as a source of complex partial seizures, also

has been demonstrated in a number of other studies (Penfield and Jasper 1954; Dodge 1958; Walker 1966).

The exact percentage of patients with complex partial seizures who have specific interictal epileptiform EEG abnormalities is difficult to determine and depends on the population being studied, the total duration of recording time, and the proximity of the recording to a preceding seizure because a recent study has shown a significant tendency for postictal activation of interictal epileptiform abnormalities (Gotman and Marciani 1985).

In complex partial seizures of temporal lobe origin, the interictal spikes or sharp waves are usually confined to one temporal lobe. However, because temporal spikes frequently show a basal field spread, a unilateral spike can be detected in the contralateral basal recording sites, especially when nasopharyngeal and sphenoidal electrodes are used. In addition, spikes can arise in a bilateral and independent manner. The exact frequency of bilaterally independent spikes will also be influenced by the patient population and whether or not depth electrodes are used. With or without accompanying spikes or sharp waves, slowing and distortion of the background activity can be seen in the interictal record of patients with temporal lobe seizures (Klass 1975). At times, rhythmic slow-wave activity is clearly a portion of a spike and slow-wave complex (Figs. 12.2, 12.3). At other times, rhythmic slow-wave activity in the temporal regions is not associated with a

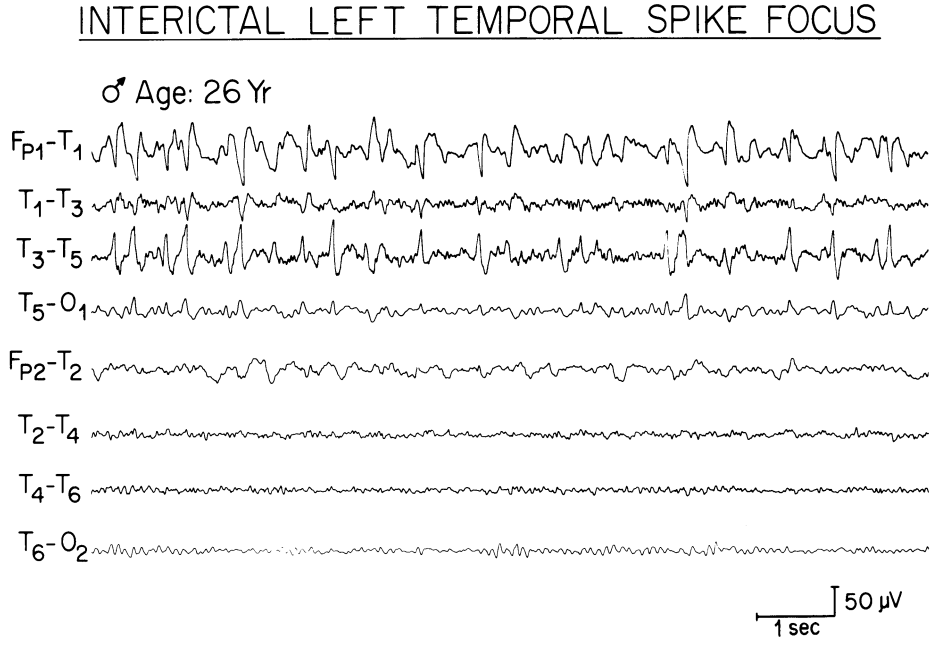


Fig. 12.2. This patient's interictal EEG shows almost continuous repetitive spikes and sharp waves intermixed with slow activity in the left temporal region. Such sustained epileptiform activity is sometimes interpreted as a subclinical electrographic seizure discharge. However, because this type of pattern is almost never associated with clinical symptoms and is attenuated at the onset of a clinical seizure (see Fig. 12.3), it is best considered as a repetitive interictal and not a subclinical electrographic seizure discharge.

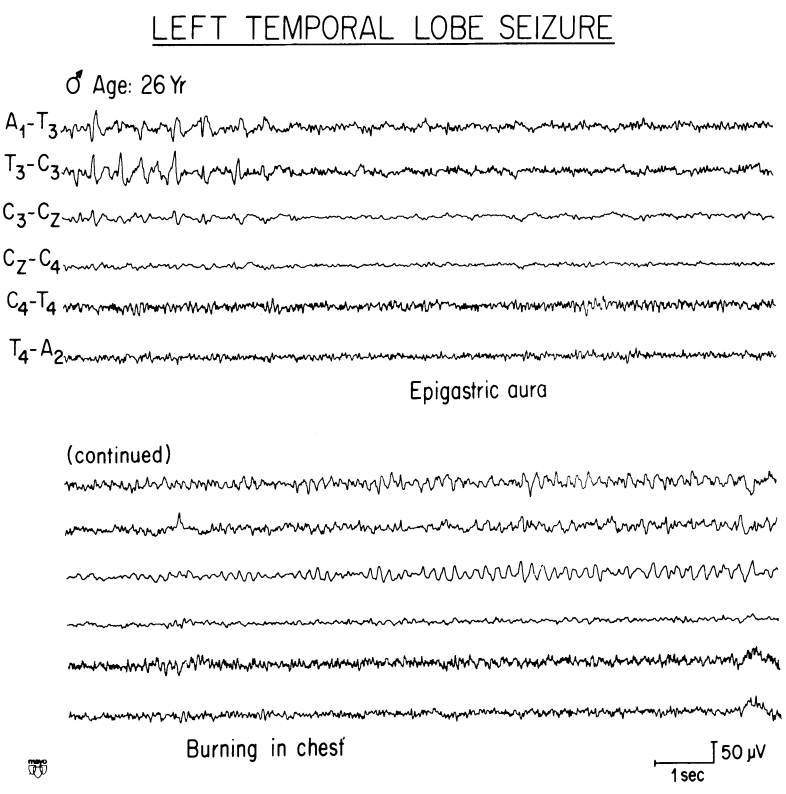


Fig. 12.3. Sudden attenuation of repetitive interictal left temporal spikes (beginning after approximately 3 s into the upper segment) is the sole scalp electrographic manifestation at the onset of the simple phase (formerly designated as an aura) of this patient's left temporal lobe seizure, characterized clinically by an epigastric sensation. It was not until later in the progression of the seizure that a rhythmic theta-range seizure discharge (without obvious spikes or sharp waves) became apparent in the left temporal scalp recording. Note the clear difference between the rhythmic theta-range seizure discharge and the previous repetitive interictal spikes not associated with symptoms. As the electrographic discharge spread bilaterally, the patient's seizure progressed into a complex phase with an automatism (not shown in this figure).

definite spike detectable at the surface (Fig. 12.1). Even in this subgroup, however, cortical recordings, either at the time of operation or with chronically implanted subdural strips, may demonstrate spikes undetected at the scalp that are occurring in association with the more widespread rhythmic slow activity that can be detected at the scalp (Klass 1975).

Finally, it must be emphasized that both in patients with complex partial seizures and in normal individuals, misleading nonspecific findings can be seen, especially during sleep, and be misinterpreted as potentially epileptogenic abnormalities. The most important of these potentially misleading findings are small

sharp spikes that are of no proven clinical significance; they are discussed in detail elsewhere (Klass 1975). In addition to focal abnormalities in patients with complex partial seizures of temporal lobe origin, more widespread and persistent slowing of background as well as intermittent widespread slow activity can be seen, frequently maximum in the anterior head region (frontal intermittent rhythmic delta activity, FIRDA). These latter abnormalities are usually due to a combination of factors, including medication effect, drowsiness, or recent seizure activity.

Interictal abnormalities of extratemporal origin, whether frontal, parietal, or occipital, may vary in a manner similar to those seen with the interictal temporal lobe abnormalities. However, in our experience, a majority of surgical candidates with complex partial seizures outside the temporal lobe have a scalp distribution of their interictal abnormality that is distinctly different from those seizures of temporal lobe origin.

Ictal Manifestations

During the simple phase preceding a complex partial seizure of temporal lobe origin, the accompanying electrographic findings may be subtle or not detected at the scalp in at least 30% of cases. Although the simple phase of a complex partial seizure may not produce a detectable electrographic seizure discharge at the surface, it nonetheless may produce a definite focal attenuation of the interictal pattern in the temporal lobe from which the seizure is originating (Figs. 12.1, 12.3).

Once the complex phase with impairment of responsiveness and amnesia has begun, a technically satisfactory EEG recording almost invariably shows identifiable EEG change. In fact, in two separate studies all patients with scalp-recorded partial seizures showed changes during the complex phase of the seizure (Klass 1975; Delgado-Escueta and Walsh 1985). In addition to attenuation of the interictal pattern, either in a focal or more generalized manner, evolving rhythmic discharges (with or without identifiable epileptiform components) occur which, although usually more prominent in one temporal lobe, are nonetheless commonly reflected bilaterally in the scalp EEG (Figs. 12.1, 12.4, 12.5). However, in the complex phase, although bilateral temporal depth involvement is the rule, occasionally the depth discharge is only detected unilaterally (Gloor et al. 1980).

In one study (Klass et al. 1973) of EEG recordings during 116 partial seizures (a mixture of simple and complex seizures), the initial manifestation was only attenuation in 25%, a rhythmic seizure discharge without epileptiform morphological features in 14%, and repetitive epileptiform discharges in 30%. No EEG change was detected at the onset of clinical symptoms in 10%. However, in this study, no complex partial seizures, as currently defined, failed to demonstrate an EEG change throughout the entire attack. In a more recent study of 66 scalp-recorded seizure discharges (Blume et al. 1983), the initial electrographic manifestation was only attenuation in 10%, rhythmic seizure discharge without epileptiform morphological features in 43%, and rhythmic seizure discharge with epileptiform components (spikes or sharp waves) in 41%.

With scalp-recorded seizures of temporal origin, the initial frequency of the electrographic seizure pattern is seldom in the beta range. Whatever the initial frequency of the seizure discharge, it tends to change during the sequential clinical

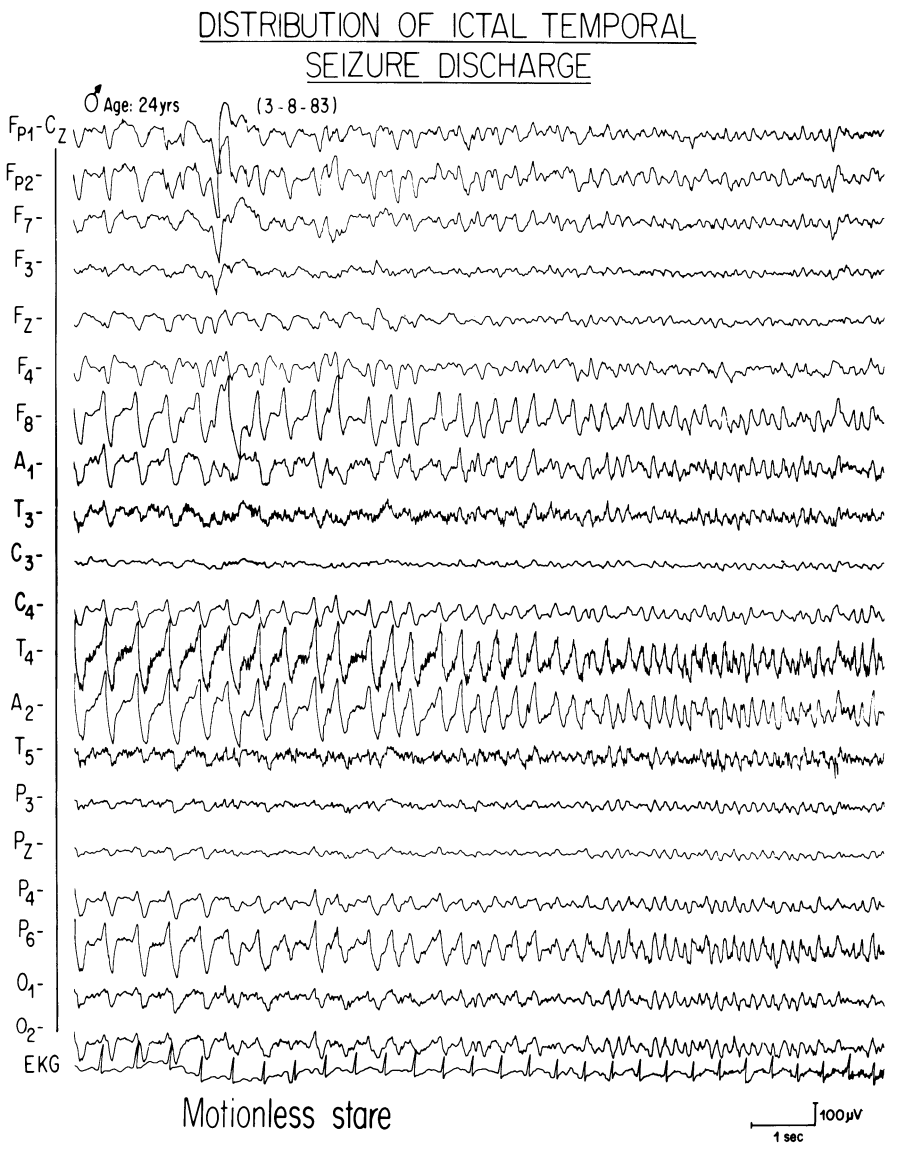


Fig. 12.4. This is a direct continuation of the seizure demonstrated in Fig. 12.1. The initial theta-range seizure discharge is temporarily replaced by a 3-Hz seizure discharge containing repetitive sharp waves (the heart rate increasing from 90 to 120 beats/min) before being replaced by a low-voltage 7- to 8-Hz seizure discharge (without epileptiform spikes or sharp waves) (refer to Fig. 12.5 for further evolution of the electroclinical manifestations of this seizure).

evolution of the seizure and, in contrast to earlier suggestions, the frequency of the ictal discharge is just as likely to increase (Fig. 12.4) as to decrease (Figs. 12.6, 12.7) during the course of the seizure (Blume et al. 1983).

After a temporal lobe seizure with a complex phase that does not progress to a generalized convulsion, there is generally long-wavelength irregular slowing and

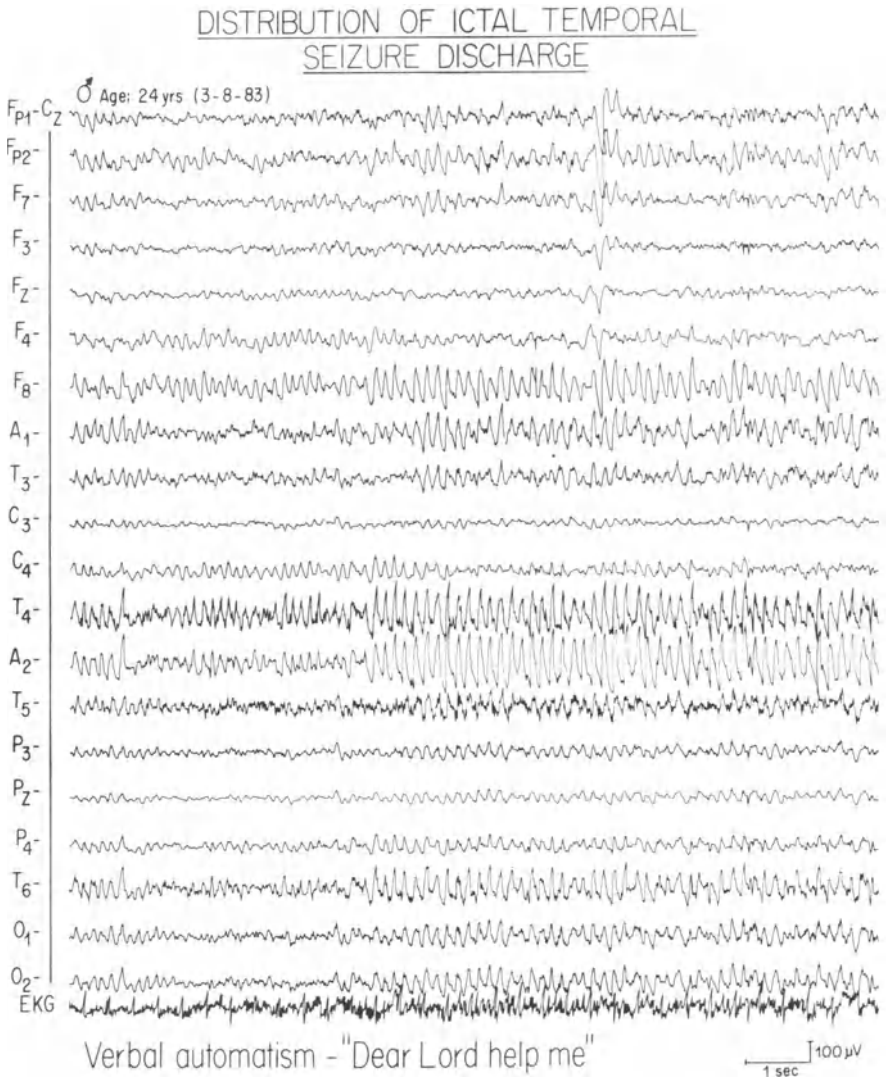


Fig. 12.5. This recording is a direct continuation of the seizure in Fig. 12.4 in which the lower voltage 7-Hz seizure discharge is suddenly replaced by a higher voltage, slightly slower 6-Hz seizure discharge as the patient manifests a verbal automation quite characteristic of his usual seizure. Note that during the course of this seizure, the frequency of the discharge began in the theta range without epileptiform components (Fig. 12.1), slowed in the delta range with the appearance of epileptiform components (sharp waves seen in the first part of Fig. 12.4), and then was replaced by a 7- to 8-Hz low-voltage seizure discharge without epileptiform components that, in turn, was replaced by a higher voltage 6-Hz seizure discharge without epileptiform components.

increased disorganization of the background on the side of origin, which then gradually returns to baseline in 30–45 min.

The electrographic discharge with seizures of frontal lobe or other extratem-

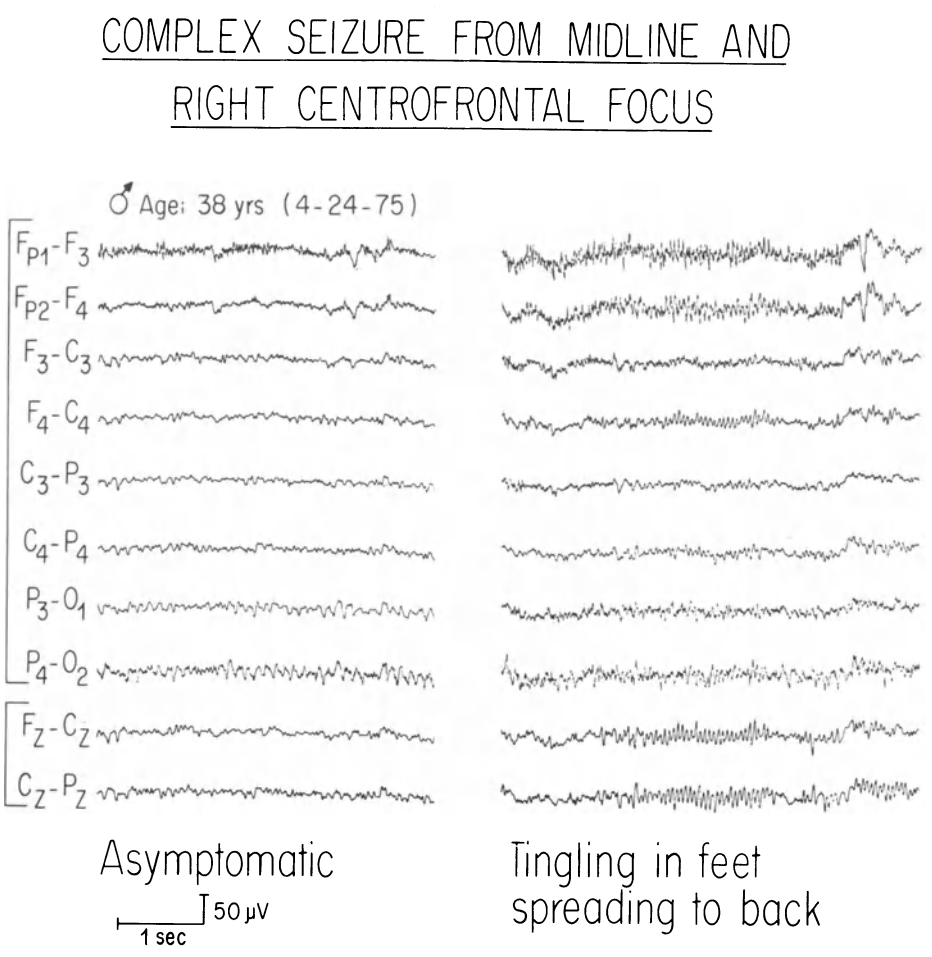


Fig. 12.6. This patient's interictal record failed to show epileptiform discharges (*left*). However, at the onset of his seizure's simple phase, manifested by tingling paresthesias in both feet spreading up to his back, he developed a prominent beta-range seizure discharge, maximum in the central midline with more spread to the right frontocentral area than to the left (see Fig. 12.7 for continuation of seizure).

poral origin at times generalizes more rapidly and more frequently is recorded at the scalp as a beta-range seizure discharge (Fig. 12.6). With complex partial seizures of extratemporal origin, especially if they are quite brief with little or no postictal impairment of consciousness, the surface-recorded ictal EEG pattern is often very subtle but usually detectable at the scalp, provided appropriate montages are used. However, with these extratemporal foci, lateralization of the ictal discharge is often more difficult than it is in seizures of temporal lobe origin (Fig. 12.6). The postictal changes with complex partial seizures of frontal lobe origin are generally similar but, like the ictal changes, may be less prominent than those seen with temporal foci.

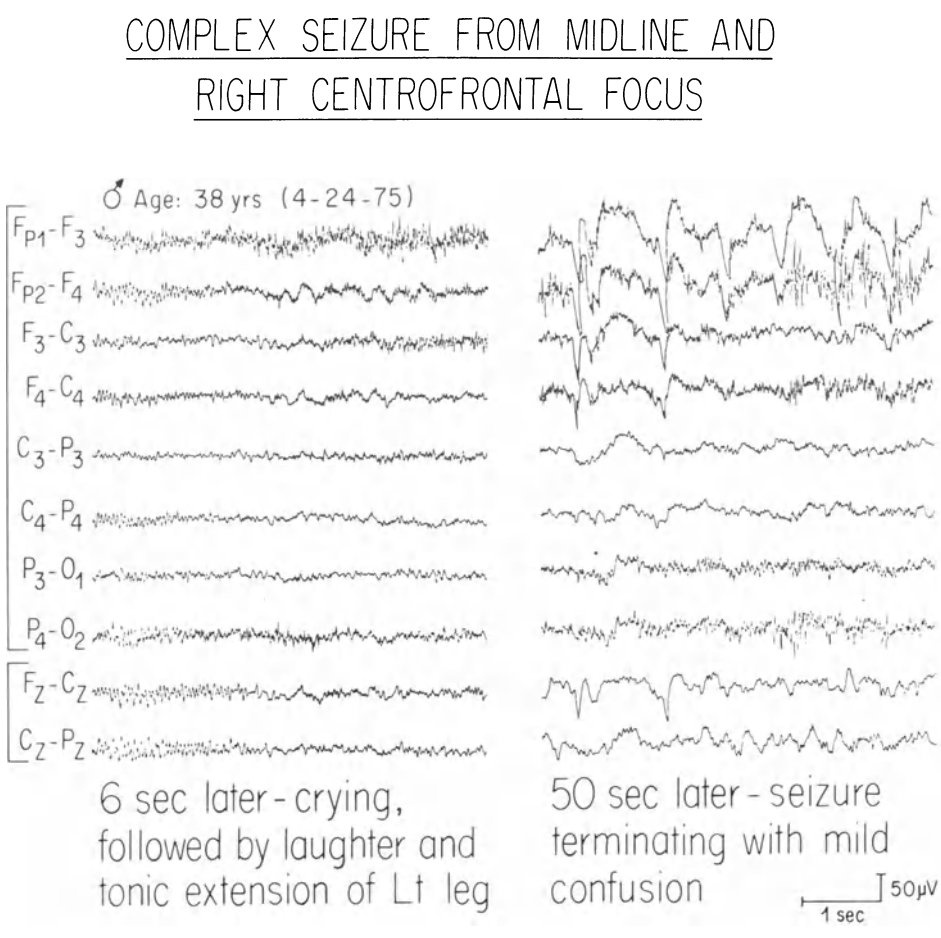


Fig. 12.7. During the complex phase of the seizure, associated with crying followed by laughter, the EEG was partially obscured by muscle activity. However, as the seizure evolved, the electrographic discharge became more obvious as it slowed into the theta–delta range. The total duration of the seizure was 1 min, with rapid recovery. No electrographic discharge was recorded in the temporal derivations (not shown in this illustration). As more commonly occurs with complex partial seizures arising from extratemporal rather than temporal regions, this patient's seizure frequency was quite high, averaging approximately 10–15 per day with as many as 30 in 1 day.

Activating Technique and Special Electrodes

If the waking EEG in patients with complex partial seizures is free of specific epileptiform abnormalities, sleep recordings have proved to be the most convenient and effective way of activating interictal abnormalities. In a study of 330 sleep recordings from patients with partial seizures, mainly of complex type, there was activation of new or additional significant epileptiform activity in approximately one-half of cases, with unilateral activation in 80% of cases and bilateral activation in 20% (Klass 1975). In this same group, 9% showed activation of

patterns without clear-cut clinical significance (mainly small sharp spikes). Many early studies suggested that nasopharyngeal and sphenoidal electrodes may frequently add significant additional information that cannot be obtained by using scalp recordings (Rovit and Gloor 1960; Rovit et al. 1960). In contrast, some recent studies suggest that when basal (nasopharyngeal and sphenoidal) electrodes are compared with lateral inferior electrodes (TI-T2 and A1-A2) they rarely, if ever, detect abnormalities that are not at least partially reflected in these lateral electrodes (Sperling and Engel 1984; Starkey et al. 1984). In our experience, this comparison is facilitated by recording from the nasopharyngeal, sphenoidal, true anterior temporal, and ear electrodes simultaneously against a common reference, preferably Cz (Starkey et al. 1984).

Epidemiology, Etiology, and Pathology

Because of changing definitions, it is difficult to be certain about the prevalence of complex partial seizures (as currently defined) in specific populations. Only rough estimates can be made, but on the basis of interpretation of earlier studies (Hauser and Kurland 1975), one can conclude that complex partial seizures are likely to represent approximately 42% of partial seizures or approximately 25% of all seizures. Most patients with complex partial seizures have seizure onset before age 40. In a population study of complex partial seizures beginning before age 40, seizure onset occurred before age 5 in 43%, between ages 5 and 15 in 40%, and after age 15 in only 17% (Rocca et al. unpublished data).

The frequency of identifiable causes is unselected patients with complex partial seizures is unknown. In the population study of Hauser and Kurland (1975), there was an identifiable cause in 28% of all cases of partial seizures, with a lower frequency of identified causes in the complex than in the simple partial group (using the original definition). The most detailed studies of causes come from a highly selected surgical group; because of the nature of the selection process, these studies tend to concentrate on complex partial seizures originating from the more surgically accessible foci in the temporal lobes. In large series using block dissection, the most common pathological entity identified in complex partial seizures of temporal lobe origin is hippocampal sclerosis, with occurrence rates of 30%–50% (Falconer 1971; Mathieson 1975). A number of causes of hippocampal sclerosis have been proposed (Earle et al. 1953; Falconer 1971) and, taken as a whole, tend to emphasize the significance of discrete episodes in the early life of an individual, including birth trauma and complicated febrile convulsions in childhood. In one study of 140 temporal lobectomy cases showing hippocampal sclerosis (Mathieson 1975), 18% gave a history of significant febrile convulsive episodes without birth trauma, 3.5% gave a history of significant febrile convulsions as well as birth trauma, and 8% gave a history of birth trauma only. In the same study, of 44 cases of temporal lobectomies without evidence of hippocampal sclerosis, 7% gave a history of complicated febrile convulsions, none had a history of a combination of complicated febrile convulsions and birth trauma, and 11% had a history of birth trauma only. In a later review of the Montreal surgical experience (Rasmussen 1979), 13% of 1572 patients who underwent operation for medically refractory seizures had a history of convulsions with fever in childhood.

In surgical series, the incidence of discrete lesions other than hippocampal sclerosis usually is in the order of 15% or more (Mathieson 1975). The most common discrete lesion found is a glioma, usually indolent and often well circumscribed. Less common lesions include post-traumatic meningocerebral cicatrix, hamartomas, vascular malformations, and residua of infarcts that occurred earlier in life. Interestingly enough, even with current sophisticated radiological techniques, some of these lesions, including gliomas, are not identified prior to surgical removal of the specimen.

In our experience with 100 temporal lobectomies performed for complex partial seizures between 1972 and 1980, 31 patients gave a history of complicated febrile seizures in childhood. Because in this series the hippocampus was not removed with block resection, the exact percentage of these that showed hippocampal sclerosis could not be determined. Nonetheless, none of these 31 cases demonstrated any other gross pathological features to explain the seizures. Nineteen of these 100 cases showed a glioma that was usually low-grade and well localized. There were two cases with arteriovenous malformation. Of the 21 cases with discrete structural lesions, five were unrecognized prior to surgical intervention.

Although a history of seizures with fever in infancy appears to be an important contributing factor to the later development of complex partial seizures, with uncomplicated febrile convulsions (i.e., no history of preceding brain damage, seizure of less than 15 min duration without postictal neurological deficit, one seizure in 24 h, a normal EEG when taken at least 10 days after the seizure, and a total of no more than five seizures) only 1.1% of patients become epileptic (Nelson and Ellenberg 1976). However, with complicated febrile convulsions (i.e., history of preceding brain damage, focal seizures, seizures lasting longer than 15 min, two or more seizures in 24 h, a total of more than five seizures, or a significantly abnormal EEG more than 10 days after the seizure), the incidence of epilepsy is 9.2% (Nelson and Ellenberg 1976). Therefore, uncomplicated febrile seizures do not appear to be a significant risk factor for later epilepsy, whereas complicated febrile seizures do. Possible explanations for the relationship between the complicated febrile seizures and later epilepsy include (a) the original insult producing the complicated epileptic seizure may also have produced incidental permanent brain damage, or (b) the brain damage occurred because of the prolonged nature of the seizure itself.

Finally, it must be pointed out that most of the foregoing evidence suggesting that complicated febrile seizures and birth trauma are significant etiological factors for complex partial seizures is derived from very highly selected surgical series. Some population-based epidemiological studies have not supported these findings (Leviton and Cowan 1981). However, the negative epidemiological studies are flawed because they treat all seizures as a single disease rather than identifying complex partial seizures as a separate entity. Hopefully, future case-control study of complex partial seizures in defined populations will further clarify the role of these proposed etiological factors (Rocca et al., unpublished data).

Treatment and Prognosis

Management of Etiological and Precipitating Factors

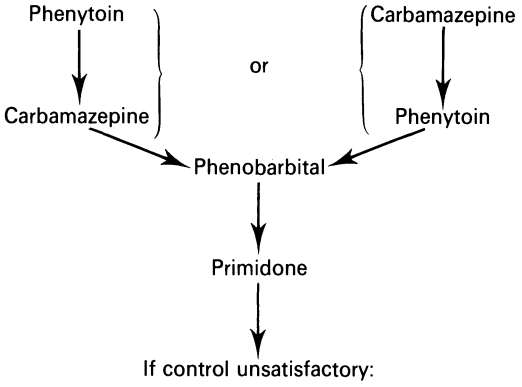
As emphasized, the cause of complex partial seizures is multiple and, unfortunately, unless they are due to highly circumscribed lesions such as a tumor or gliosis that can be surgically removed, there is no specific treatment that can be directed to the cause of the seizures. In certain primary generalized seizures, important major precipitating factors can be identified (such as medical noncompliance, alcohol abuse, sleep deprivation, and photic sensitivity), but unfortunately in complex partial seizures most of these factors, except medical noncompliance and alcohol abuse, play such a minor role that attempts to manipulate them are seldom rewarding. Therefore, the cornerstone of the treatment of complex partial seizures is first and foremost medical.

Medical Management

Complex partial seizures respond to carbamazepine, phenytoin, barbiturates, and other sedative drugs. However, because sedative drugs more often have undesirable effects on mental function and personality characteristics, the first two drugs are preferred (Theodore and Porter 1983). Whenever possible, monotherapy is recommended. However, because many complex partial seizures prove to be medically refractory, it is common for patients to take a combination of at least two medications. Combined use of phenytoin and carbamazepine may alter the metabolism of both medications compared with monotherapy and, in addition, may decrease the blood level of an individual drug that can be tolerated by the patient without producing toxicity. In spite of these problems, some authors still think that in selected refractory patients, a combination of the two medications may be preferred to one alone (Porter et al. 1980).

When initiating therapy for a previously untreated patient with complex partial seizures, it is advisable to pursue monotherapy first with one drug and then with another if the initial drug either did not produce satisfactory control at nontoxic levels or produced dangerous idiosyncratic reactions requiring that the drug be discontinued even if seizure control had been complete.

A strategy for the systematic trial of monotherapy is as follows:



In most cases monotherapy is begun with carbamazepine or phenytoin; if it is not successful, the first drug is replaced by the other. If it still is not successful, then the second drug may be replaced by phenobarbital and, if needed, phenobarbital may be replaced by primidone. At that point, the chance that any other medication alone will work more effectively than the preceding drugs is so small that it is reasonable to consider going back to the single drug in the trial that was the most effective or to combine the two most effective drugs. If the two most effective drugs are combined, a decision ultimately must be reached on whether this combination is better than the single most effective drug used alone.

If at this point in the medical trials bothersome complex partial seizures still persist, some physicians will occasionally try valproic acid or even methsuximide, but the chance that these medications will bring about satisfactory seizure control when the others mentioned above have failed is so remote that their use is seldom justified.

The foregoing outlines a strategic, systematic way of approaching medical therapy of complex partial seizures. The tactics for applying any one particular drug require appropriate use of serum antiepileptic drug levels as well as monitoring for potential serious idiosyncratic consequences of these drugs, which are well outlined elsewhere (Karnes and Sharbrough 1983; Porter 1984). However, it should be pointed out that the tactical application of a single drug, in the absence of dangerous idiosyncratic side effects, usually requires starting at a low dose and gradually increasing the dose until complex partial seizures are completely controlled or unacceptable serum level-related side effects are encountered. If this approach is used, a significant percentage of patients will experience complete control without side effects either below or above the quoted therapeutic range for the drug being used. Thus, as many have emphasized, the therapeutic range of antiseizure medications is a general guide to treatment but should not be used as a sole criterion to determine whether the current dose is insufficient or excessive (Lesser et al. 1984; Schmidt and Haenel 1984).

Prognosis in Complex Partial Seizures

Despite recent advances in medical treatment, a significant number of complex partial seizures remain refractory. The exact percentage of all complex partial seizures that are medically refractory is difficult to determine because most of the studies come from epilepsy referral centers, which tend to collect a higher percentage of the refractory cases. However, based on one population study (Annegers et al. 1980), a reasonable estimate of the complex partial seizures that prove to be medically refractory is approximately 35%. It is in this smaller subgroup that surgical intervention is frequently considered.

Surgical Management

Surgical treatment is considered only in epileptic patients who have medically intractable, handicapping partial seizures arising from an area of the brain that can be surgically removed with relatively low risk and a good chance of success but without undue expense and inconvenience. Determining which epileptic patients fit into this category involves a complicated, stepwise, decision-making process.

Patients are identified as having medically intractable, handicapping partial seizures if, after systematic application of the medical treatment described above, they continue to have sufficiently frequent (usually more than one per month and frequently more than one per week) seizures that are handicapping or dangerous (with rare exceptions, these are predominantly complex partial seizures). Such medically intractable, handicapping seizures are amenable to surgical management if they arise from a portion of the brain that can be removed with relatively low risk of injury. Generally, this requires the identification of seizures that arise from one temporal or one frontal lobe in patients in whom the contralateral hemisphere is relatively normal. The only time that operation for medically intractable seizures is usually directed to other regions of the brain is when these regions are severely and irreversibly damaged, as in patients with severe infantile hemiplegia. In such patients, removal of any portion of the hemisphere, or even the entire hemisphere, is a feasible and effective method of managing refractory and handicapping partial or secondarily generalized seizures.

Although various techniques are available for identifying favorable surgical candidates, no matter what technique is used, the success rate (based on the patient becoming seizure-free after operation on a decreased program of medication) seldom exceeds 70%. However, when one considers that the patients operated on are those who are having frequent seizures in spite of the optimal use of all available medications, this is a reasonable option to offer patients who are sufficiently handicapped. Independent of whether or not seizures are controlled after operation, there are obviously risks associated with surgical intervention. These include a risk to life, which in the most experienced hands is probably about 1 in 400, as well as a risk of a significant new and permanent neurological deficit, which in experienced hands probably will occur in about 1% of cases. The expense, depending on whether or not the selection is made on scalp recordings or extremely

prolonged depth recordings, may be estimated from a low of between $16 000 and $20 000 to a high of more than $60 000.

The initial stage of identifying those patients with medically intractable complex partial seizures who are likely to be surgical candidates is usually performed by a neurologist not directly associated with a center performing operation for epilepsy. This initial decision-making process is based on the usual techniques of evaluation, including a history and physical examination, supplemented by appropriate laboratory tests, including serum antiepileptic drug levels, a computed tomographic (CT) scan, and an EEG during wakefulness and sleep. Based on this initial evaluation, potential surgical candidates can be identified. After a preliminary discussion, patients in this group interested in pursuing operation can then be referred to various centers that specialize in identifying the most favorable surgical candidates with the best chance of success and the lowest risk of complication.

Evaluations at specialized centers begin with a review of the clinical and laboratory information already available on the patient and supplement this by additional testing as needed, such as psychometrics, speech, and visual field evaluation. When available, CT information is now supplemented by magnetic resonance image (MRI) scanning because current information suggests the latter is slightly more sensitive than the CT scan alone (Baker et al. 1985). For example, in a recent series of 50 lobectomies performed at the Mayo Clinic with preoperative CT scan, MRI scan, and angiograms, there were 8 cases with pathologically proven glioma and 1 case with an arteriovenous malformation (AVM). One glioma was completely undetected prior to surgical intervention. Two gliomas were detected by MRI but not by CT scan. The remaining lesions (five gliomas and one AVM) were detected on both the CT and the MRI scan. The AVM was the only lesion detected by angiography. However, even with the combined use of MRI and CT scanning, most cases clearly do not have an identifiable structural lesion to go along with the clinical and EEG findings of localized abnormalities. Of all the imaging techniques yet available, it appears that positron emission tomography (PET) is the one that most frequently gives evidence to support the electrophysiological data localizing the epileptic focus. For example, in one study, 70% of patients demonstrated an area of hypometabolism that correlated with the site of epileptogenicity based on scalp and depth interictal and ictal EEG recording and supported by microscopically determined pathological changes in the brain at the time of operation (Engel et al. 1982).

In the past, a number of centers initially relied primarily on the interictal epileptiform spiking in the EEG, but currently most centers require in addition video-recorded seizures with EEG documentation, frequently with sphenoidal or nasopharyngeal leads or both (Ward 1983). If this identifies a consistent focus, and especially if it correlates with other evidence of localized disease on CT, MRI, or PET scan, then most centers will proceed directly to operation after performing an arteriogram, usually supplemented by an amobarbital test in an attempt to make certain that the site of operation is not essential for long-term memory function.

In more complicated cases, a definite decision cannot be arrived at based on the foregoing information. However, as many as half of these individuals can be identified as surgical candidates if more invasive studies are made, which usually include implantation of a depth or subdural electrode strip and video recordings of seizures monitored from the implanted electrode sites (Rasmussen 1983). Most centers specializing in operation differ mainly in the availability of specialized scanning techniques and the frequency and type of implantation technique used. In

spite of these differences, the success rate in the various centers is similar; however, a superficial comparison of success rate may be misleading because centers with a higher percentage of decisions based on implantation techniques are often dealing with the more difficult cases (Spencer 1981). In the selection process, one of the more difficult questions to answer is whether an individual who otherwise appears to be a good candidate has a significant risk for memory impairment after a standard left temporal lobectomy. Although the amobarbital test is the standard way to identify patients at risk for memory loss (Blume et al. 1973), it is by no means infallible (Lüders et al. 1986). Until recently, it was thought that the amygdala and hippocampus were the most important structures in the temporal lobe for memory function, but a number of investigators now think that cortical structures, especially the medial ones, may play an essential role in the memory function of the temporal lobe (Wieser and Yaşargil 1982). Attempts to identify essential cortical areas include stimulation intraoperatively (Ojemann and Dodrill 1984) or with chronically implanted subdural electrodes (Lüders et al. 1986). To date, no ideal method seems to be available, but current investigation is likely to allow for more reliable identification and avoidance of operation in those patients at major risk for significant surgically induced memory loss.

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Chapter 13

Benign Focal Epilepsy of Childhood

Hans Lüders, Ronald P. Lesser, Dudley S. Dinner, and Harold H. Morris III

Synonyms

In discussing the terminology used to identify this electro-clinical syndrome it is convenient to deal independently with (a) terms used to describe the characteristic location of the EEG sharp waves and (b) terms used to identify the electroclinical syndrome itself. In historical order, the following terms were used to describe the characteristic location of the EEG sharp waves:

Prerolandic sharp waves (Gastaut 1952; Nayrac and Beaussart 1957)

Midtemporal sharp waves (Gibbs and Gibbs 1952, 1959–60; Little et al. 1967; Lombroso 1967)

Rolandic sharp waves (Bancaud et al. 1957; Faure and Loiseau 1959; Loiseau et al. 1963; Blom and Brorson 1966; Beaussart 1972; Beaumanoir et al. 1974; Dalla Bernardina and Tassinari 1975; Kajitani et al. 1980; Miyazaki and Nishiura 1980; Gastaut 1982a; Loiseau et al. 1983; Gregory and Wong (1984)

Central sharp waves (Smith and Kellaway 1964; Blom and Brorson 1966)

Temporal–central sharp waves (Bray and Wiser 1964a, 1965)

Centrotemporal sharp waves (Bray and Wiser 1964b; Beaussart 1972; Blom et al. 1972; Heijbel et al. 1975a, 1975b; Lerman and Kivity 1975; Loiseau et al. 1983)

Sylvian sharp waves (Little et al. 1967; Lombroso 1967)

In describing the electroclinical syndrome, usually one of the terms listed above was used in combination with other adjectives to define other characteristics of the syndrome. The following is a list of these terms in approximate historical order of

usage; the list emphasizes the different adjectives used to characterize the syndrome:

Prerolandic sharp waves *without focal significance* (Gastaut 1952; Nayrac and Beaussart 1957; Faure and Loiseau 1959). This term stresses the functional character of the sharp waves.

Mid-temporal epilepsy (Gibbs and Gibbs 1959–60; Bray and Wiser 1964a,b; Lombroso 1967; Loiseau et al. 1983), stressing the typical location of the sharp waves.

Benign epilepsy of children with rolandic paroxysmal foci (Beaussart 1972; Blom et al. 1972; Beaumanoir et al. 1974; Heijbel et al. 1975a, 1975b; Lerman and Kivity 1975; Gastaut 1982a; Gregory and Wong 1984), stressing the benign evolution of the epilepsy.

Familial temporal–central focal epilepsy (Bray and Wiser 1965) stressing the familial tendency of the syndrome.

Benign focal epilepsy of *childhood* (Lerman 1970; Blom et al. 1972; Beaussart 1972; Editorial 1975; Dalla Bernardina and Tassinari 1975; Eeg-Olofsson et al. 1982), stressing its occurrence in children.

History

Electroencephalography was essential for the delineation of this electroclinical syndrome. In 1952, Gibbs and Gibbs, in a systematic study of EEG in children, noticed that *midtemporal spike foci* were extremely common in children but progressively less frequent in older age groups. They correctly noted that in a high percentage of cases (53%) the sharp waves disappeared. They reported also, however, that in 15% of cases the sharp waves "migrated" anteriorly into the anterior temporal area, where they were frequently seen in adults with complex partial seizures (Gibbs et al. 1954), an observation not confirmed by later studies.

Simultaneous with the report by the Gibbses, Y. Gastaut (1952) described "*prerolandic*" *sharp waves* in children, defining most of the essential characteristics of benign focal sharp waves of childhood, such as location and frequent bilateral, independent occurrence. She also stressed that these prominent sharp waves could occur without associated epileptic symptoms and interpreted them as an expression of a prerolandic "hyperexcitability" to proprioceptive afferent impulses.

The first clear description of the *electroclinical syndrome* itself can be credited to Nayrac and Beaussart in 1957. They not only described the EEG and clinical characteristics of the syndrome but also emphasized that the presence of a strikingly focal EEG abnormality does not necessarily imply the presence of a focal structural lesion.

The *familial* tendency of the syndrome was first described by Bray and Wiser (1964a, 1965), who stressed the high incidence of epilepsy in close relatives and coined the term "familial temporal–central focal epilepsy."

The "*benign*" nature of midtemporal sharp waves had already been recognized by the Gibbses (Gibbs and Gibbs 1952; Gibbs et al. 1954; Gibbs and Gibbs 1959–

60). Soon thereafter, other authors verified this observation. It was Beaussart (1972), however, who first drew attention to the facts that these focal sharp waves in children are not the result of an underlying pathology, that they tend to be associated with only infrequent seizures which are easily controlled with anticonvulsants, and that they almost invariably disappear with maturation.

Some of the characteristics of the *partial seizures* associated with centrotemporal sharp waves, such as preferential involvement of the face and frequent early speech arrest, had already been cited in the report by Gibbs and Gibbs (1952). The first detailed description, however, can be found in the report on facial seizures in children by Lossky and Lerique-Koechlin (1962), who emphasized the relatively short duration of these seizures, the preservation of consciousness, and the occasional occurrence of somatosensory auras. Lombroso (1967) defined the clinical characteristics further and coined the term sylvian seizures. Finally, Blume (1982) gave one of the most detailed descriptions of the seizures in his *Atlas of Pediatric Electroencephalography*.

The characteristic of the sharp waves of this syndrome which has been given most emphasis by almost all authors is its *typical location* in the centrotemporal region. As mentioned above, "centrotemporal" or an equivalent expression has been used by the majority of investigators to identify this syndrome. The fact that these sharp waves have in addition a *typical morphology* has been stressed to different degrees by several authors, including particularly Blom et al. (1972), Lerman and Kivity (1975), Engle et al. (1977), Lüders (1979), and Blume (1982). Various authors have also stressed the peculiar and very characteristic distribution field of the sharp waves, which in many cases suggests a horizontal dipole (Faure and Loiseau 1959; Lüders 1979; Blume 1982; Gregory and Wong 1984). Several authors have also noted that centrotemporal sharp waves may occur with independent sharp waves in other locations (Gibbs et al. 1954; Bancaud et al. 1957; Blom and Brorson 1966; Lerman and Kivity 1975; Lerman and Kivity-Ephraim 1981; Engle et al. 1977). Gibbs et al. (1954) and Lerman and Kivity (1975) even observed in longitudinal studies of selected cases that occipital spikes can be replaced or occur simultaneously with sharp waves in the centrotemporal region in follow-up EEG studies. Blume (1982) also described "rolandic-like" spikes in parietal and vertical locations. None of these authors, however, applied these facts to modify the concept of centrotemporal benign epilepsy of childhood, in which location is the essential characteristic of the sharp waves. It seems to us, however, that the available evidence indicates that the determining factor is *not the location* but the *typical morphology* of the sharp waves (Lüders et al. 1986a). Younger patients with benign focal epilepsy of childhood tend to have sharp waves in the posterior temporal–occipital regions and with maturation the sharp waves "migrate" into the temporocentral or vertex region and less frequently also into the frontal areas (Lüders et al. 1986a). This conclusion is supported by the facts that in patients with benign focal epilepsy of childhood (a) sharp waves in these different locations have almost identical morphologies and are affected similarly by physiological parameters, (b) with maturation, sharp waves may appear in different locations ("migration"), and (c) not infrequently, sharp waves of identical morphology occur simultaneously in different locations. Furthermore, patients with sharp waves of typical morphology but occurring in different locations have an equally "benign" clinical course (Engle et al. 1977), and focal sharp waves of similar morphology can be seen in the temporal and occipital region of normal controls (Eeg-Olofsson et al. 1971).

Nosology and Definition of Syndrome

Shortly after the initial discovery of the high incidence of focal centrotemporal sharp waves in the EEGs of children, Nayrac and Beaussart (1957) divided these children into four groups:

1. Centrotemporal sharp waves with no neurological deficit and no seizures
2. Centrotemporal sharp waves with neurological deficit but no seizures
3. Centrotemporal sharp waves with neurological deficit and seizures
4. Centrotemporal sharp waves with seizures but no neurological deficit

Later studies have concentrated primarily on the group without neurological deficits, particularly the last group of patients with benign focal epileptiform discharges of childhood and clinical seizures. These studies, without necessarily offering a rigid definition, have described a constellation of electroclinical characteristics which are sufficiently well delineated to constitute a useful syndrome. The main features of the syndrome are:

1. Seizure onset or first recording of typical sharp waves between 2 and 16 years, in the majority of cases between 4 and 12 years
2. No clinical evidence of brain damage, and normal intelligence
3. No seizures at all or infrequent, easily controllable partial or generalized tonic–clonic seizures
4. Typical focal sharp waves in the EEG

Definition of this syndrome, independent of whether or not it is a clear nosological entity, is useful because of its prognostic value. Disappearance of the focal sharp waves and no recurrence of clinical seizures is the rule after 16 years of age.

Benign focal epilepsy of childhood is most probably a nosological entity but, as with other epileptic syndromes, only the typical cases can be categorized with certainty. It seems that the main pathogenic factor is a genetically determined diffusely increased cortical epileptogenicity whose EEG or clinical expression is governed by maturational factors (see below). Sharp waves and/or seizures occur exclusively in childhood, and it is likely that its focal expression is due to selective rates of maturation of the different cortical areas. In general the degree of heightened epileptogenicity is only minimal, explaining the high incidence of clinically asymptomatic sharp waves: only a minority of patients develop seizures, and these are usually infrequent and easily controllable with medication. There is also evidence to suggest that focal pathology (clinical or subclinical) may interact synergically with the hereditary factor and participate in the generation of focal sharp waves or seizures (see below). It is in these cases, however, that delineation of the limits of the nosological entity appears most difficult, if not impossible. In some such cases the focal pathology is the determining factor behind the focal sharp waves or seizures and, therefore, these cases are unrelated to the syndrome of benign focal epilepsy of childhood. In other cases, the focal pathology has no pathogenic role or only participates in determining the focal expression of the seizures. These are cases of benign focal epilepsy of childhood with a complicating

focal pathology, and we can expect them to have the typical benign evolution. This explains the reports of focal motor seizures ipsilateral to the neurological lesion or typical sharp waves in the hemisphere contralateral to the macroscopic pathology. Unfortunately, in cases of focal sharp waves or seizures and neurological deficit, it is usually impossible to determine whether the seizures and/or sharp waves are the result of the focal pathology, a genetically heightened epileptogenicity, or of both these factors. These are the cases that fall into the margins of this nosological entity and for which prognostic prediction is of only limited value.

Incidence and Prevalence

There is general consensus that benign focal epilepsy of childhood is a frequent syndrome, actually one of the most frequently seen epileptic syndromes in patients less than 15 years old. In Heijbel et al.'s (1975a) study, benign focal epilepsy of childhood represented 15.7% of all nonfebrile seizures seen in patients 0–15 years old. There were more patients with primary generalized tonic–clonic seizures (28.6%), but patients with absence seizures (4.3%) were 3.7 times less frequent. Cavazzuti (1980) reported benign focal epilepsy of childhood in 23.9% of epileptic school age children (5–14 years); this was the most common epileptic syndrome, primary generalized tonic–clonic seizures (15.4%) and absence seizures (8.0%) being 1.6 and 3.0 times less frequent, respectively. Lerman and Kivity (1975) reported benign focal epilepsy of childhood in 14.4% of their children with epilepsy (age range of patients not defined), compared with a figure of 10.5% for patients with generalized absence seizures.

Heijbel et al. (1975a) observed 11 cases of a new onset benign focal epilepsy of childhood (first seizure within last year) in a population of 52 252 children 0–15 years of age and calculated an incidence of 21/100 000. Blom et al. (1972) reported a prevalence (at least one seizure in the last 3 years) of 107 per 100 000 children 0–15 years of age. Brorson (1970) reported a similarly calculated prevalence for absence seizures of 16.7 per 100 000 children, indicating that benign focal epilepsy of childhood is 6.4 times more frequent than absence seizures.

There are numerous reports in the literature stressing that sharp waves of the type seen in benign focal epilepsy of childhood also occur frequently without seizures. Fois (1968) reported on 110 patients with benign focal sharp waves but no seizures. Smith and Kellaway (1964) reported that 59% of 200 children with central sharp waves had no seizures, and Engle et al. (1977) observed that 30% of 37 patients with benign focal sharp waves had no clinical seizures. These percentages, however, are mainly an expression of the relative case mix referred for EEG testing in the corresponding laboratories. In a laboratory where only children with definite epilepsy are referred for EEG testing we would expect to find no benign focal sharp waves without accompanying clinical seizures, regardless of the real prevalence of that situation. We can calculate that prevalence, however, from the information available in the literature. Eeg-Olofsson et al. (1971) studied 743 normal children 1 to 15 years of age and observed focal midhemispheric sharp waves in 14 cases (1.6%). Comparing this percentage with the prevalence of benign focal epilepsy of childhood calculated by Blom et al. (1972) (0.107%), we can conclude that only 8.8% of children with benign focal sharp waves have clinical

seizures. These calculations are in good agreement with the 12% reported by Bray and Wiser (1965) in their study of seizures and sharp waves in family members of patients with benign focal epilepsy of childhood. Blume (1982) made similar calculations but compared the *incidence* of benign focal epilepsy of childhood calculated by Heijbel et al. (1975a) (21/100 000) with the percentage of normal controls with centrotemporal benign focal epileptiform discharges of childhood (1.2%) and concluded that only an extremely low percentage (1.75%) of patients with benign focal epileptiform discharges of childhood have seizures. The EEG is a good tool for estimating the *prevalence* of benign focal epileptiform discharges of childhood in the population at large because these sharp waves tend to be abundant and, therefore, the chance of missing them in a sample EEG is minimal. However, such a survey is not an estimate of the appearance of benign focal epileptiform discharges of childhood over the last year (*incidence*). It is very likely that many of the patients who show sharp waves in a sample EEG have already had sharp waves for many years (*prevalence*).

Age of Onset

Tables 13.1 and 13.2 show the age of onset of seizures and the age at which focal sharp waves were first observed in the EEGs of children by various authors. In spite of significant differences between subjects included in the studies, the results are fairly uniform. Seizure onset almost always occurred between 2 and 13 years of age: seizure onset below 2 years was reported in only two studies, and there were no reports of seizure onset after 13.5 years. In all the studies except one, the seizure onset occurred between 4 and 11 years in 60%–86% of cases. Benign focal sharp waves occurred in essentially the same age groups. Excluding the series of Gibbs and Gibbs, which certainly includes many nonbenign focal sharp waves, the age range was 1–16 years, with 80%–86% of the sharp waves occurring between 4 and 10 years.

Table 13.1. Age of onset of seizures

Author	No. of cases	Age range			Age range of highest frequency	% of cases within age range of highest frequency
		Low	High	Mean		
Nayrac and Beaussart (1957)	20	2.5	9		2.5–5	55%
Bancaud et al. (1957)	29	1.5	13.5			
Faure and Loiseau (1959)	15		10		7–10	73%
Little et al. (1967)	75				6–12	Majority
Beaussart (1972)	221	2	13		4–10	80%
Blom et al. (1972)	40	1	13		5–9	60%
Beaumanoir et al. (1974)	26	4	13			
Heijbel et al. (1975a)					7–11	73%
Heijbel et al. (1975b)	19	1	10	6.7	5–10	79%
Lerman and Kivity (1975)	100	3	13	9.9		
Blume (1982)		2	12		5–9	Majority
Gregory and Wong (1984)	10	5	12	8		

Table 13.2. Age of onset of sharp waves

Author	No. of cases	Age range			Age range of highest frequency	% of cases within age range of highest frequency
		Low	High	Mean		
Gibbs and Gibbs (1959–60)					5–15	65%
Loiseau et al. (1963)					4–10	Large majority
Blom and Brorson (1968)		1		15		
Fois (1968)		2		16	5–9	Large majority
Beaussart (1972)	221				9	Large majority
Engle et al. (1977)	37				4–10	80%
Lerman and Kivity-Ephraim (1981)	100	3	15	7.7	4–10	86%

Gender

Table 13.3 shows the sex distribution of the syndrome, revealing a slight but extremely constant predominance of males (male–female ratio approximately 6:4). Note that all the studies (except that by Bray and Wiser, which included cases with nonbenign focal epilepsy) showed a higher frequency of males (55%–69%). The

Table 13.3. Sex distribution of benign focal epilepsy of childhood[a]

Author	No. of cases	Sex		
		Male	Female	Frequency of males (%)
Bray and Wiser (1964)	12	4	8	33
Blom and Brorson (1966)	26	18	8	69
Blom et al. (1972)	94	54	40	57
Beaumanoir et al. (1974)	26	18	8	69
Lerman and Kivity (1974)	30	18	12	60
Heijbel et al. (1975a)	11	6	5	55
Heijbel et al. (1975b)	19	10	9	
Lerman and Kivity (1975)	100	62	38	62
Loiseau et al. (1983)	79	50	29	63
Total seizures	397	240	159	60.5
Fois (1968)	100	64	46	64

[a] All the series refer to patients with benign focal seizures of childhood, except the series of Fois (1968), which consisted of patients with benign epileptiform discharges of childhood but no seizures.

sex distribution reported by Fois et al. (1968) for benign focal epileptiform discharges also shows a similar higher frequency in males (64%).

Past History and Neurological Examination

Statistics about the frequency with which neurological deficits are reported in patients with benign focal epilepsy of childhood are meaningless because they depend mainly on the definition of benign focal epilepsy of childhood (Table 13.4). Some authors have rigorously excluded all cases with neurological deficits (Beaumanoir et al. 1974; Faure and Loiseau 1959; Lombroso 1967; Lerman 1970; Blume 1982) whereas others have used a more flexible definition, leading to inclusion of a number of patients with different degrees of neurological deficit (Bancaud et al. 1957; Nayrac and Beaussart 1957; Blom et al. 1972). The frequency with which "significant etiologies" have been described is most probably also a function of material selection. In other words, one would expect neurologically normal patients to have a relatively low frequency of significant pathological conditions in their past history as compared with neurologically impaired patients.

Inclusion of neurologically impaired patients in the case material is not necessarily an error. In some of these patients, two conditions, namely benign focal epilepsy of childhood and the neurological deficit, coexist without mutual interaction. This is most probably the case in the not so infrequent situations where the focal seizures are ipsilateral to the brain lesion, the benign focal epileptiform discharges of childhood occur in the hemisphere contralateral to the pathological condition (Bancaud et al. 1957), or the neurological deficit is due to infratentorial pathology (Nayrac and Beaussart 1957; Heijbel et al. 1975a). In other cases, however, the brain pathology may interact with the benign focal epilepsy of childhood, determining the localization of the sharp wave focus and seizures or transforming what would have been an asymptomatic sharp wave focus into a focal seizure disorder. Finally, there may even be cases in which the focal sharp waves and possibly also the seizures are the result of the focal neurological deficit, without any pathogenic role being played by the benign focal epilepsy of childhood. This is probably the case in most instances where focal seizures occur in patients with cortical brain tumours. In other words, case material which includes patients with neurological deficits will almost always be contaminated by cases in which some and occasionally all of the epileptic manifestations are unrelated to the benign focal epilepsy of childhood.

How often is focal brain pathology a crucial factor in the development of benign focal epilepsy of childhood? This question cannot be answered with precision because, as explained above, it is impossible to define how often focal sharp-wave and/or focal seizures in children with brain pathology are due to an associated benign focal epilepsy of childhood. The occurrence of benign focal epileptiform discharges of childhood in 1.9% of normal controls (carefully tested to exclude subclinical deficits) (Eeg-Olofsson et al. 1971) clearly indicates that a neurological deficit is not a prerequisite for the development of focal sharp waves. Besides the frequent reports of benign focal epilepsy of childhood in children without any neurological deficit or significant etiology in their past history confirms this observation (Lombroso 1967; Lerman 1970; Beaussart 1972; Beaumanoir et al.

Table 13.4. Neurological deficits and accompanying disorders in patients with benign focal epilepsy of childhood[a]

Author	No. of cases	Normal	Pre- or post-mature	Perinatal complications	Congenital deformities	Cerebral palsy, focal neural	Mental retardation	Seizures first year	Febrile convulsions	Breath holding	Meningitis, encephalitis	Head trauma	Migraine, headache	Minor deficits[b]	Seizure or sharp waves
Nayrac and Beaussart (1957)	22		4.5%	13.5%	4.5%	18%		9%			22.7%				Seizures
Blom and Brorson (1969)	26				7.6%	15.4%	3.8%						19.2%		Seizures
Blom et al. (1972)	40					2.5%	2.5%					5%	5%	2.5%	Seizures
Beaussart (1972)	221		3%	13%				8%			1.3%	0.9%			Seizures
Beaumanoir et al. (1974)	26												15.4%	11.5%	Seizures
Heijbel et al. (1975a)	11				9%										Seizures
Heijbel et al. (1975b)	19		5.2%	5.2%								5.2%			Seizures
Lerman and Kivity (1975)	100		2%	6%		3%	1%		9%	2%	3%	4%			Seizures
Gregory and Wong (1984)	10								20%						Seizures
Gibbs and Gibbs (1952)		79.2%													Seizures
Fois (1968)	110		7.2%	6.4%					3.6%			10%	17%	Almost 100%	Sharp waves

[a] All the series refer to patients with benign focal seizures of childhood except the series of Fois (1968), which consists of patients with benign focal epileptiform discharges of childhood but no seizures.

[b] Hyperactivity, nervousness, sleep disturbance, abdominal pain, speech retardation, vertigo, enuresis, syncope, allergies, etc.

1974; Faure and Loiseau 1979; Blume 1982). A slightly more quantitative answer to this question can be obtained by analyzing the frequency of focal neurological pathology in children who show focal sharp waves in their EEG without preselection of the material according to clinical criteria. Gibbs and Gibbs (1952) reported no neurological deficit or significant etiological factor in 55.4% of 296 cases with midtemporal sharp waves. Smith and Kellaway (1964) observed no neurological deficit in 47% of 200 cases with central sharp waves. These reports indicate that, even if we assume that benign focal epilepsy of childhood plays a role in the generation of sharp waves in most of the patients with neurological deficits, benign focal epileptiform discharges of childhood tend to occur with at least the same frequency in patients without neurological deficit as in those with such deficit.

Seizure Type

The characteristic seizures seen in patients with centrotemporal sharp waves are *partial seizures* with involvement of the *face*. This was already recognized in the early reports of Gibbs and Gibbs (1952) and has been stressed in the majority of subsequent reports. The frequency with which partial facial seizures are reported varies from one study to another according to the criteria used to select the material. However, if we disregard series in which patients with seizures were excluded (Fois 1968; Lerman and Kivity-Ephraim 1981) or reports which only included facial seizures (Lossky and Lerique-Koechlin 1962), then the percentage of facial seizures is relatively similar, varying only between 11% and 20% (Table 13.5). This was also the case for series in which the material was selected exclusively by electroencephalographic criteria and should, therefore, give us a better index of relative seizure frequency (Gibbs and Gibbs 1952).

Generalized tonic–clonic seizures are by a wide margin the most frequently observed seizure type in patients with centrotemporal sharp waves, occurring in 24%–87% of the cases (2.9–6.7 times more frequently than the characteristic facial seizures). Some authors assume that these generalized seizures are actually seizures with secondary generalization (Lerman 1970; Blom et al. 1972). This hypothesis is supported by the finding of focal sharp waves in the EEG and the frequent observation of partial seizures with secondary generalization in some series (Bancaud et al. 1957; Blom et al. 1972) (21%–30%). The partial seizures preceding the generalized tonic–clonic seizure would be frequently missed because of their short duration, nocturnal occurrence, and the poor description given by the children (Lombroso 1967; Blom et al. 1972; Beaussart 1972; Dalla Bernardina and Tassinari 1975; Blume 1982).

Nonfacial partial motor seizures have also been reported frequently by some authors (Gibbs and Gibbs 1952; Nayrac and Beaussart 1957). These include particularly adversive seizures, partial motor seizures involving the upper extremities, and jacksonian seizures. Partial motor seizures affecting mainly the legs are rare (Blume 1982). With the more comprehensive definition of benign focal epilepsy of childhood (including sharp waves of typical waveform arising from extra centrotemporal locations) which was introduced only recently, we would expect the relative frequency of nonfacial partial seizures to increase. In a number

Table 13.5. Seizure types

Author	No. of cases	Percentage with seizures	Generalized seizures	Elementary partial seizures					Secondary generalization	Ratio of generalized seizures to facial partial seizures	Hemi-convulsions	Complex partial seizures	Other
				Total	Face	Arm	Leg	Jacksonian					
Gibbs and Gibbs (1959–60)			52%	35%	18%					2.9			
Bancaud et al. (1957)	29	7%	34%	38%					21%			10%	10%
Nayrac and Beaussart (1957)	18	11%	33%		11%		32%			3.0	11%		11%
Faure and Loiseau (1959)	15		87%		13%					6.7			
Lossky and Lerique-Koechlin (1962)	22				100%								
Bray and Wiser (1964)	18		83%	11%								28%	6%
Blom and Brorson (1966)	26	46%										38%	
Fois (1968)	110	100%											
Blom et al. (1972)	40	38%	60%						30%			0%	
Beaussart (1972)	221			20%							12%		
Heijbel et al. (1975b)	19		68.5%	31.5%									
Turner (1977)	10	40%	40%	20%									
Miyazaki and Nishiura (1980)	30			100%									
Lerman and Kivity-Ephraim (1981)	100	100%											
Loisseau et al. (1983)			24%	83.5%									

of reports the occurrence of hemiconvulsions has been mentioned (Nayrac and Beaussart 1957; Beaussart 1972; Blume 1982). Blume (1982) and Gastaut (1982a) indicated that hemiconvulsions are particularly frequent in younger patients (less than 5 years old), reflecting the tendency of the partial epileptic discharge to spread throughout all or most of the corresponding hemisphere without propagation to the other hemisphere.

There is now more or less general consensus that *nonmotor partial seizures*, particularly psychomotor seizures, do not occur in patients with benign focal epilepsy of childhood (Lombroso 1967; Blom et al. 1972; Engle et al. 1977). There were some early reports that included psychomotor seizures in the material (Bancaud et al. 1957; Bray and Wiser 1964; Blom and Brorson 1966); it seems, however, that children with psychomotor seizures, even if the sharp waves may be maximum in the midtemporal region, usually do not have typical benign focal epileptiform discharges of childhood and that the evolutions do not tend to be benign. So, for example, most patients with psychomotor seizures included in Bray and Wiser's series (1964) were adults rather than children. In a number of reports isolated cases of *akinetic* (Nayrac and Beaussart 1957; Beaussart 1972) and *absence* (Bray and Wiser 1964; Beaussart 1972) seizures have been included. These cases also most probably do not correspond to benign focal epilepsy of childhood; the focal sharp waves observed probably represent examples of the multifocal independent sharp waves frequently seen in patients with generalized primary epilepsies (Lüders et al. 1984).

It has been reported that the *typical facial seizures* are preceded by a *somatosensory aura* in a variable percentage of cases, from "rare" in Lerman and Kivity's (1975) study, 14% in Lossky and Lerique-Koechlin's (1962) series, and 27% in Miyasaki and Nishiura's study (1980), to almost 100% in Lombroso's (1967) report. However, even intelligent adults have difficulty differentiating between sensory and motor phenomena. During cortical stimulation for functional localization in patients being evaluated for surgical treatment of epilepsy, it is not infrequent for a patient to confuse a small movement with a sensory phenomenon (unpublished observations). Therefore it is possible that some of the percentages given above are too high. The somatosensory aura most frequently affects the tongue but may also involve the inner cheek, lips, gums, single teeth, or lower face (Lombroso 1967; Lerman 1970; Lerman and Kivity 1975; Blume 1982). The sensation is reported as pins and needles, prickling, or a freezing sensation (Blume 1982). The reports of a freezing sensation are of particular interest if we consider that cortical stimulation in that area frequently produces negative motor phenomena which the patient perceives like a freezing sensation (Lüders et al. 1983; Lüders et al. 1985b).

The *motor phenomena* may be tonic, clonic, or tonic–clonic (Lombroso 1967; Beaussart 1972; Blume 1982) and most frequently affect the corner of the mouth (lower face and lips), the muscles of mastication (stiffness of jaw, trembling of chin, or chattering of teeth), or, less frequently, the pharynx (choking sensation and guttural sounds) or eyelids (Lossky and Lerique-Koechlin 1962; Lerman 1970; Heijbel et al. 1975a; Lerman and Kivity-Ephraim 1974; Lerman and Kivity 1975; Blume 1982). Spreading to involve the hand or arm of the same side is not infrequent (Little et al. 1967; Lombroso 1967; Lerman 1970; Lerman and Kivity 1975; Blume 1982). In some cases a typical jacksonian march can be seen (Lombroso 1967).

Speech arrest is a typical feature of the facial seizures seen with benign focal

epilepsy of childhood (45% in Lossky and Lerique-Koechlin's 1962 series) (Lombroso 1967; Beaussart 1972; Heijbel et al. 1975a; Lerman and Kivity 1975; Blume 1982). From cortical stimulation studies for functional localization in patients being evaluated for surgical treatment of epilepsy, we know that speech arrest without alteration of consciousness can be elicited from the low rolandic region by three mechanisms (Lüders et al. 1986b), namely a positive motor effect (Penfield and Roberts 1959), a negative motor effect (Penfield and Jasper 1954; Lesser et al. 1984; Lüders et al. 1983; Lüders et al. 1985b), and interference with the language process itself (Penfield and Rasmussen 1949, 1950; Penfield and Jasper 1954; Penfield and Roberts 1959; Fedio and Van Buren 1974; Ojemann 1978, 1979; Rapport and Whitaker 1983; Lesser et al. 1984). Speech arrest due to interference with the language process itself can be elicited only by stimulation of the dominant hemisphere, whereas speech arrest due to a positive or negative motor effect can be produced by stimulation of either the dominant or the nondominant hemisphere. Most authors have assumed that the speech arrest in these children is due to a positive motor effect (Lossky and Lerique-Koechlin 1962; Lombroso 1967; Blume 1982). We feel, however, that a negative motor effect may well be the cause in some children and that interference with the language process is a causative factor in other children having focal seizures arising from the dominant hemisphere.

Another sign frequently seen in association with facial benign focal seizures of childhood is *salivation* (Lombroso 1967; Heijbel et al. 1975a; Lerman and Kivity 1975; Blume 1982). In cortical stimulation studies, all the signs mentioned above (orofacial muscle contractions, orofacial paresthesias, and speech arrest due to one or more of the mechanisms explained above) can be observed in all patients in whom the low rolandic area is stimulated. However, in our experience of cortical stimulation of more than 50 patients, we have had only one patient in whom the stimulation produced salivation (Dinner, personal observation). In this case 5-s stimulation of a subdural electrode in the low rolandic, immediately suprasylvian region produced profound salivation on repeated trials. These results suggest that, similar to the secondary sensory area (Lüders et al. 1985a), a salivatory center is usually located in the superior bank of the sylvian fissure and only exceptionally on the suprasylvian convexity. In other words, the frequent observation of salivation in patients with benign focal facial seizures is most probably due to involvement of the superior bank of the sylvian fissure. However, drooling could also be due to postictal facial paresis with swallowing difficulties.

The typical benign focal facial seizures are *not associated with loss of consciousness* (Lossky and Lerique-Koechlin 1962; Lombroso 1967; Beaussart 1972; Lerman 1974; Lerman and Kivity 1975; Blume 1982); not infrequently the children get out of bed and run to their parents (Lerman and Kivity 1975). The seizures also tend not to be associated with amnesia or postictal confusion (Lombroso 1967). Apparently, partial seizures without loss of consciousness are most frequent during the day (Blume 1982), whereas during the night there is a greater tendency toward secondary spreading with loss of consciousness. It is also possible that some of the more restricted focal seizures do not wake up the child and therefore pass unnoticed (Dalla Bernardina and Tassinari 1975; Blume 1982). *Automatisms and psychic and perceptual symptoms* to suggest spreading of the discharge into the temporal lobe do not occur (Lombroso 1967; Blom et al. 1972). *Postictal Todd paralysis* is observed in 10% (Blume 1982) to 21% (Bancard et al. 1957) of the cases.

Seizure Duration

Typical benign focal facial seizures tend to be brief, their estimated duration varying from 30 to 60 s (Beaussart 1972) to less than 2–3 min (Lossky and Lerique-Koechlin 1962) to a few minutes (Lerman and Kivity 1975). The only recorded seizure was reported by Dalla Bernardina and Tassinari (1975) and had a duration of 60 s.

Day–Night Distribution of Seizures

One of the main characteristics of benign focal epilepsy of childhood is that the seizures tend to occur while the patient is asleep or shortly after awakening. As shown in Table 13.6, benign focal seizures occur only while the patient is asleep in 51%–80% of cases. In addition, the seizures occurring while the patient is awake tend to occur shortly after awakening (Faure and Loiseau 1959; Lerman and Kivity 1975). This observation correlates well with the typical activation of benign focal epileptiform discharges of childhood with sleep.

Table 13.6. Day–night distribution of seizures

Authors	No. of cases	Awake only	Sleep only	Awake and asleep	Unknown	Comment
Nayrac and Beaussart (1957)			Frequent			
Faure and Loiseau (1959)	15		60%	40%		Usually during awakening (usually while still in bed)
Little et al. (1967)			Frequent			
Lerman (1970)			Usually at night			
Beaussart (1972)		29%	51%	13%	7%	
Blom et al. (1972)	40		55%			
Lerman (1974)	40		75%	25%		
Heijbel et al. (1975a)	11		55%			
Heijbel et al. (1975b)	19	31.8%	63%	5.2%		
Lerman and Kivity (1975)	100		76%	17%		
Blume (1982)			Most			
Gregory and Wong (1984)	10		80%			

Seizure Frequency

The epileptogenicity of benign focal epileptiform discharges of childhood tends to be extremely low. This explains the frequent occurrence of asymptomatic benign focal epileptiform discharges of childhood, which we estimate to be as high as

91.2% (see above). In addition, it is consistent with the extremely low frequency of seizures in symptomatic patients. Lerman and Kivity (1975) reported that 13 of their 100 patients had only one seizure and no recurrence in spite of the fact that six received no anticonvulsants. Sixty-six of the 100 patients had one seizure every 2–12 months, whereas only 21 had more than one seizure every 2 months. Similarly, 3 of 15 patients in Faure and Loiseau's (1959) series had only a single seizure and the other 12 had only two to six seizures over 1–2 years. This low epileptogenicity of the focus may also explain the good response of the seizures to anticonvulsants and the disappearance of the focus, with maturation.

Genetics

There is sufficient evidence in the literature to conclude that benign focal epilepsy of childhood is a genetic disease. As shown in Table 13.7, patients with benign focal seizures have a positive family history of seizures (one or more members of the family with seizures) in 8.9%–68% of cases and a positive family history of sharp waves (one or more members of the family with sharp waves in the EEG) of 30%. This clearly exceeds the percentage of positive findings in the families of control cases [in the study of Bray and Wiser (1965) only 5% of the family members of controls had sharp waves in the EEG]. It also exceeds the percentage of positive family histories for seizures in similarly evaluated family members of patients with absence seizures, generalized epilepsy, or partial epilepsy [13% vs 10%, 3%, and 1% respectively in the study by Beaussart (1972)].

The studies by Bray and Wiser (1965), Heijbel et al. (1975a), and Lerman and Apter (quoted in Lerman and Kivity-Ephraim 1981) also show that the incidence of benign focal epileptiform discharges of childhood in sibs and children of patients with benign focal epilepsy of childhood was 25%–36%, clearly exceeding its normal frequency, which is 1.4%–5% (Bray and Wiser 1965; Eeg-Olofsson et al. 1971). Only a small proportion of the relatives with benign focal epileptiform discharges of childhood actually had seizures (12% in the study by Bray and Wiser 1965).

The genetic nature of the disease is also supported by the reports of benign focal epilepsy of childhood and benign focal epileptiform discharges of childhood in identical twins. Kajitani et al. (1980) reported on three pairs of monozygotic twins all of whom had benign focal epileptiform discharges of childhood in the EEG between the ages of 5 and 11 years. Only three of these patients, however, had nonfebrile convulsions.

Another factor to consider is that the incidence of the seizures and sharp waves is greatly influenced by age. As explained in detail in the corresponding sections, the sharp waves and seizures tend to appear in childhood, with a peak incidence between 4 and 11 years, and almost always disappear after 15–16 years. In other words, similar to many other epilepsies (e.g. generalized absence seizures), the EEG and clinical *expression* of this genetic factor is *age dependent.*

The conclusion from Bray and Wiser's (1964, 1965) study that benign focal epilepsy of childhood is an autosomal dominant disease determined by a gene whose expression is age dependent is almost universally quoted in the literature. Bray and Wiser (1965) assumed an autosomal dominant disease from the

Table 13.7. Genetics of benign focal epilepsy of childhood[a,b]

Author	No. of cases	Seizures				Sharp waves				Sharp waves in controls
		Family	Parents	Sibs	Parents and sibs	Family	Parents	Sibs	Parents and sibs	
Bray and Wiser (1965)	40					30%	19%	36%		5%
Beaussart (1972)		13%								
Blom et al. (1972)	40	40%			17.5%					
Beaumanoir et al. (1974)	26	27%		7.6%						
Lerman and Kivity-Ephraim (1974)		9%		4%						
Heijbel et al. (1975a)	11							36%		
Heijbel et al. (1975b)	19	68%	11%/21%	15%	47%		27%	34%		
Lerman and Apter (quoted in Lerman and Kivity-Ephraim 1981)								25%		
Loiseau et al. (1983)	79	8.9%								

[a] The probands in all these series had seizures.
[b] % of sibs or parents with seizures and/or sharp waves.

inspection of 12 pedigrees with positive family histories. It is interesting to note, however, that the seizure patients over 20 years old included in this study usually had refractory complex partial seizures. It is now generally accepted that complex partial seizures are not seen in patients with benign focal epilepsy of childhood, particularly when they are refractory to medical treatment, and occur in patients over 20 years of age. Therefore, Bray and Wiser's (1965) conclusion is based on a biased case material. In spite of this limitation, current evidence strongly suggest that Bray and Wiser's (1964a,b, 1965) conclusion is correct. The incidence of consanguinity between parents of patients with benign focal epilepsy of childhood is too low [5.2% in the study of Heijbel et al. (1975b)] and the seizure incidence too high (21% in the same study) to support a recessive mode of inheritance. Assuming that benign focal epilepsy of childhood is inherited by an autosomal gene with an age-dependent expression, Heijbel et al. (1975b) calculated, using the "a priori" method of Bernstein et al. (Stern 1960), the number of siblings who should be affected if it is a dominant or a nondominant inheritance. The results in their study of 19 sibships was in excellent agreement with an autosomal dominant mode of inheritance. Heijbel et al. (1975b) also concluded that a multifactorial inheritance for the seizures and sharp waves was unlikely because of the too high prevalence of seizures and sharp waves among the sibs. For multifactoral inheritance the prevalence between sibs should be less than $\sqrt{p}$ where p is the prevalence in the population. Therefore, we would expect less than 3.3% seizures ($\sqrt{0.00107}$) or 12% sharp waves ($\sqrt{1.4}$) in the sibship. The observed prevalence of 4%–15% seizures and 25%–36% sharp waves (Table 13.7) clearly exceeds the expected prevalence for multifactoral inheritance. We can conclude, therefore, that benign focal epilepsy of childhood and benign focal epileptiform discharges of childhood are most probably inherited as an autosomal dominant gene with age-dependent penetrance.

As we mentioned before, only a small proportion (8.8%) of patients with benign focal epileptiform discharges of childhood actually have clinical seizures. It is possible that the tendency to have clinical seizures in patients who have inherited the condition is actually determined by multiple other etiological factors, including environmental and other genetic factors. The observation of Eeg-Olofsson et al. (1982) that probands and parents of patients with benign focal epilepsy of childhood had a statistically low incidence of haplotype A1B8 is interesting in this context. This haplotype is extremely frequent in the general population and could therefore have a protective function.

There is also evidence in the literature which suggests a possible genetic link between febrile convulsions and benign focal epilepsy of childhood. Frantzen et al. (1968) observed that, in 20% of patients who had had febrile convulsions, focal sharp waves appeared later in life even though none of these patients had nonfebrile seizures. An analysis of the figures illustrating these sharp waves in Frantzen et al.'s study reveals that they meet all the critieria of benign focal epileptiform discharges of childhood. Besides Engle et al. (1977), Lerman and Kivity (1975) and Gregory and Wong (1984) have reported an incidence of febrile convulsions in patients with benign focal epilepsy of childhood ranging from 9% to 20%, which clearly exceeds the incidence in the normal population.

Studies of monozygotic twins also shed light on a possible genetic link between these two types of seizure. Lennox-Buchthal (1971) studied 24 pairs of monozygotic twins in which at least one had febrile convulsions and observed that 20% of the cotwins had nocturnal convulsions and 80% febrile convulsions. Also 2 of the 24

probands (8.3%) had both nocturnal convulsions and febrile convulsions. Even if not specified by the authors, it is likely that these nocturnal convulsions actually represented benign focal epilepsy of childhood. Kajitani et al. (1980) studied in detail three pairs of monozygotic twins with all six probands showing benign focal epileptiform discharges of childhood in the EEG. Three of these twins also had benign focal seizures and five had febrile convulsions. The observation that febrile convulsions occur in sleep in at least half the cases and are related to sleep (going to sleep or awakening) in another quarter (Lennox-Buchthal 1973) also suggests a relationship between febrile convulsions and benign focal epilepsy of childhood. From these observations it is tempting to speculate that an inherited condition predisposes to febrile convulsions in the first 5 years of life and to benign focal epilepsy of childhood and the occurrence of benign focal epileptiform discharges of childhood after 3 years of age. The expression of each one of these three conditions will depend on other genetic and/or environmental factors, with maturation of the central nervous system playing a major role. An alternative hypothesis is to assume that febrile convulsions on the one hand and benign focal epilepsy of childhood and/or benign focal epileptiform discharges of childhood on the other are inherited by independent but clearly linked genes.

Electroencephalography

The typical and indispensable EEG abnormality for the diagnosis of benign focal epilepsy of childhood is the presence of benign focal epileptiform discharges of childhood. Initially it was felt that the main characteristic of benign focal epileptiform discharges of childhood was location, and all sharp waves occurring in the centrotemporal location in children were included. As mentioned in the history section, however, recent evidence suggests that other characteristics such as waveform, field of distribution, and activation by sleep are the essential features that define benign focal epileptiform discharges of childhood. These sharp waves frequently occur in the centrotemporal region but other locations are definitely not infrequent. The clinical syndrome associated with benign focal epileptiform discharges of childhood is the same independent of the location of the sharp waves, and benign focal epileptiform discharges of childhood may "migrate" with time from one location to another or occur simultaneously in various locations in the same subject. In this section we will discuss the characteristic features of benign focal epileptiform discharges of childhood.

Distribution of Benign Focal Epileptiform Discharges of Childhood

As mentioned above, until recently most reports have included only cases with sharp waves with maximum amplitude in the *centrotemporal* region. In other words, the concept of benign focal epilepsy of childhood remained linked to a specific location of the sharp waves. This was clearly expressed in the terminology

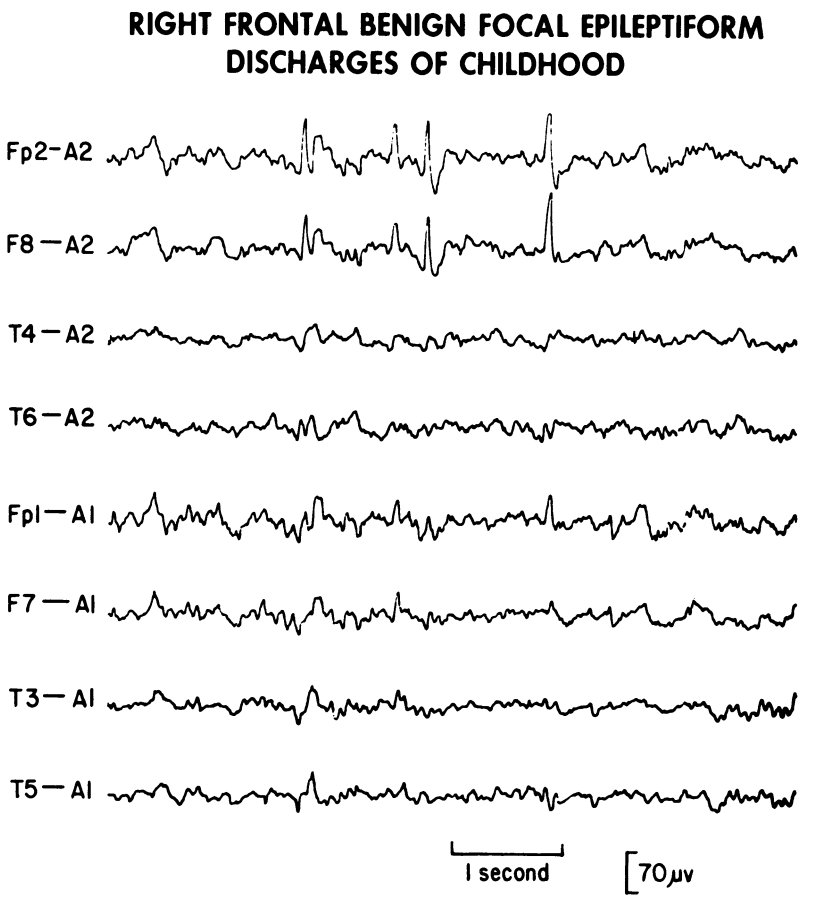

Fig. 13.1. Benign focal epileptiform discharges of typical morphology, maximum in the right frontal region.

used in identifying the syndrome, which consistently included the terms centrotemporal, midtemporal, sylvian, or rolandic.

However, a careful review of the literature shows that the close relationship between the centrotemporal sharp waves and epileptiform discharges arising from other locations (Fig. 13.1) was recognized early on. Gibbs et al. (1954) studied 45 patients with occipital sharp waves and observed that, when restudied after age 9 years, in 40% the sharp waves had disappeared and in 14% they had migrated into the midtemporal region. They described two cases in detail in which the sharp waves "migrated" from the occipital region to one or both temporal regions and from one hemisphere to another in three follow-up recordings. Both cases had a clinical history typical of benign focal epilepsy of childhood. Migration of occipital foci into the centrotemporal region has also been documented by Beaussart (1972)

and Lüders et al. (1986a). It seems, however, that centrotemporal sharp waves "migrate" much less frequently into the occipital area. With maturation they preferentially tend to disappear. When Gibbs et al.'s (1954) series of patients were restudied after 15 years of age, centrotemporal sharp waves had disappeared in 76%. Migration into the occipital region was not seen. Similar results were also reported by Beaussart (1972). This probably explains why Faure and Loiseau (1959) did not observe migration of sharp waves, i.e. because the patients they selected had centrotemporal sharp waves. The Gibbses (Gibbs et al. 1954; Gibbs and Gibbs 1959/60) also postulated that the centrotemporal foci would "migrate" into the anterotemporal region, producing complex partial seizures, or transform into 14- and 6-Hz positive spike with "diencephalic" seizures. There is now solid evidence to conclude that these two last entities are unrelated to benign focal epileptiform discharges of childhood (Lombroso 1967).

Blom and Brorson in 1966 pointed out that some patients with sharp waves in noncentrotemporal locations show a clinical syndrome indistinguishable from benign focal epilepsy of childhood.

Bancaud et al. (1957) were the first to point out that centrotemporal sharp waves may not infrequently occur simultaneously with independent sharp waves arising elsewhere. This observation was supported by the study by Beaussart (1972), who described independent foci elsewhere in 23 of 221 cases; ten were occipital foci and eight frontal foci. Similar observations were also made by Lerman and Kivity (1975) and Engle et al. (1977). From this it seems reasonable to conclude that the hereditary factor favors the occurrence of focal sharp waves which at a younger age tend to appear in the occipital region and which later, due to maturation of the cortex, "migrate" into the temporal region and finally disappear. At an intermediate stage of maturation, bifocal or multifocal independent centrotemporal and occipital sharp waves can be seen.

What is the relative frequency of sharp waves of different locations in patients with benign focal epilepsy of childhood? All of the published series are biased because only patients with seizures who had centrotemporal sharp waves were selected. To answer this question, we have to examine a number of samples selected by different criteria. Eeg-Olofsson et al. (1971) studied sharp waves in normal controls and observed temporal sharp waves in 50%, central sharp waves in 28%, occipital sharp waves in 14%, and frontal sharp waves in 8%. Lerman and Kivity-Ephraim (1981) studied 100 cases with sharp waves but no seizures and observed the following breakdown: centrotemporal sharp waves in 78%, occipital sharp waves in 5%, and centrotemporal and occipital sharp waves in 14%. Engle et al. (1977), in a study of focal sharp waves in patients with no neurological deficit (except seizures), observed centrotemporal sharp waves in 63%, occipital sharp waves in 32%, and frontal sharp waves in 5%. In a similar study, Turner (1977) reported temporal sharp waves in 60%, central sharp waves in 25%, occipital sharp waves in 10%, and parietal sharp waves in 5% of the 20 cases studied. The results in these three series coincide fairly well, suggesting that centrotemporal sharp waves are most preponderant, followed by occipital sharp waves, whereas frontal sharp waves are relatively infrequent.

The sharp waves tend to occur with approximately equal frequency in the left and right hemispheres (see Table 13.8) and not infrequently (20%–62.5%) are bifocal, occurring independently in the left and right hemispheres (Figs. 13.2–13.5). Multifocal independent sharp waves occur occasionally and were seen in 37.5% of the series of Lüders et al. (1986a). It is important to differentiate this

Table 13.8. Distribution of benign focal epileptiform discharges of childhood[a]

Author	No. of cases	Left	Right	Independent in left and right hemispheres	Bisynchronous	Other foci	Unilateral	Sharp waves or seizures
Gibbs and Gibbs (1952)				28%	2%		70%	Sharp waves and seizures
Nayrac and Beaussart (1957)	21						86%	Seizures
Beaussart (1972)	221			Approximately 30%		10.4%	70%	Seizures
Beaumanoir et al. (1974)	26	11.5%	26%	62.5%			37.5%	Seizures
Heijbel et al. (1974)	11	36%	36%				72%	Seizures
Lerman (1974)							65%	Seizures
Lerman and Kivity (1975)	100	34%	28%				62%	Seizures
Lerman and Kivity-Ephraim (1981)	78						82%	Sharp waves, no seizures
Gregory and Wong (1984)	10	20%	60%	20%			80%	Seizures

[a] These series only include EEGs with sharp waves in the temporal region.

pattern of multifocal sharp waves from the multifocal spikes seen in Lennox-Gastaut syndrome, which usually has a nonbenign prognosis. Differential diagnosis, however, is usually possible due to the characteristic waveform and field of distribution of the sharp waves (see below). The benign focal epileptiform discharges of childhood may occur, as mentioned above, contra- or ipsilateral (Beaumanoir et al. 1974) to the clinical symptomatology. This is not surprising if we consider that in follow-up EEGs the sharp waves frequently "migrate" from one side to another. Faure and Loiseau (1959) stressed that the focus tended to be maximum at C6 (between the central C4 and midtemporal T4 electrode). Lombroso (1967), Beaussart (1972), and later authors made similar observations. It is interesting to observe that C6 is approximately located at the point where the rolandic fissure meets the sylvian fissure. We would expect seizures originating from this location to produce exactly the set of symptoms described above for partial facial seizures, which are the most typical type of seizure seen in benign focal epilepsy of childhood.

BICENTRAL INDEPENDENT AND BISYNCHRONOUS SHARP WAVES

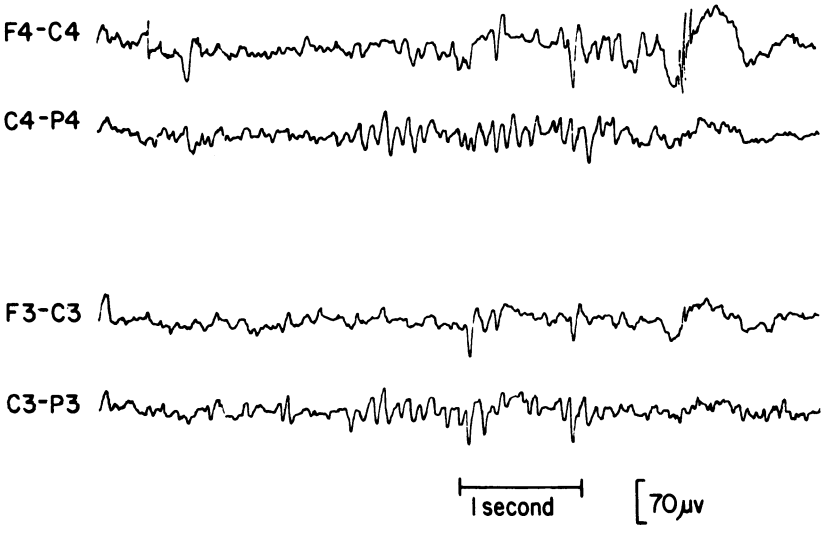

Fig. 13.2. Benign focal epileptiform discharges occurring independently and bisynchronously at C4 and C3.

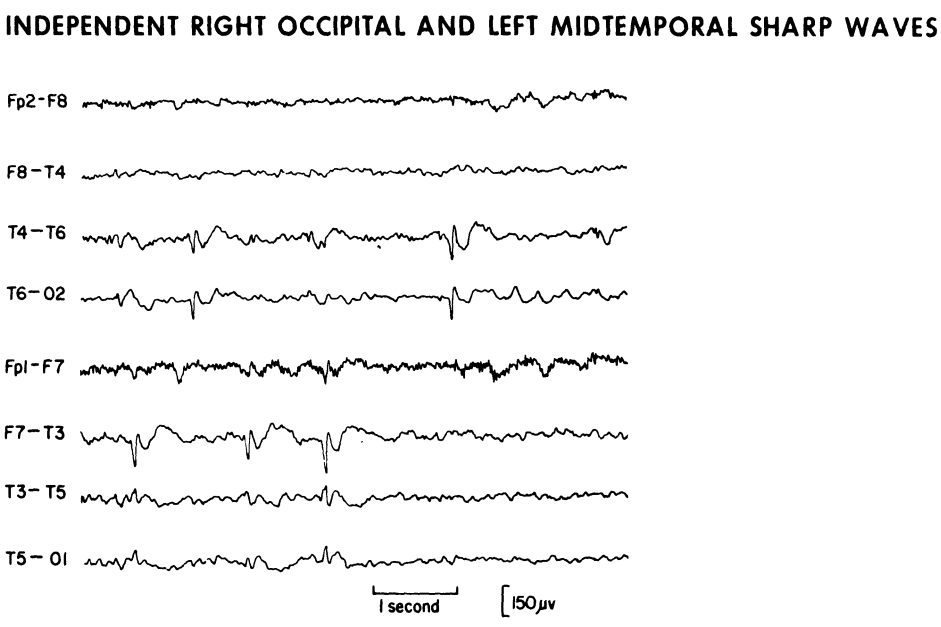

Fig. 13.3. Independent right posterior temporal–occipital and left midtemporal benign focal epileptiform discharges of childhood.

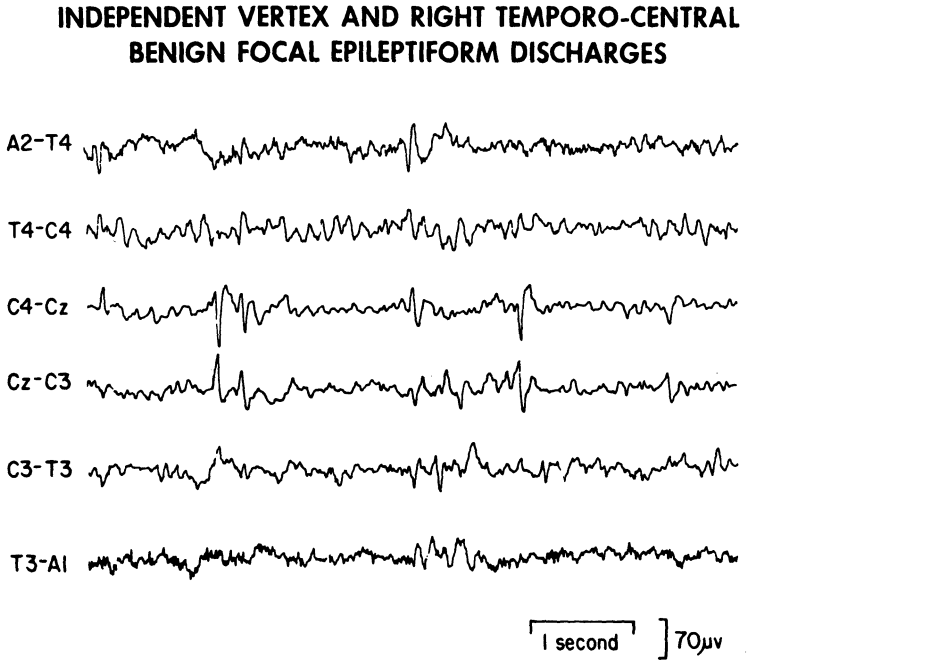

Fig. 13.4. Independent vertical and right temporocentral benign focal epileptiform discharges of childhood.

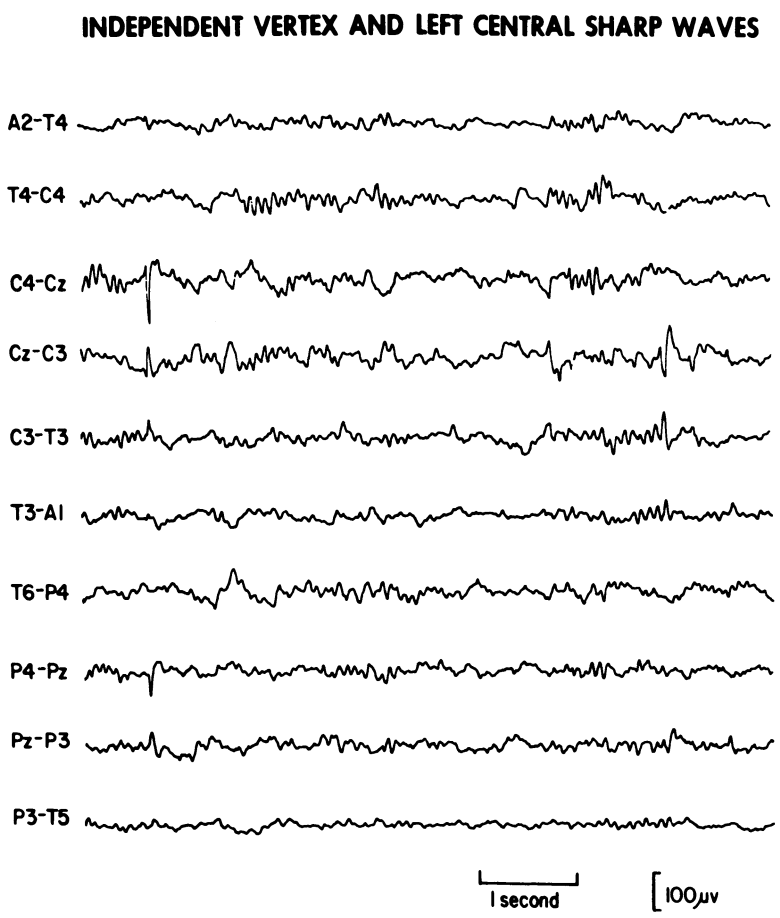

Fig. 13.5. Independent vertical and left central benign focal epileptiform discharges of childhood.

Waveform

The waveform of the benign focal epileptiform discharges of childhood is very characteristic (Blom et al. 1972; Blume 1982; Lüders et al. 1986a). The most prominent element is a negative sharp wave (duration of more than 80 ms) which has a relatively rounded peak (the upgoing and downgoing traces which form the peak do not meet at paper speeds of 3 cm/s) (Nayrac and Beaussart 1957; Faure and Loiseau 1959; Beaussart 1972; Lerman and Kivity 1975; Lüders et al. 1986a). This negative sharp wave is preceded by a well defined, short duration prepositivity and followed by a prominent positive wave whose amplitude is frequently up to 50% that of the preceding negative sharp wave (Lüders et al. 1986a). In general the following negative slow wave is inconspicuous and almost always of lower amplitude than the preceding negative sharp wave (Nayrac and Beaussart 1957;

Beaussart 1972; Kajitani et al. 1980; Lüders et al. 1986a). The sharp waves do not tend to form polyspikes (Lüders et al. 1986a). Another outstanding characteristic of the sharp waves is their tendency to have a constant, stereotyped waveform and field of distribution for any given recording sample (Blom et al. 1972; Blume 1982; Lüders et al. 1986a). These typical features are exemplified in Figs. 13.1–13.10. Lüders et al. (1986a) analyzed the EEGs of patients with focal sharp waves who otherwise had no neurological deficit, and by waveform criteria alone it was possible to select accurately patients who had no seizures or benign focal epilepsy of childhood as opposed to those with intractable focal seizure disorders. This finding points to the selectivity of the waveform of benign focal epileptiform discharges of childhood.

Many authors have stressed the fact that benign focal epileptiform discharges of childhood are of relatively high amplitude (Bancaud et al. 1957; Nayrac and Beaussart 1957; Loiseau et al. 1963; Beaussart 1972; Lerman and Kivity 1975; Blume 1982). In the study by Lüders et al. (1986a) approximately 66% of the sharp waves were over 100 μV. Miyasaki and Nishiura (1980) observed that the amplitude of the sharp waves is a function of age. Patients less than 3 years old had sharp waves of less than 50 μV. The highest amplitudes were seen between 3 and 10 years, with values up to 200 μV. In patients over 10 years old the amplitude of the sharp waves tended to decrease with age.

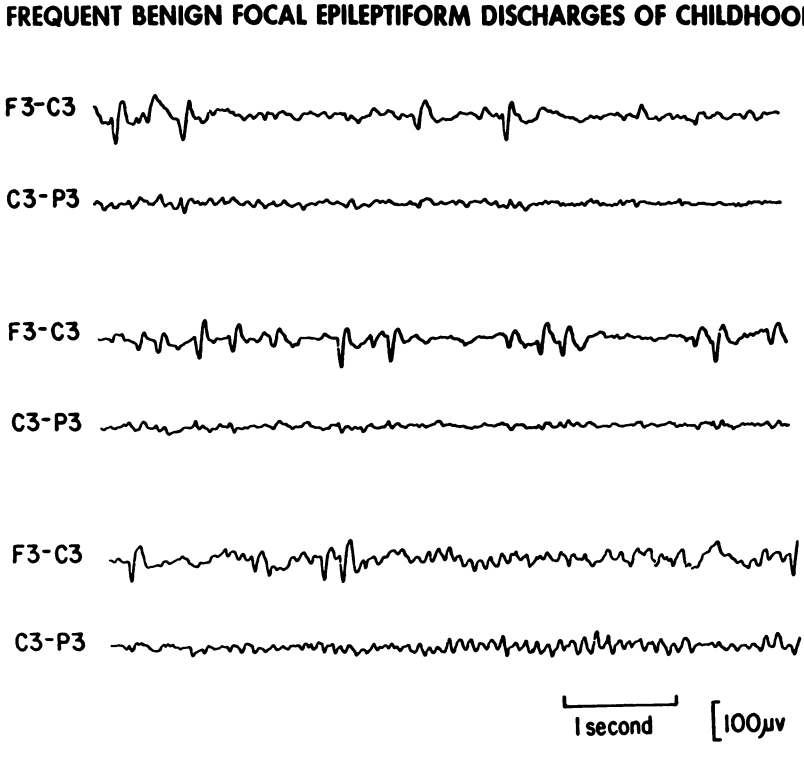

Fig. 13.6. Frequent left centroparietal benign focal epileptiform discharges of childhood.

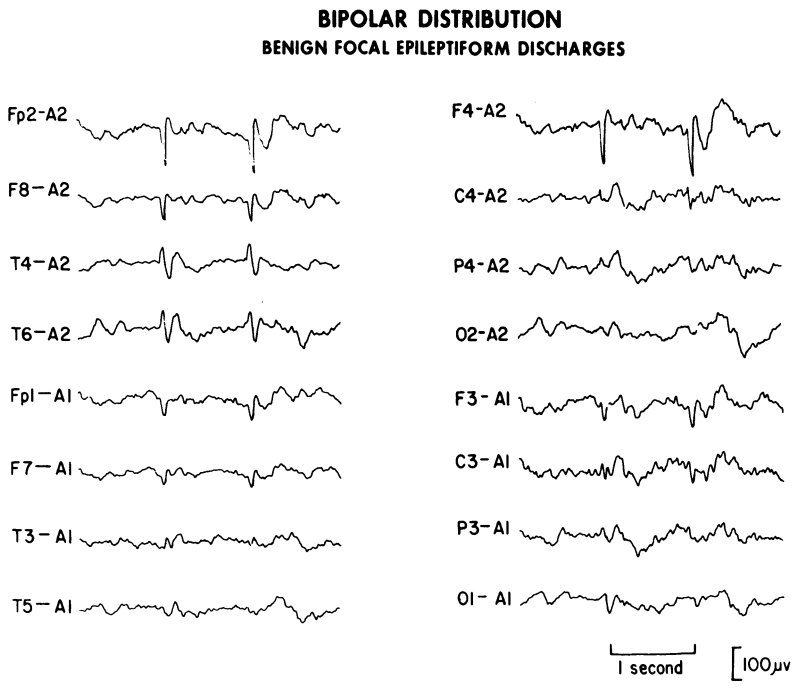

Fig. 13.7. Bipolar distribution of benign focal epileptiform discharges of childhood, showing a positive pole at Fp2 F4 F8 and a negative pole at T4 T6.

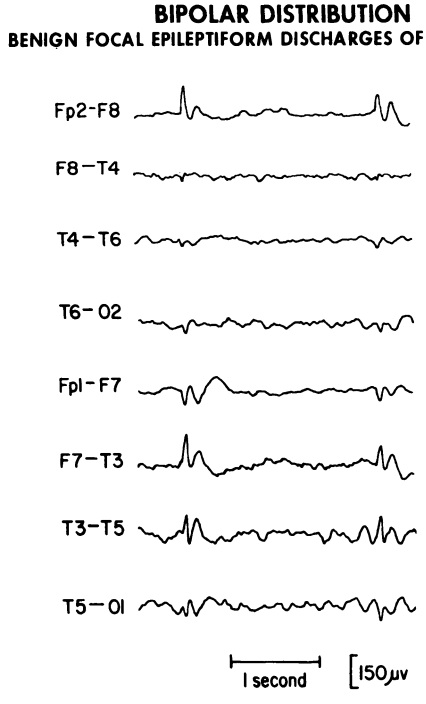

Fig. 13.8. Bipolar distribution of benign focal epileptiform discharges of childhood, showing a negative pole at Fp2 Fpl F7 and a positive pole at T4 T6.

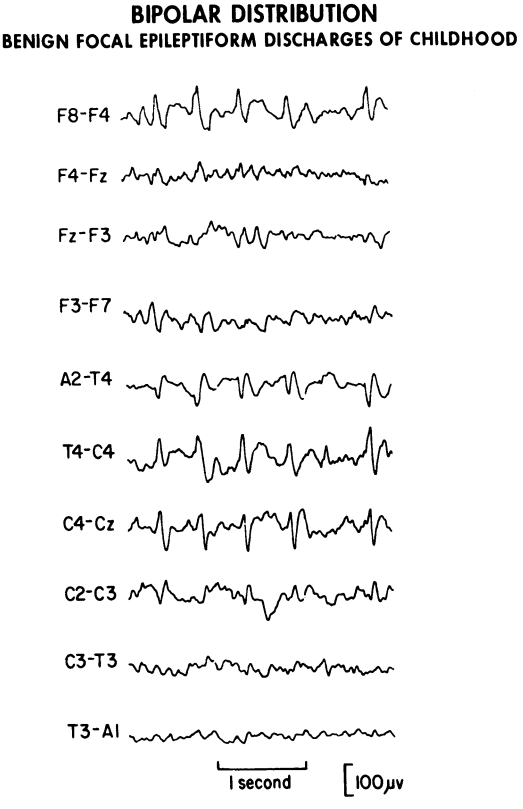

Fig. 13.9. Bipolar distribution of benign focal epileptiform discharges of childhood, showing a maximum negative pole at F8 T4 and a maximum positive pole at Fz F3 Cz.

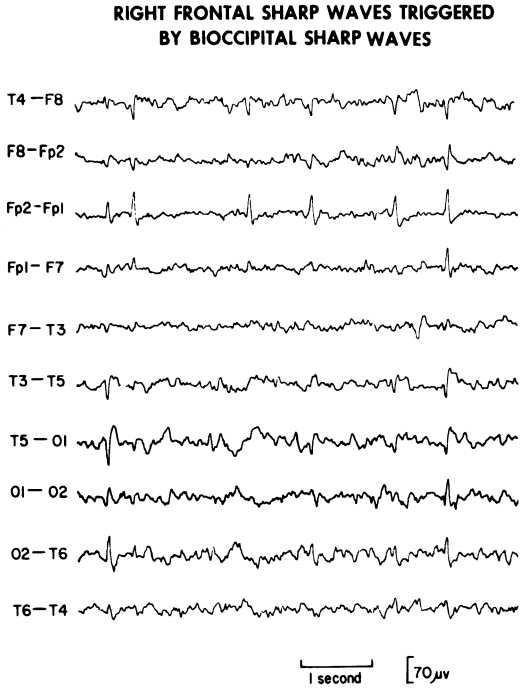

Fig. 13.10. Benign focal epileptiform discharges of childhood maximum at F8 Fp2, preceded (triggered) by sharp waves maximum at 01.

Field of Distribution

The field of distribution of benign focal epileptiform discharges of childhood is frequently arranged like a dipole with typical features which are almost pathognomonic for benign focal epileptiform discharges of childhood (Figs. 13.7–13.9). Gibbs and Gibbs (1952) were the first to indicate that these sharp waves tend to spread as positive spikes into the frontal areas, and this was stressed by Faure and Loiseau (1959). Lüders (1979) also emphasized the bipolar distribution of benign focal epileptiform discharges of childhood. Blume (1982) gave a detailed description of centrotemporal sharp waves, indicating that they have a negative pole at the midtemporal–central electrode and a positive pole at the superior frontal electrode. The negative pole tends to spread into the posterior temporal–auricular–parietal region and the positive pole into the frontopolar area. This distribution explains the typically high amplitude deflection seen at international 10–20 System superior frontal–central derivations (F3–C3 or F4–C4) and the relative cancellations at centroparietal derivations (C3–P3 or C4–P4) (Figs. 13.1, 13.5). This finding was confirmed further by Gregory and Wong (1984), who speculated that this special distribution was due to sharp waves produced by horizontal dipoles with the generator located at the isopotential line between the two poles. This hypothesis would be consistent with sharp waves originating from the base of the rolandic fissure or in the sylvian fissure (including the insula), as would be expected from the clinical symptomatology of the typical facial seizures.

Blume (1982) described "rolandic-like" sharp waves in sagittal derivations. They may appear like negative potentials in the sagittal derivations but reflect like positivities into the parasagittal derivations. It is possible that these dipoles are due to sharp waves generated within the sagittal fissure.

Occasionally patients with benign focal epilepsy of childhood present EEGs that closely resemble the generalized slow spike and slow waves seen in Lennox-Gastaut syndrome. Careful study of the field of distribution of the sharp waves reveals, however, a number of features which distinguish the two patterns (Blume 1982). In some cases a typical centrotemporal/frontal bipole, as would be expected in patients with benign focal epilepsy of childhood, reveals the benign nature of the pattern. In other cases the distribution shows two independent maxima (occasionally even with a variable time delay) in the anterior and posterior head regions. This evidence suggests that these apparently generalized patterns are most probably the result of multiple benign focal epileptiform discharges of childhood that are triggering each other, resulting in relatively synchronous discharge patterns (Fig. 13.10). Not infrequently it is possible to confirm this mechanism of generation by observing that occasionally one or another of the benign focal epileptiform discharges of childhood may occur independently. Benign focal epileptiform discharges of childhood simulating generalized bisynchronous sharp waves are infrequent, suggesting that mutual triggering of multifocal sharp wave usually does not occur. This is consistent with the observation that bitemporal independent benign focal epileptiform discharges of childhood are significantly less frequent than bitemporal bisynchronous benign focal epileptiform discharges of childhood (Gibbs and Gibbs 1952; Beaussart 1972; Nayrac and Beaussart 1957; Bancaud et al. 1957).

Repetition Rate

Benign focal epileptiform discharges of childhood tend to occur frequently (Fig. 13.6) (Nayrac and Beaussart 1957; Lerman and Kivity 1975; Blume 1982) but may also occur infrequently in an occasional patient (Lerman and Kivity 1975; Faure and Loiseau 1959). Beaussart (1972) indicated that the rare, low amplitude benign focal epileptiform discharges of childhood are most frequent at onset of the disease or during treatment. They tend to have an irregular repetition rate and not infrequently are grouped in short bursts of 1.5–3 Hz (Nayrac and Beaussart 1957; Faure and Loiseau 1959; Loiseau et al. 1963; Blom and Brorson 1966; Beaussart 1972; Blom et al. 1972; Lerman and Kivity 1975; Blume 1982). Beaumanoir et al. (1974), Lerman and Kivity (1975), and Blume (1982) reported that the sharp-wave frequency was unrelated to the seizure frequency or seizure duration. The frequent observation that patients with no seizure may show almost continuous benign focal epileptiform discharges of childhood in the EEG confirms Beaumanoir et al.'s (1974) report.

Activation Procedures

One of the most outstanding characteristics of benign focal epileptiform discharges of childhood is their marked activation with sleep (Gibbs et al. 1954; Nayrac and Beaussart 1957; Faure and Loiseau 1959; Little et al. 1967; Lombroso 1967; Beaumanoir et al. 1974; Heijbel et al. 1974; Lerman 1974; Kajitani et al. 1980). Not infrequently sharp waves appear only during sleep (2.5% in Lerman's 1974 study, 17.7% in Lüders et al.'s 1985a study, 18% in Heijbel et al.'s 1974 study, and 35% in Lombroso's 1967 study). This observation indicates that the electroencephalographic evaluation of a child with symptoms compatible with benign focal epilepsy of childhood should not be considered complete unless a sleep study has been obtained. Activation by sleep was observed in all ten cases of Gregory and Wong (1984), and a more than 100% increase of sharp waves was seen in 25 of 34 patients (73.5%) in the study by Lüders et al. (1986a).

Most authors agree that eye opening, photic stimulation, and hyperventilation have no effect on benign focal epileptiform discharges of childhood (Gastaut 1952; Beaussart 1972; Kajitani et al. 1980; Lüders et al. 1986a). Attenuation of the sharp waves by proprioceptive input has been reported repeatedly (Gastaut 1952; Bancaud et al. 1957; Niedermeyer 1970). In this context it is interesting to note that benign focal epileptiform discharges of childhood occur (Kuroiwa et al. (1969b), possibly reflecting interaction of the sharp waves with the incoming somatosensory information.

Background Rhythm and Other Epileptiform Abnormalities

Background rhythms are usually reported as normal (Faure and Loiseau 1959; Lombroso 1967; Beaussart 1972; Blume 1982). This, however, is also dependent on the selection of material. Authors who applied a less strict definition and included patients with structural lesions frequently observed, as would be expected, focal or hemispheric slowing corresponding to the side of the lesion (Nayrac and Beaussart 1957). In addition, when sharp waves occur almost continuously the backgrounds in that area may appear slow, suggesting a structural lesion (Blume 1982).

Reports addressing the frequency with which generalized epileptiform discharges occur in patients with benign focal epilepsy of childhood are contradictory. In many reports no generalized epileptiform paroxysms are mentioned and this is in good agreement with our study, where none were seen (Engle et al. 1977; Lüders et al. 1986a). In our clinical EEG experience, we frequently encounter EEGs with benign focal epileptiform discharges of childhood but have seen only very isolated examples in which generalized epileptiform discharges coexisted. Coexistence of generalized spike and waves with benign focal epileptiform discharges of childhood would actually be expected in a small percentage of cases because of the relatively high incidence of these two patterns. The observations mentioned above, however, are clearly contradictory to Schiefer's (1973) report that 50% of all children with partial seizures show generalized spike and wave complexes and Gerken et al.'s (1974) finding that 70% of all children with partial sharp waves have "centrencephalic tendencies" (photosensitivity, generalized spike and slow-wave complexes, or abnormal theta). It is likely that these discrepancies are due to differences of EEG interpretation, particularly of paroxysmal slow waves with hyperventilation or hypnagogic hypersynchrony. These patterns were probably interpreted as normal variants by one group but as abnormal epileptiform patterns by the other. Various authors also reported photoparoxysmal responses (Blom and Brorson 1966; Blom et al. 1972; Gerken et al. 1974; Blume 1982). It is important to remember, however, that in normal children Eeg-Olofsson (1971) reported an 8.3% incidence of photoparoxysmal responses. Therefore, it is possible that this is also a physiological pattern.

Sharp Waves in Children Without Seizures

Focal sharp waves in children frequently occur without any history of clinical seizures (see section on incidence and prevalence); according to our calculations only 8.8% of children with sharp waves report clinical seizures. This incidence explains the numerous reports of children with sharp waves but no clinical seizures (Green 1961; Berges et al. 1968; Fois 1968; Eeg-Olofsson et al. 1971; Lerman and Kivity-Ephraim 1976, 1981). It is possible that a significant percentage of benign focal seizures remain unnoticed or unreported because of the partial nature of the seizures and their tendency to occur primarily during sleep. In this context it is interesting to note that the only report of a recorded seizure (Dalla Bernardina and Tassinari 1975; Tassinari et al. 1977) concerned a short duration elementary partial seizure which occurred while the patient was asleep and of which the patient was

totally amnesic. There is extensive evidence which permits us to conclude that the majority, if not all, of these sharp waves in normal children are an expression of the same benign focal epilepsy of childhood at a subclinical or asymptomatic level. Careful inspection of the figures and of the descriptions of the sharp waves indicates that they have identical electroencephalographic characteristics (distribution, waveform, field of distribution, effect of activation procedures) to the above-described benign focal epileptiform discharges of childhood. So, for example, in the study by Eeg-Olofsson et al. (1971) 10 of 14 sharp waves were maximal centrotemporally and 2 of 14 were maximal in the occipital leads; 5 of 14 had bifocal independent sharp waves and the sharp waves were more frequent with sleep (awake index: 8.4 sharp waves/min; sleep index: 15.6 sharp waves/min). Moreover, the occipital sharp waves occurred in the youngest children, aged 2 and 5 years. The sharp waves shown in their figures have all the morphological characteristics enumerated above, including small prepositivity, rounded peak of negative sharp waves, prominent following positive waves, but relatively small negative slow waves. The age of appearance of the sharp waves and their disappearance with maturity also fit exactly with the time evolution of benign focal epileptiform discharges of childhood. By extrapolation of the symptomatology in patients with benign focal epilepsy of childhood, it can be expected that many patients would be asymptomatic in spite of strikingly abnormal EEGs. Patients with benign focal epilepsy of childhood usually have only infrequent seizures and there are reports of patients who actually have had only one clinical seizure with no recurrence in spite of never taking anticonvulsants (Blom and Heijbel 1982). In addition, it is generally recognized that seizure frequency has no relationship to the frequency of benign focal epileptiform discharges of childhood (see above). We would expect, therefore, that many patients with the disease would have no clinical seizures or that minor nocturnal partial seizures could pass unreported or unnoticed.

Prognosis

One of the main characteristics of this syndrome is the excellent prognosis. There is consensus that all or almost all the patients become seizure-free after age 15–18 years and that no progressive neurological deficit occurs (Faure and Loiseau 1959; Lossky and Lerique-Koechlin 1962; Loiseau et al. 1963; Lombroso 1967; Lerman 1970; Beaussart 1972; Blom et al. 1972; Lerman 1974; Editorial 1975; Lerman and Kivity 1975; Blume 1982; Blom and Heijbel 1982). Beaussart (1972) reported on 85 children with a follow-up of at least 1 year (11 patients for more than 10 years) after treatment was stopped. Anticonvulsants were discontinued before age 12 years in 46% of the patients and before age 14 years in 76%. Seizures recurred in only one patient, in whom treatment was discontinued after age 16 years.

Blom et al. (1972) reported on 40 patients with benign focal epilepsy of childhood aged 15–24 years at the time of follow-up study. Thirty-eight of the 40 were seizure-free with or without therapy for 4–13 years. Twenty-eight of the 38 patients had discontinued anticonvulsants for 1–13 years (mean 9.0 years). Thirty-eight of the 40 patients were neurologically normal and two patients had a persistent slight hemiplegia. No patients had deteriorated neurologically. The 23

patients of 18 or more years of age had had no difficulty in school and also no problems in choosing a profession. Ten of the 23 patients, however, had difficulty getting a driver's license. Regarding the two patients with recurring seizures, one was 15 years old and was noncompliant and the other was 17 years old and had had one generalized tonic–clonic seizure 3 years after discontinuing anticonvulsants. Blom and Heijbel (1982) restudied 37 of these 40 patients 10 years later (14–23 years observation period). All except one were seizure-free and 32 had been off anticonvulsants for more than 5 years (5–22 years). The only patient with recurrent seizures had had two alcohol withdrawal seizures in the last 8 years. None had developed any progressive neurological disease. Five still had difficulty getting a driver's license.

Lerman and Kivity (1975), in a follow-up study of 100 patients, observed that seizures recurred from 0 (a single fit) to 11 years with a mean of 2.4 years. They observed that seizures ceased in all cases over age 15 years. Four patients with cerebral palsy included in this group had an equally good prognosis, suggesting that the presence of brain damage does not necessarily worsen the prognosis of benign focal epilepsy of childhood. Loiseau et al. (1983), in a follow-up study of 79 patients with benign focal epilepsy of childhood, observed that 15% had an upper-level managerial job (as opposed to 7.1% of the general population) whereas only 7% were manual workers (as opposed to 29.4% in the control group). It could be speculated that this is an artificial difference, possibly related to the fact that families of above average income are more likely to report infrequent, minor partial seizures.

The early studies of benign focal epileptiform discharges of childhood already observed that the evolution of the sharp waves in patients less than 15 years old is extremely variable and not necessarily closely related to the clinical evolution. In many patients, with treatment the sharp waves disappear (Nayrac and Beaussart 1957; Faure and Loiseau 1959; Lerman and Kivity-Ephraim 1974) or are replaced by sharp waves of smaller amplitude and shorter duration (Nayrac and Beaussart 1957). Persistence of sharp waves with treatment in spite of a favorable clinical evolution (no seizures) is, however, not infrequent (Bancaud et al. 1957; Nayrac and Beaussart 1957; Faure and Loiseau 1959; Gibbs and Gibbs 1959–60; Blom and Brorson 1966; Lombroso 1967; Blom et al. 1972; Beaussart 1972; Lerman 1974). So, for example, in Lerman's (1974) study, 28 of 40 seizure-free patients had persistence of benign focal epileptiform discharges of childhood in the EEG. There are even reports of EEG deterioration (increase of sharp wave frequency), in spite of no recurrence of seizures (Bancaud et al. 1957; Beaussart 1972). Nayrac and Beaussart (1957) reported on a patient whose initial EEG was normal but in whom repeat studies obtained 2 and 6 weeks later showed numerous sharp waves. Occasionally also a temporary normalization occurs; in other words the sharp waves may reappear after one to four normal EEGs (recorded over up to 4 years) in spite of no clinical seizures (Nayrac and Beaussart 1957; Blom and Brorson 1966).

As discussed in detail above, in longitudinal studies the benign focal epileptiform discharges of childhood may "migrate" and unifocal sharp waves may become multifocal or vice versa. In clear contrast with this unpredictable evolution, the benign focal epileptiform discharges of childhood consistently disappear in patients over 15–18 years of age. Gibbs and Gibbs (1959–60) observed that sharp waves disappeared in 84% of 120 patients over 18 years who had had a midtemporal sharp wave focus. This series included patients with nonbenign focal

epileptiform discharges of childhood as evidenced by the fact that the majority of the patients with persistent sharp waves also had persistent complex partial seizures. Blom et al. (1972) reported on the EEGs of 38 patients aged 15–24 years at the time of the follow-up study. Thirty-seven of the 38 cases had a normal EEG and one patient with persistent seizures had generalized spike and wave complexes. Blom and Heijbel (1974) reported on follow-up EEGs (obtained more than 14 years after the last seizure) of 26 of these patients and all except two with nonspecific abnormalities had a normal EEG. No benign focal epileptiform discharges of childhood were seen. Benign focal epileptiform discharges of childhood occurring in patients without clinical seizures show a similar evolution with maturation. Lerman and Kivity-Ephraim (1981) performed a longitudinal study of 77 of these cases and reported normalization of the EEG (defined as no sharp waves in two records) in 45 (58%) within 1–11 years' follow-up.

There are no systematic follow-up studies to determine the frequency of seizures in patients who had benign focal epileptiform discharges of childhood in the initial EEG but no seizures at that time. Green (1961), however, in a study of nine children with behavioral abnormalities and benign focal epileptiform discharges of childhood, observed that one of the children developed seizures within 1 year. A bigger sample would be necessary to reach any definite conclusions, but it is interesting that this percentage (11.1%) is approximately equivalent to the percentage of patients with benign focal epileptiform discharges we expect to have seizures (8.8%).

Treatment

All reports agree that the seizures are usually easy to control with small amounts of anticonvulsants (Lombroso 1967; Lerman 1970; Beaussart 1972; Lerman and Kivity-Ephraim 1974; Lerman and Kivity 1975; Blume 1982), although there are a small minority of cases in which the seizures are difficult to control (Blom and Heijbel 1982). It is important to remember, however, that the natural evolution of the disease also appears to be extremely benign. In other words, a "good response" to anticonvulsants may be a placebo effect (Editorial 1975). In this context, it is also worthwhile mentioning that in Blom and Heijbel's (1982) study of 32 patients, there was no recurrence of seizures in three who never took anticonvulsants, nor in an additional three who were on anticonvulsants only for a couple of months.

There are no good studies comparing the effectiveness of different anticonvulsants. All the major anticonvulsants (phenobarbital, phenytoin, and carbamazepine) are usually effective in controlling the seizures. There are, however, a number of reports indicating that the use of phenobarbital is associated with significant side effects, particularly behavioral problems. So, for example, Faure and Loiseau (1959) reported behavioral problems in 6 of 15 patients treated with phenobarbital (and phenytoin). Lerman and Kivity-Ephraim (1974) discouraged the use of phenobarbital, reasoning that it is a soporific and, therefore, could enhance the occurrence of benign focal seizures which occur primarily during sleep. Results of treatments with phenytoin and carbamazepine are equally good. Both are effective in controlling the seizures and side effects are infrequent. Lerman and Kivity-Ephraim (1974) actually reported a positive psychotropic effect of carbamazepine,

indicating that in 13 of 16 patients with behavioral problems the ability to concentrate increased.

There is general agreement that patients with two or more seizures and benign focal epileptiform discharges of childhood in the EEG will need treatment with anticonvulsants. But what about patients with one isolated seizure? We know from the prolonged and careful follow-up study by Blom and Heijbel (1982) that there are a number of patients with a single seizure who will have no recurrence even if they do not take anticonvulsants. Unfortunately, we do not know what the chance of recurrence of seizures in this group of patients is. The occurrence of a seizure suggests, however, that the patient most probably has a relatively higher tendency to have seizures than the average patient with benign focal epileptiform discharges of childhood who has never had a seizure. Since 8.8% of patients with benign focal epileptiform discharges of childhood have seizures, we would expect that their chance of having another seizure is probably at least 8.8%. These statistics can be discussed with the patient and his family, stressing also that frequently the seizures are focal and usually occur at night. Under these circumstances, the decision to treat or not will vary from patient to patient.

What about the patient with benign focal epileptiform discharges of childhood who has never had a seizure? Applying the same reasoning explained above, we can assume that in general the tendency to develop seizures is less than 8.8%, but there are no systematic studies to confirm this (see above). It is, however, well known that patients with benign focal epileptiform discharges of childhood may never develop seizures and the sharp waves essentially tend to disappear with maturation (Lerman and Kivity-Ephraim 1981). As we also mentioned before, the number of sharp wave foci or the frequency of sharp waves is unrelated to the frequency of seizures. It is unlikely, therefore, that these parameters will help us to predict the chance of seizures occurring in asymptomatic patients with benign focal epileptiform discharges of childhood. Given these facts, we would suggest, at least until more evidence has been accumulated, that we should adhere to the principle that "anticonvulsants should not be used to treat the EEG"; in other words, we would recommend not treating with anticonvulsants patients with benign focal epileptiform discharges of childhood but no clinical seizures. This contradicts the recommendation of some authors like Green (1961), Kellaway et al. (1965), and Fois (1968) who considered the benign focal epileptiform discharges of childhood definitely pathological and recommended treatment with anticonvulsants. However, more recent reports tend to agree with our conclusion (Cavazutti et al. 1980; Lerman and Kivity-Ephraim 1981).

How long should the treatment be continued? Many epileptologists apply the same general principles to this type of epilepsy as to any other type. In other words, they slowly withdraw anticonvulsants after a 3- to 5-year seizure-free period and do not feel that the EEG is of any help in this decision. We feel, however, that the natural evolution of this disease is sufficiently well known that it should probably be handled differently. We know that in most patients the seizures and also the benign focal epileptiform discharges of childhood disappear between 12 and 15 years. It seems reasonable to recommend, therefore, that treatment with anticonvulsants should continue until 15 years of age, independent of the age of seizure onset. However, the occurrence of benign focal epileptiform discharges of childhood as a function of age follows closely the corresponding curve for seizure occurrence. This suggests, as would be expected, that it is an index of potential epileptogenicity. Therefore, we feel that the recommendations to continue anticon-

vulsants until age 15 years should be modified by the EEG findings. In other words, patients who have been seizure-free for 3 years and have a normal awake and complete sleep EEG should have the anticonvulsants slowly discontinued. A repeat EEG should be obtained shortly after all anticonvulsants have been stopped. Moreover, at the age of 15 years an EEG (awake and sleep) should be obtained and the anticonvulsants should not be discontinued if the EEG is still abnormal. This approach is based on indirect evidence; more direct evidence to support its rationale as outlined above is badly needed.

Pathogenesis and Related Syndromes

Pathogenesis

The evidence presented above indicates that benign focal epilepsy of childhood is a *hereditary condition* transmitted most probably by a single dominant autosomal gene. The condition inherited consists of a *diffuse tendency* of the cortex to produce foci of elevated epileptogenecity. This tendency is greatly modified by the following factors:

1. *Maturational factors.* In young children (2–5 years) benign focal epileptiform discharges of childhood occur mainly in the occipital region. These foci apparently have a very low clinical expressivity but occasionally produce secondary generalized seizures.

In older children (5–12 years) benign focal epileptiform discharges of childhood tend to occur mainly in the centrotemporal region and less frequently in the parasagittal or frontal areas. Children with centrotemporal sharp waves have the highest relative clinical expressivity, with typical partial seizures (facial seizures) and secondary generalized seizures. These are the patients most frequently detected clinically.

Finally, in adolescents (13–17 years) the benign focal epileptiform discharges of childhood, as well as the clinical seizures, disappear; this justifies the designation "benign." The marked influence of maturational factors on the benign focal epileptiform discharges of childhood explains their temporal and spatial variability. The so-called migration of the sharp wave foci is nothing more than the fact that with maturation new cortical areas become epileptogenic whereas others which were previously epileptogenic "mature into normality." The focal nature of the EEG is most probably due to different cortical areas reaching the stage of active epileptogenicity at different times (in general the occipital areas do so before the centrotemporal regions). Disappearance and reappearance of sharp waves is also the consequence of maturation, occurring when one area has "matured into stability" whereas other areas still have to mature further to reach the stage of epileptogenicity. Finally, bifocality or multifocality occurs when two or more areas of the cortex (in one or both hemispheres) reach the stage of epileptogenicity at the same time. "Migration" of the sharp wave foci also explains why the correlation between the partial seizures and localization of sharp waves may be very poor if the

EEG test is not obtained during or immediately after the clinical seizure.

2. *Brain damage.* As explained above, it seems that in many patients the location of the focus is determined by a maturational factor. This has given origin to the concept that the focus is "functional" (Gastaut 1952; Bancaud et al. 1957; Nayrac and Beaussart 1957; Beaussart 1972). In support of a "functional" focus is the frequent observation of benign focal epileptiform discharges of childhood in patients who have had a normal neurological and psychological examination, with no abnormalities in X-ray studies and shifting EEG focus and clinical seizures (Beaussart 1972).

There is some evidence, however, to suggest that brain damage may facilitate the occurrence of benign focal epileptiform discharges of childhood. Benign focal epileptiform discharges of childhood are frequent in the central regions in patients with cerebral palsy and tend to occur on the side of the lesion despite reports of sharp waves on the contralateral side (Bancaud et al. 1957). Benign focal epileptiform discharges of childhood occur frequently in patients who have had febrile convulsions and the great majority (78%) are seen on the same side on which focal slowing was seen shortly after the febrile convulsion (Frantzen et al. 1968). Moreover, benign focal epileptiform discharges of childhood are significantly more frequent in children with migraine (9%), suggesting either that there is a hereditary link or that the subclinical brain damage produced by the migraine attack may facilitate the occurrence of benign focal epileptiform discharges of childhood (Ziegler and Torres 1956; Kinast et al. 1982).

The sharp waves seen in patients with benign focal epilepsy of childhood have a *typical waveform* and other characteristics which tend to differentiate them from the sharp waves seen with partial epilepsies due to a focal brain lesion (Lüders et al. 1986a). It seems, however, that this typical waveform is primarily an expression of sharp waves of extremely *low epileptogenicity*. As explained above, one of the main characteristics of the benign focal epileptiform discharges of childhood is the extremely stereotyped waveform. A stereotyped waveform, however, implies that the neuronal pool participating in the generation of the sharp waves is always the same. This in turn indicates that there is no tendency to involve new neurons with each discharge and, therefore, that the tendency to produce clinical seizures is extremely low. Low epileptogenicity explains many of the crucial characteristics of benign focal epilepsy of childhood, i.e., (a) the low incidence of seizures and their easy control with anticonvulsants; (b) the frequent observation of asymptomatic benign focal epileptiform discharges of childhood (in other words, why only 8.8% of the patients with benign focal epileptiform discharges of childhood have seizures); (c) why benign focal epileptiform discharges of childhood are greatly influenced by maturational factors and their relative sensitivity to intravenous benzodiazepines (when compared with nonbenign focal epileptiform discharges) (Niedermeyer 1970). At the same time, conceiving the typical characteristics of benign focal epileptiform discharges of childhood just as an expression of sharp waves of low epileptogenicity implies that they are not pathognomonic for patients with benign focal epilepsy of childhood. In other words, we feel that sharp waves with the same characteristics as benign focal epileptiform discharges of childhood can be produced by structural lesions without the genetic factor. Therefore, when a patient has a focal structural lesion and sharp waves which have all the characteristics of benign focal epileptiform discharges of childhood it is impossible to decide whether the patient has (a) benign focal epilepsy of childhood and a structural

lesion or (b) merely a structural lesion which produces low epileptogenicity sharp waves, without genetically determined benign focal epilepsy of childhood. An exception is the group of cases in which the benign focal epileptiform discharges of childhood and the structural lesion are in different locations (Bancaud et al. (1957).

Relationship of Benign Focal Epilepsy of Childhood with Complex Partial Seizures and Other Nonepileptic Symptoms

There is clear evidence that benign focal epileptiform discharges of childhood can generate either partial facial seizures or secondary generalized tonic–clonic seizures, even if in only a minority of patients (8.8%). There is, however, no evidence of a causal relationship with other signs or symptoms. *Complex partial seizures* (psychomotor seizures) occur mainly in patients with mesial temporal sharp waves who have underlying brain damage, and they tend to be unresponsive to anticonvulsants (Lerman 1974). The characteristics of the sharp waves seen in association with complex partial seizures are usually easy to differentiate from benign focal epileptiform discharges of childhood (Lüders et al. 1986a). There is no evidence to suggest that benign focal epileptiform discharges of childhood can generate complex partial seizures. Besides, benign focal epileptiform discharges of childhood have been described in association with a long list of symptoms, including dyspraxias (Berges et al. 1968), nonspecific motor, affective, or perceptomotor problems (Lairy et al. 1964, 1966), and behavioral disorders (Green 1961). Unfortunately, none of these studies considered the possibility of a chance association between the benign focal epileptiform discharges of childhood and these symptoms. An exception are patients with migraine who, as mentioned above, have a significantly higher incidence of benign focal epileptiform discharges of childhood (9% vs 1.9% in controls, Kinast et al. 1982). However, even in these patients there is no evidence to suggest that the benign focal epileptiform discharges of childhood bear a causal relationship to the migraine. In other words, there is no basis for suggesting that anticonvulsant treatment of migraine or other nonepileptic symptoms (so-called epileptic equivalents) should help (Lerman and Kivity-Ephraim 1981).

Relationship of Benign Focal Epilepsy of Childhood with Febrile Convulsions

There seems to be a close relationship between benign focal epilepsy of childhood and febrile convulsions; this is expressed by the high frequency of benign focal epileptiform discharges of childhood in patients who have had febrile convulsions (Frantzen et al. 1968), and conversely in the relatively high frequency of febrile convulsions in patients with benign focal epilepsy of childhood (Lerman and Kivity 1975; Gregory and Wong 1984). The studies of Engle et al. (1977), Lennox-Buchthal (1971), and Kajitani et al. (1980), discussed above, also support this conclusion.

Relationship of Benign Focal Epilepsy of Childhood with Generalized Epileptiform Discharges

Beaumanoir (1974) described subclinical absences (detectable only with EEG-video recordings) with 3- to 4-s bursts of generalized 3-Hz spike and waves in 11 of 15 patients with benign focal epilepsy of childhood. He also observed benign focal epileptiform discharges of childhood in 11 of 26 patients with typical absences and 3-Hz spike and wave bursts. He concluded from this observation that a close link exists between benign focal epilepsy of childhood and idiopathic centroencephalic epilepsy. Other authors have also reached the same conclusion based on the frequent observation of generalized paroxysms in patients with benign focal epilepsy of childhood (Lombroso 1967; Schiefer 1973; Gerken et al. 1974). This conclusion, however, is not supported by most of the more recent detailed studies of benign focal epilepsy of childhood (Blom et al. 1972; Lerman and Kivity 1975; Blume 1982). In our experience the occurrence of generalized spike and wave complexes in patients with benign focal epilepsy of childhood is extremely rare, and we have not seen benign focal epileptiform discharges of childhood in patients who have clinical and electroencephalographic evidence of generalized absence seizures. This leads us to conclude that benign focal epilepsy of childhood, even if essentially a generalized epilepsy, is not a condition related to generalized absences or other generalized epilepsies except febrile convulsions. It is possible, as discussed above, that the generalized paroxysms described by some authors in patients with benign focal epileptiform discharges of childhood correspond to physiological paroxysms (particularly frequent in children) such as bursts of hypnagogic hypersynchrony or photoparoxysms. Moreover, the focal epileptiform discharges described by Beaumanoir et al. (1974) in patients with absence seizures could well correspond to the frequent focal spikes seen in these patients (Lüders et al. 1984).

Location of Focus

The typical partial facial seizures are most probably an expression of epileptic discharges in the lower portion of the rolandic fissure where it meets the sylvian fissure (Loiseau et al. 1967; Lerman and Kivity 1975). As explained above, all the typical symptoms and signs can be reproduced by electrical stimulation of that area. This conclusion is also supported by the frequent centrotemporal location of the benign focal epileptiform discharges of childhood. Sharp waves generated as horizontal bipoles within the rolandic or sylvian fissure would explain the typical bipolar field of distribution. Many authors have speculated that the primary focus is actually subcortical because of its activation by sleep (Faure and Loiseau 1959), the association with generalized spike and wave discharges, alternating occurrence on both hemispheres, absence of focal lesions (Lombroso 1967), or occurrence in association with subtentorial tumors (Nayrac and Beaussart 1951). We feel that benign focal epileptiform discharges of childhood most probably originate at the cortical level and that none of the arguments given above actually establishes or even favors a subcortical origin.

The Concept of Benign Partial Epilepsy

Tissot in 1772 described in his *Treatise of Epilepsy* patients with a predisposition to epilepsy who had no brain lesion and had a tendency to have a relatively benign evolution. For a long time it was assumed that focal epilepsy was always secondary to a focal brain lesion. In 1951, however, Gastaut suggested the existence of a functional ("benign") partial epilepsy when he wrote that "as a principle, functional epilepsy exclusively presents as generalized seizures of the grand mal or petit mal type; however, it remains to be proven whether this conclusion is valid or whether there exists an idiopathic epilepsy of the "partial" type, since many observations plead in favor of the latter hypothesis (Gastaut 1951). In his review paper in 1982, he concluded that "benign partial epilepsies" exist but that they are the result of a generally lowered convulsant threshold due to genetic factors and a discrete lesion which determines its focal expression. We agree that this is one mechanism of production of benign focal epileptiform discharges of childhood, but from the frequent observation of benign focal epileptiform discharges of childhood in patients with absolutely no evidence of brain lesion and the common occurrence of multifocal sharp waves or migration of sharp waves we conclude that in many cases the genetic factor alone is sufficient to produce benign partial epilepsy and that the focal expression is only a manifestation of differential rates of maturation of different areas of the cortex. We feel, however, that epilepsy should only be classified as *benign* if it is (a) unrelated to a brain lesion (idiopathic, essential, genuine, common, true or primary epilepsy); (b) relatively easily controlled with anticonvulsants during its active phase (producing no or only a minimal handicap to the patient); and (c) greatly affected by maturational factors which assure its total disappearance with age (excellent prognosis). Benign focal epilepsy of childhood meets all these criteria.

Relationship of Benign Focal Epilepsy of Childhood with Other Benign Partial Epilepsies

There are a number of other less well defined entities that have also been described as benign partial epilepsies. Gastaut (1982a) described a "*benign partial epilepsy of infancy*." According to Gastaut (1982a) it occurs in infants 30 days to 2 years old who have no known brain lesion, frequently a positive family history, and a normal neuropsychiatric status. These patients have mainly elementary motor seizures (frequently unilateral seizures) which tend to occur during sleep. The EEG shows a normal background with uni- or multifocal sharp waves. In other words, "benign partial epilepsy of infancy" is identical to benign focal epilepsy of childhood but occurs in a younger age group. Additional studies would be necessary to establish its existence and longitudinal follow-up studies would be essential to determine whether it is an independent entity or just benign focal epilepsy of childhood occurring in infancy.

Dalla Bernardina et al. (1978) recently described a group of four children which Gastaut (1982a) classified as a subgroup of benign partial epilepsy of children, coining the term "*benign epilepsy with affective symptomatology and temporal*

spikes." The main clinical feature in these children was absence seizures associated with bursts or generalized 3-Hz spike and wave complexes which with sleep became more or less continuous. The absences started at age 4–10 years, were difficult to control, but had a tendency to disappear with maturation. Together with the appearance of clinical absences the patients showed psychomotor instability, disorientation in space and time, and marked deterioration in school performance. Two children had focal atrophic lesions in neuroradiographic studies and clinically had a congenital hemiparesis. The only focal features were that all four children had had infrequent (in three cases a single) partial seizure with focal "rolandic" sharp waves at an average age of 3 years 6 months and that subclinical focal electroencephalographic seizure patterns were seen during sleep in association with the more or less continuous generalized spike and wave complexes. This syndrome definitely should not be classified with the benign partial epilepsies. They are patients who primarily have generalized epilepsy, and they do not meet any one of the three conditions enumerated above to classify them as benign: two of the four patients had major brain lesions; the seizures were extremely difficult to control, producing significant psychological deficits; and total disappearance of clinical and EEG manifestations was demonstrated in none of the patients. This syndrome is apparently related to the sleep-induced "electrical status epilepticus" observed in Patry et al.'s (1971) children. However, more extensive and detailed studies would be necessary to define the syndrome better.

Recently Gastaut (1982a) described another type of epilepsy which he identified as "*benign partial epilepsy of childhood with occipital spike–waves*." According to his report, this epilepsy is approximately half as frequent as benign focal epilepsy of childhood, the mean age of seizure onset is 6 years, and it occurs slightly more frequently in females (61%). Family history of epilepsy is positive in 47% and for migraine in 19%. Neuropsychiatric, neuroradiological, CT, and ophthalmological examinations are almost always normal. The EEG shows normal background activity and high amplitude sharp waves in the occipital–posterior temporal area which are not activated by photic stimulation. The seizures are associated with amaurosis in 65% of the cases, elementary visual symptoms (phosphenes) in 58%, and complex visual symptoms (hallucination or illusions) in 35%. In addition, partial motor seizures occur in 44%, complex partial seizures in 19%, and generalized tonic–clonic seizures in 8% of the cases. These seizures usually follow the visual symptomatology. Moreover, in 36% of cases the epileptic symptoms are followed by long-lasting cephalalgia accompanied by nausea and vomiting. Seizures disappear before the age of 19 years in 92% of cases.

Gastaut's (1982b) estimate that this seizure type is approximately half as frequent as benign focal epilepsy of childhood does not agree with our experience. In Engle et al.'s (1977) study of patients with focal sharp waves but no neurological deficit (except seizures), 32% had occipital seizures but none actually had reported partial seizures with visual symptomatology. This certainly does not mean that we never see patients with occipital sharp waves and visual partial seizures; it just implies that these cases are very rare compared with the extremely frequent occurrence of benign focal epilepsy of childhood. We also cannot agree with Gastaut's (1982b) statement that postictal migraine occurs almost exclusively in this type of epilepsy. So, for example, in the workup of temporal lobe seizure patients for surgery of epilepsy it is not infrequent to observe patients who consistently complain of severe headaches after a seizure. Regarding the syndrome

itself, we feel that it most probably consists of a mixture of at least two clearly separate entities.

On the one hand, we have patients with benign focal epilepsy of childhood who at one stage of maturation (generally at a young age) show mainly benign focal epileptiform discharges of childhood in the occipital region. We have never seen visual partial seizures in these patients, but more extensive, systematic studies would be necessary to clarify this point. It is interesting that one of the four examples given by Gastaut (1982b) actually evolved to have benign focal epileptiform discharges of childhood in the midtemporal region at a later stage. The so-called visual seizures of this 2-year-old child consisted of turning his head to the side contralateral to the focus "as if he was looking at something."

A second group of patients have occipital sharp waves secondary to a focal occipital progressive or nonprogressive brain lesion. In our experience, these patients frequently have visual partial seizures or (most probably due to spread of the discharge into the temporal lobe) complex partial seizures. In this context, it is interesting to note that 19% of the cases in the series of Gastaut (1982b) had complex partial seizures, which never occur in patients with benign focal epilepsy of childhood. A recent report by Dvorkin et al. (1984) strongly supports our assumption that a subgroup of these patients have focal occipital lesions. They saw six patients in their first and second decades who had occipital seizures preceded by visual auras which initially appeared benign and were easily controlled for several years. Later they were associated with prolonged and increasingly severe migraines, producing large alternating occipital infarcts. Four patients died and pathological studies revealed cortical infarcts and cortical vascular hyperplasia. Therefore, we can conclude that Gastaut's (1982b) syndrome of "benign partial epilepsy of childhood with occipital spike-waves" may represent more than one entity. Additional studies will be necessary to establish whether there exists a subgroup of patients who should be classified as having "*benign partial epilepsy of childhood with occipital spike–waves*" as defined by Gastaut (1981), or whether such cases comprise both (a) patients representing a subgroup of benign focal epilepsy of childhood and (b) patients having occipital sharp waves secondary to a focal brain lesion.

Finally, Loiseau and Orgogozo (1978) described a "*benign partial epilepsy of adolescence*." They studied 83 patients (72% males) with partial seizures (mainly focal motor or focal sensory seizures) with or without secondary generalization and with seizure onset between 12 and 18 years. The majority were neurologically intact and in all cases the seizures were under good control in follow-up studies. The EEG was normal in the majority of patients or showed only nonspecific abnormalities. As is the case for other previously mentioned syndromes, additional systematic studies are necessary to document the nature of this syndrome. It is likely that it includes some patients who actually do not have seizures. This is particularly likely if we consider that there is no objective proof of the existence of an epileptic condition (normal EEG or only nonspecific EEG abnormality) and that this group included an unusually high percentage of focal sensory seizures (27.7%), which in general are seen only infrequently. It is also possible that a group of these patients had benign focal epilepsy of childhood but showed a normal EEG (the authors do not indicate whether a sleep tracing was obtained).

From the detailed analysis given above it is clear that benign focal epilepsy of childhood is the only well defined benign partial epilepsy. All the other syndromes

either are not benign, are very poorly defined, only concern a subset of cases occurring at one of the extreme age groups (infancy or adolescence), or have benign focal epileptiform discharges of childhood in a special location (occipital sharp waves).

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Chapter 14

Focal Status Epilepticus: Modern Concepts

Antonio V. Delgado-Escueta and David M. Treiman

Introduction

Twenty-five years have now passed since the Marseille Conference on status epilepticus was organized by H. Gastaut (1967; Gastaut et al. 1967). Perhaps the most important advance to stem from that conference was the extension of the term "status epilepticus" to mean "epileptic seizures that are so frequently repeated or so prolonged as to create a fixed and lasting epileptic condition." The Commission on Terminology—established by the International League Against Epilepsy (ILAE)—,The World Federation of Neurology, and the International Federation of Societies for Electroencephalography and Clinical Neurophysiology have all accepted this definition of status epilepticus. Thus, in addition to tonic–clonic status epilepticus, somatomotor partial status, and epilepsia partialis continuans, prolonged status of nonconvulsive absence and complex partial seizures were accepted as forms of status epilepticus (Gastaut 1983). Simultaneous with these developing concepts on status epilepticus, rapid advances in medical genetics, the epidemiology of seizure disorders, and documentation of epileptic attacks by closed circuit television videotaping (CCTV) and EEG biotelemetry have led to improved understanding of the epilepsy syndromes. These two evolving streams of thought converged in the Santa Monica International Symposium on Status Epilepticus in 1980 and brought into focus conceptual advances in mechanisms of brain damage, classification, and treatment of status epilepticus (Delgado-Escueta and Bajorek 1982; Delgado-Escueta et al. 1982b). This chapter is not an all-inclusive recapitulation of the literature on focal status epilepticus. Rather, it is a selective treatment of the swiftly changing concepts in respect of partial epilepsies and their implications for how the electroclinical features of focal status epilepticus should be interpreted. We also discuss the causes and consequences of focal status, prognosis, and treatment. In particular, we highlight the new clinical research efforts of the last 5 years that are closing important gaps in our knowledge of focal status epilepticus.

Focal Status

"Status epilepticus can assume as many forms as there are varieties of epileptic seizures" (Gastaut 1967, 1983; Gastaut and Tassinari 1975; Gastaut et al. 1967). To this we should add that status epilepticus can present and occur in as many forms of epilepsy (epilepsy syndromes) as there are. When verifying the presence of a fixed and lasting epileptic condition, the physician should note the clinical and electrographic character of the seizure, the duration of the fixed epileptic state, and the possible etiology(ies) and trigger mechanisms. If information about the age at onset of seizures, a family history, and the interictal neurological state is obtained, the physician may be able to define the specific form of epilepsy in which status epilepticus is occurring. The physician may also acquire good clue(s) as to which drugs are most effective in stopping status of specific epileptic seizures. All of this information may be quickly obtained at the bedside while the clinician provides emergency treatment.

Although no satisfactory classification of the focal epilepsies presently exists, Table 14.1 is a simplified and short version of the ILAE classification on focal or partial epilepsy syndromes (Commission on Classification and Terminology of the International League Against Epilepsy 1985). It distinguishes idiopathic or primary epilepsies (with major genetic contributions) from symptomatic or secondary epilepsies (which are caused by structural lesions or "lesional").

Table 14.1. Focal or partial epilepsies[a] (after Appel 1986)

I. Primary focal or partial epilepsies:

Genetically determined with specific age penetrance and spontaneous recovery:

a) Benign rolandic epilepsy with centrotemporal spikes
b) Benign occipital epilepsy of childhood with occipital spike–wave complexes or sharp waves
c) Benign partial epilepsy with affective symptomatology
d) Benign partial epilepsy with language disorders (Landau-Kleffner syndrome)

II. Secondary or symptomatic focal or partial epilepsies:

Caused by a structural lesion(s) or "lesional"

Secondary or symptomatic partial epilepsies commonly without loss or impairment of consciousness:

a) Sensorimotor epilepsies
b) Somatomotor and postural motor
c) Kojewnikow's syndrome or Koshevnikoff epilepsy
d) Occipital epilepsies
e) Temporal neocortical epilepsies

Secondary or symptomatic partial epilepsies commonly with loss or impairment of consciousness:

a) Temporal lobe epilepsies
    1. Hippocampal epilepsy or medial basal limbic
    2. Amygdalar or anterior temporal polar–amygdalar epilepsy
    3. Lateral posterior temporal neocortical epilepsy
    4. Opercular–insular or island of Reil epilepsy
b) Frontal lobe epilepsies
    1. Cingulate epilepsies
    2. Supplementary motor epilepsies
    3. Orbitofrontal and prefrontal epilepsies
    4. Dorsolateral frontal epilepsies
c) Medial occipital-hippocampal epilepsies

Table 14.1. (*continued*)

III. Secondary or symptomatic generalized epilepsies:
Caused by a structural lesion(s) of "lesional"
Secondary tonic-clonic epilepsies: simple partial evolving to tonic–clonic seizures caused by various structural lesions
Infantile spasms (propulsive petit mal, infantile myoclonic encephalopathy with hypsarrhythmia or West syndrome)
Myoclonic astatic or atonic epilepsies (epileptic drop attacks, atypical absence, tonic seizures of Lennox-Gastaut in children with mental retardation)
Progressive myoclonic epilepsies in adolescent and adults with dementia (myoclonic epilepsies of Lafora, Lundborg-Hartung, Hunt or Kuf)
IV. Unclassified partial epilepsies
V. Special syndromes of partial epilepsies

[a] Modified from ILAE proposal for classification of epilepsies and epileptic syndromes (Commission on Classification and Terminology of the International League Against Epilepsy 1985).

Focal Status Evolving into Secondary Tonic–Clonic Status

[Synonyms: secondary generalized status epilepticus, secondary convulsive status epilepticus, tonic–clonic status with partial onset (Gastaut 1967, 1983; Gastaut et al. 1967)].

Focal status epilepticus can occur in any of the clinical settings listed under idiopathic/primary partial epilepsies and symptomatic/lesional partial epilepsies. More often than not, "status epilepticus" conjures up an image of the generalized tonic–clonic status. Tonic–clonic status epilepticus is, in fact, the most common, most awesome, and most serious form of status epilepticus in children, adolescents, and adults. However, careful observation of clinical patterns by Janz and Kautz (1964), Janz (1961, 1963, 1975, 1983), Celesia (1983), and Delgado-Escueta and co-workers (Delgado-Escueta and Bajorek 1982; Delgado-Escueta et al. 1982b) shows that about 70%–80% of patients with tonic–clonic status epilepticus have a partial onset (partial motor or adversive head and eye movements). Clinical signs of partial engagement of brain structures evolve into generalized tonic–clonic seizures. Generalized clonic–tonic–clonic convulsive status, on the other hand, almost always implies a primary genetic basis and does not have a partial onset. Generalized tonic status always occurs as a result of diffuse organic brain disease that causes the Lennox-Gastaut syndrome; thus, such cases should not be classified under the heading of primarily generalized status. They are considered forms of symptomatic generalized epilepsies and status epilepticus.

Symptomatic or secondary tonic–clonic status epilepticus is, therefore, the most common variety of status epilepticus and the most common form of fixed epileptic state in partial epilepsies. Since so many tonic–clonic status patients have a partial onset, an active central nervous system lesion should be ruled out. Tonic–clonic status most frequently results from (a) acute central nervous system insults, e.g., acute cerebral infarctions, meningitis, encephalitis, head trauma, and cerebral anoxia from cardiorespiratory difficulties, or (b) old cerebral infarcts. Not infrequently, secondary tonic–clonic status results from withdrawal of antiepileptic

drugs in chronic epileptics and metabolic diseases such as renal failure and electrolyte imbalance (Delgado-Escueta and Bajorek 1982; Delgado-Escueta et al. 1982b).

Whenever tonic–clonic status constitutes the initial epileptic manifestation, an acute cerebral insult should be considered, particularly space-occupying lesions. Some series, such as those of Janz and Kautz (1964), Janz (1961, 1963, 1975, 1983), and Oxbury and Whitty (1971a,b), have emphasized brain tumors as an important cause of status epilepticus. These authors report that 22%–25% of cases of tonic–clonic status result from cerebral neoplasm. In their retrospective study, Oxbury and Whitty also emphasized frontal or frontotemporal brain tumor as a common cause of the syndrome of isolated status epilepticus. In this syndrome, adults present with tonic–clonic status epilepticus against an apparently healthy background without a previous history of epilepsy (Oxbury and Whitty 1971a).

Somatomotor, Postural Motor, and Sensorimotor Partial Status

[Synonyms: partial status epilepticus, without a march; local epileptic status epilepticus; partial status epilepsy; Jacksonian status epilepticus, focal status with a march or Bravais-Jacksonian status (Gastaut 1967, 1983; Gastaut et al. 1967)].

The second most common form of status epilepticus, namely, simple partial status (without impairment of consciousness), also occurs most commonly in the clinical settings of one of the symptomatic partial epilepsies, namely, the somatomotor, postural motor, and sensorimotor epilepsies. Perhaps the earliest documented form of focal status was the repeated somatomotor attacks first described by Hippocrates and then Aretaeus. Our early concepts on partial motor status epilepticus were then refined by the observations of Bravais and Jackson, who distinguished a progressive "march" of local muscular contractions (Gastaut 1967, 1983; Gastaut and Tassinari 1975) which followed the somatotopic prerolandic representation of the human homunculus in the primary motor cortex. The "cheilo-oral" propagation is frequently cited—the march of myoclonic contractions from the thumb to the ipsilateral labial muscles (Gastaut 1967, 1983; Gastaut et al. 1967).

CCTV–EEG correlations now show that somatomotor partial status most frequently occurs without the Bravais-Jacksonian march, localized clonic jerks most often engaging the thumb, big toe, lips, or eyelids. They also indicate that the seizure focus is in the primary motor cortex.

In neurological and consulting practice, somatomotor partial status, postural motor status epilepticus with contraversive or ipsiversive conjugate deviation of the eyes (tonic ocular movements or oculogyric or oculotonic status or oculoclonic status or sustained epileptic nystagmus), and/or rotation of the trunk (partial or complete body turns or gyratory status epilepticus) are frequently encountered and commonly serve as points of referral for the medical services. These forms of focal status are commonly symptomatic of an active disease process in the premotor regions of the frontal lobe. The forms of postural motor status described above should be further differentiated from the fencing posture produced by epileptogenic paroxysms in the supplementary motor cortex of the medial frontal lobe. Adversive movements of the head and eyes, flexion of the ipsilateral arm, extension

of the ipsilateral leg and contralateral arm, and repeated vocalizations constitute the simultaneous appearance or repeated sequence of movements. Not infrequently urinary incontinence accompanies these seizures with the fencing posture.

Practitioners frequently have arguments about the minimal duration of seizures required for calling elementary partial seizures a form of status epilepticus. In other words, when are focal seizures considered "unvarying, enduring and fixed," so as to be called status epilepticus? For focal seizures, where consciousness is preserved, we accept continuous clinical and electrographic seizures of 30 min or more as clear status epilepticus. When focal seizures persist as long as 10–15 min, status epilepticus should be suspected and electrographic verification sought.

Kojewnikow's Syndrome

[Synonyms: epilepsia partialis continua of Kojevnikov (Gastaut and Tassinari 1975), epilepsia partialis continuans of Koshewnikoff (Roger et al. 1974)].

The true epilepsia partialis continuans of Kojewnikow (Kojewnikow 1895) consists of (a) a combination of Bravais-Jacksonian march of repeated clonic jerks and in between the march of seizures, and (b) the appearance of myoclonus or myoclonias in the same body parts engaged by the Bravais-Jacksonian march, but without reflecting somatotopic organization of the motor cortex. In 1966, Juul-Jensen and Denny-Brown studied the pathology of epilepsia partialis continuans and observed the presence of multiple subcortical lesions in addition to the rolandic focus. These observations are consistent with Gastaut's concept that partial status epilepticus signifies the involvement of cortico-subcortical interconnections by epileptogenic discharges, e.g., corticothalamic sectors.

In 1970, Bancaud et al. pointed out the existence of two types of Kojewnikow's syndrome:

1. The first type is seen in both adults and children, and is caused by a rolandic lesion of various etiologies such as focal ischemia, glioblastoma multiforme, astrocytoma, or angioma venosum. The clinical manifestations are as described above, but myoclonias appear later than the somatomotor seizures. The electroencephalogram has normal background activities, while spikes, sharp waves, or rhythmic 6- to 18-Hz rapid spikes occupy the rolandic region. Aside from the possible progressive behavior of the underlying etiology, this form of Kojewnikoff's syndrome does not show the malignant course of progressive dementia and paralysis seen in the second type. Moreover, when the underlying etiology is a static lesion, neurosurgical excision of the seizure focus, when possible, has led to a cure of the syndrome.

2. The second form of Kojewnikow's syndrome is a malignant progressive illness probably caused by a slow viral agent (though this is still unproven). It is peculiar to children and adolescents, most often appearing at 6 years of age. The

1. The reader should note the different spellings of Kojewnikoff's, Kojewnikow's, or Kojevnikov's, used by various authors for this syndrome.

age of onset ranges from 2 to 10 years. Progressive mental deterioration appears with paralysis and other focal neurological signs. Myoclonias appear early in the course of illness, occupying the same site as that engaged by the Bravais-Jacksonian march. But soon the myoclonias become erratic, diffuse, and persist during sleep. Partial somatomotor seizures frequently evolve to secondary tonic–clonic seizures. The EEG shows diffuse 0.5- to 3-Hz irregular slow waves as background rhythms deteriorate. Interictal and ictal rhythms occupy other areas aside from the rolandic region. Brain imaging shows diffuse, progressive multiple lesions.

Rarer Forms of Partial Status Epilepticus Without Impairment of Consciousness

Before the 1980 International Symposium on Status Epilepticus in Santa Monica, California, the best documented forms of partial status epilepticus were secondary tonic–clonic status, focal somatomotor status, and complex partial status epilepticus. At the 1980 symposium and during the last 5 years, prolonged and fixed epileptic states characterized by isolated fear (McLachlan and Blume 1980; Zappoli et al. 1983), auditory simple sensations (noise, pure tone, or repeated hiss or chants), auditory hallucinations, speech arrest, cognitive symptoms (Drake and Coffey 1983; Giorvani et al. 1985; Nakada et al. 1984; Sacquegna et al. 1981; Sommerville and Bruni 1983; Wieser et al. 1985) and true dysphasia (Billard et al. 1981; De Pasquet et al. 1976; Dinner et al. 1981; Marrosu et al. 1983) have been described (Table 14.2).

Table 14.2. Partial status epilepticus

Well documented forms

A. Convulsive status epilepticus
- I. Secondarily generalized convulsive status
  - a. Tonic–clonic status with partial onset
  - b. Tonic status, e.g., in Lennox-Gastaut syndrome
  - c. Secondary myoclonic status, e.g., in progressive myoclonus syndromes
- II. Focal or simple partial status
  - a. Partial motor status including somatomotor status
  - b. Postural motor status
  - c. Epilepsia partialis continuans of Kojewnikow

B. Nonconvulsive status epilepticus
- I. Complex partial status
  - a. Complex partial status of hippocampal or hippocampal and amygdalar origin
  - b. Complex partial status of presumed extratemporal origin
- II. Late onset spike–wave stupor (presumed secondary bilateral synchrony)
- III. Nonconvulsive focal status
  - a. Partial sensory status including somatic sensory status, and visual sensory status and auditory sensory status
  - b. Partial status with vegetative or autonomic symptoms
  - c. Partial status with cognitive symptoms, e.g., déjà vu, jamais vu, vivid recall
  - d. Partial status with affective symptoms, e.g., fear

Table 14.2 (*continued*)

Documentation required[a]
1. Simple partial status with affective symptoms, e.g., elation
2. Simple partial status with cognitive symptoms, e.g., forced thinking, double consciousness
3. Complex partial status of opercular origin
4. Complex partial status of medial occipital–hippocampal origin
5. Complex partial status of lateral temporal neocortical origin
6. Complex partial status of frontal lobe origin, e.g., cingulate gyrus, or supplementary motor or prefrontal or orbitofrontal origin
7. Complex partial status of amygdalar origin

[a] Documentation by CCTV-EEG and/or stereo-EEG.

In 1980, Racy et al. described two adults who presented with epileptic aphasia as a first onset of prolonged monosymptomatic status epilepticus. These two patients had no previous history of seizures and the epileptic nature of the aphasia was confirmed by EEG and a dramatic therapeutic response to anticonvulsant medication.

In 1981, Billard et al. described four cases of acquired aphasia in epileptic children, associated with subcontinuous bitemporal paroxysmal activities during sleep. Clinical improvements always followed the decrease or the unilateralization of paroxysmal activities. Persistence or aggravation of aphasia was observed when paroxysmal activities became bitemporal and subcontinuous. In the same year, Dinner et al. reported a 60-year-old diabetic who was aphasic for 12 days due to epileptiform paroxysms in the left hemisphere. Marrosu et al. also reported epileptic aphasia and a form of partial status in 1983.

In a case report of psychomotor status epilepticus, Wieser documented long-lasting hallucinations of music without impairment of consciousness during ictal paroxysms of the right gyrus of Heschl (Wieser 1980). Isolated fear in a similar patient with complex partial status epilepticus was documented by McLachlan and Blume (1980).

Sacquena et al. (1981) reported a 16-year-old patient whose only abnormalities during partial status epilepticus consisted of impaired cognitive functions detected by formal neuropsychology tests. Vigilance, orientation, and behavior were unimpaired. Although EEG showed diffuse slow waves and the electroclinical pattern was interrupted by break of contact concomitant with high-frequency spike discharges, the condition was considered to be a form of partial seizure.

More recently, Wieser et al. (1985) assessed cognitive functions with tachistoscopic tasks during limbic status epilepticus in the left side and proved the association of impaired lexical decision task performance (a left hemisphere function) with sustained ictal paroxysms in the left hippocampus. Facial matching task performance (a right hemisphere function) was normal. In the same patient, aura continua of olfactory and/or gustatory sensations also corresponded to hippocampal status activity. Interestingly, in two patients (cases 3 and 4) these authors also associated left hippocampal status epilepticus with behavioral and personality changes, namely, episodic aggressivity, unusual stickiness, and episodes of sexual exhibition. These latter behavioral manifestations disappeared after amygdalohippocampectomy.

Complex Partial Status Epilepticus

[Synonyms: prolonged epileptic twilight state; prolonged epileptic fugue; psychomotor status epilepticus; temporal lobe status epilepticus; poriomania].

In 1975, Gastaut and Tassinari wrote, "temporal lobe status epilepticus has rarely been described electrographically and clinically. Temporal lobe status epilepticus is a rare condition". In 1970, Oller-Daurella pointed out that he could find only three studies with complete electrographic and clinical data. In 1980, at the Santa Monica International Symposium, Gastaut (1983) and Treiman and Delgado-Escueta (1983) noted that about 50 possible cases had been reported, 24 of them as individual case reports. Since then more than 80 further cases of complex partial status epilepticus have been documented in 16 separate studies (Aguglia et al. 1983; Ballenger et al. 1983; Behrens 1980; McBride et al. 1981; McLachlan and Blume 1980; Nakada et al. 1984; Pritchard and O'Neal 1984; Russell et al. 1980; Sacquegna et al. 1981; Shapiro et al. 1981; Treiman and Delgado-Escueta 1983; Treiman et al. 1981; Weiner 1981; Wieser 1980; Wieser et al. 1985; Zappoli et al. 1983). The literature, therefore, has now listed over 100 cases of documented psychomotor status epilepticus over the past 25 years. In our opinion, complex partial status epilepticus should no longer be considered rare. It is still an infrequent condition and we now encounter three to four cases of psychomotor status epilepticus a year. Improved recognition and documentation of this disorder is perhaps best explained by the increased number of intensive CCTV–EEG monitoring units around the world.

If status epilepticus can assume as many forms as there are varieties of epileptic seizures, complex partial status can present in as many forms of complex partial epilepsies. Accordingly, complex partial epilepsies may be either temporal or frontal lobar in origin (see Tables 14.3 and 14.4), and epileptogenic paroxysms may actually originate in the amygdalohippocampal complex or in structures outside the amygdala or hippocampus. In the latter instance, a secondary invasion by epileptogenic paroxysms of the amygdalohippocampal complex may occur.

In contrast to the case in simple partial status epilepticus, impairment of consciousness is present in complex partial status, usually because epileptogenic paroxysms have involved amygdalohippocampal regions on both sides and/or deeper subcortical areas. Gastaut and Tassinari (1975) have suggested that two types of complex partial status epilepticus can be distinguished. One type consists of frequently recurring complex partial seizures that display classic psychomotor, psychosensory, or psychoaffective symptoms, but with interictal recovery of consciousness to nearly normal. The second form of complex partial status, according to Gastaut and Tassinari, consists of continuous long-lasting episodes of mental confusion and/or psychotic behavior with or without automatic behavior.

Our recent experiences have provided two explanations for the existence of these two forms of complex partial status epilepticus. Firstly, in patients with complex partial status of amygdalohippocampal origin (proven by stereo-EEG) or complex partial status of anterior temporal polar origin (presumed site of origin) or of lateral temporal origin (presumed site of origin) but with spread to the amygdalohippocampal complex, the above-described forms of complex partial status may constitute two ends of a continuum of clinical behavior. As long as a patient is having repeated or continuous complex partial seizures with stereotyped and reactive automatisms, and does not fully recover between seizures to a completely

Table 14.3. Temporal lobe epilepsies[a] (Appel 1986)

Regional localization	Aura	Clinical seizure patterns	EEG and stereo-EEG	Brain imaging	Psychology[b]	Common etiologies
Hippocampal epilepsy[a] or medial basal, limbic epilepsy	Strange, indescribable feeling, experiential hallucinations, interpretative illusions	Arrest (motionless stare) oral and alimentary automatisms and amnesia averaging 2 min >60% with s TC	*Interictal*: anterior temporal sharp waves, especially during sleep *Ictus*: initial unilateral flattening, especially temporal lobe and background EEG changes; or nonfocal or nonlateralizing surface EEG changes; or focal or lateralized. 4- to 6-Hz sharp waves *Stereo-EEG*: high-frequency 16- to 28-Hz low-voltage spikes building up in hippocampus, propagating to amygdala and cingulate and parietal regions	*Skull X-ray*: asymmetry of skull, especially sphenoid fossa *CAT scan*: usually negative *PEG*: enlarged temporal horn *Metrizamide CT scan*: signs of tentorial herniation *NMR*: may be useful *Bilateral carotid angiography*: rule out anterior choroidal aneurysm	Impaired recent memory (verbal-dominant hemisphere; visuospatial-nondominant hemisphere)	*More commonly*: incisural or hippocampal sclerosis *Less frequently*: gangliogliomas, hamartomas, AV malformations, astrocytomas, oligodendrogliomas, focal gliosis, rarely aneurysms (cicatrix)
Amygdalar epilepsy or anterior polaramygdalar epilepsy	Rising epigastric discomfort, nausea, autonomic symptoms and signs including borborygmia, belching, pallor, fullness of face, flushing of face, arrest of respiration, pupillary dilation. Fear, panic, olfactory–gustatory hallucinations	Gradual onset of unconsciousness, staring, oral and alimentary automatisms, confusion, amnesia Less commonly (30%) with sec. TC seizures; REM sleep facilitates partial symptomatology	*Scalp EEG*: same as above *Stereo-EEG*: high-frequency, low-amplitude, 16- to 28-Hz rhythm in amygadala or amygdala and anterior temporal pole with spread to homolateral fronto-orbital regions and contralateral homologous areas	Same as above *Metrizimide CT scan*: may be useful	Reduced autonomic responsivity[c]	Gangliogliomas, focal gliomas, atypical cell layers in amygdala (and hippocampal formation), anterior temporal pole gliosis, AV malformations, hamartomas, trauma with focal gliosis
Lateral posterior temporal–parietal epilepsy	Auditory hallucinations, visual perceptual hallucinations, language disorder when lateralized to hemisphere dominant for language	Dysphasia, disturbed orientation, and prolonged auditory hallucinations; head movement to one side; sometimes staring automatisms and amnesia	*EEG*: lateral midtemporal or posttemporal spikes *Stereo-EEG*: low-frequency rapid spikes (16- to 28-Hz) building up in the supramarginal angular gyrus and posterior temporal regions	Normal skull films, but CT, PEG, A/G, PET, and NMR are recommended	*Dominant*: anomia (Benson); impaired word-sorting (Hiatt) *Nondominant*: tonal memory and Timbre tests (Seashore), McGill Picture Anomalies *Lateralizing*: dichotic auditory detection	Most commonly due to trauma with focal gliosis postinfectious, glioma, postcerebral infarction

Table 14.3 (*continued*)

Table 14.3 (*continued*)

Regional localization	Aura	Clinical seizure patterns	EEG and stereo-EEG	Brain imaging	Psychology[b]	Common etiologies
Opercular or island of Reil or insular epilepsy	Vestibular hallucinations, followed by borborygmi, belching, autonomic symptoms or olfactory-gustatory hallucinations due to spread to medial temporal structures	Similar to amygdalar epilepsy except for initial vestibular hallucinations	*EEG and stereo-EEG*: isolated opercular rapid spikes (16- to 28-Hz) with minimal spread	Normal skull films, CT, PEG, but PET and NMR may be useful	Unknown	Glioma, astrocytoma, AV malformations, aneurysms, post-cerebral infarction

[a] Synonyms: Primary rhinencephalic psychomotor epilepsy of Bancaud, Szikla and Talaraich et al. (1965)
CPS, type I of hippocampal origin (Delgado-Escueta and Walsh 1985)
Mesial–basal limbic epilepsy (Wieser 1983)
Constitutes 70%–80% of temporal lobe epilepsies
Commonly combines with amygdalar epilepsy
Mode of recurrence: random or cluster

[b] In this column are listed the neuropsychological tests which most specifically indicate functional damage in the region of the focus. However, it is important to note that functional damage and the seizure focus are not necessarily in the same place. In particular, recent memory deficits, suggestive of hippocampal damage, frequently occur in complex partial epilepsy, especially if there is a history of status epilepticus. A discrepancy of 20 or more points between verbal and nonverbal IQ suggests generalized dysfunction of one hemisphere. If confirmed, this helps to lateralize the focus, although it does not indicate the location of the focus within the hemisphere. Psychomotor slowing is a very common but nonspecific sign of organic brain damage and/or antiepileptic drug side effect.

[c] Hypothesized correlate based on isolated report.

Table 14.4. Frontal lobe epilepsies[a]

Regional localization	Clinical seizure patterns	EEG and stereo-EEG	Brain imaging	Psychology[e]	Common etiologies
Supplementary motor	Postural, PMT, vocalization, speech arrest, fencing, PCS, urinary incontinence	Flattening rhythmic polyspike (16- to 24-Hz) and secondary generalization Depth electrode exploration[b]	*Normal skull X-rays and CTs*: Focal atrophic lesion on PEG. PET and NMR may be useful	*Dominant*: impaired verbal fluency *Nondominant*: impaired design fluency	Focal atrophy, tumors, AV malformations
Cingular	PCS with initial automatisms with sexual features, vegetative signs, urinary incontinence	Depth electrode exploration[c]	*Normal skull X-rays; CT; PEG*. PET and NMR may be useful	*Dominant*: impaired verbal fluency *Nondominant*: impaired design fluency	Focal atrophy, tumors, AV malformations
Orbitofrontal	PCS with initial automatisms; olfactory hallucinations	Flattening rhythmic polyspikes (16- to 24-Hz) and secondary generalization. Nasoethmoidal and orbital electrodes[d]	*Skull*: signs of trauma; *CT*: signs of trauma; *PEG*: focal atrophy. PET and NMR may be useful	Lability of mood[f]	Trauma, astrocytomas, oligodendrogliomas
Dorsolateral	PMT, versive, aphasia, PCS with initial automatism	Satisfactory interictal and ictal localization	*Normal skull X-rays. CT*: usually localizes lesion; *PEG*: often not required. PET and NMR may be useful	Perseveration, poor recency judgments, response disinhibition	Trauma, astrocytomas, oligodendrogliomas

PMT, partial motor tonic; PCS, partial complex seizure

[a] Very frequent, short attacks stimulating absence with minimal or no postictal confusion can occur in frontal lobe epilepsies. When bizarre behaviors appear as automatisms longer attacks are frequently mistaken for psychogenic seizures.

[b] Often required.

[c] Mandatory.

[d] Varies from poor to good in demonstrating cerebral lesion.

[e] In this column are listed the neuropsychological tests which most specifically indicate functional damage in the region of the focus. However, it is important to note that functional damage and the seizure focus are not necessarily in the same place. In particular, recent memory deficits, suggestive of hippocampal damage, frequently occur in complex partial epilepsy, especially if there is a history of status epilepticus. A discrepancy of 20 or more points between verbal and nonverbal IQ suggests generalized dysfunction of one hemisphere. If confirmed, this helps to lateralize the focus, although it does not indicate the location of the focus within the hemisphere. Psychomotor slowing is a very common but completely nonspecific sign of organic brain damage and/or antiepileptic drug side effect.

[f] Hypothesized correlate based on isolated report.

normal state, the patient can be considered to be in status. On recovery from such psychomotor status, the patient is amnesic for all events. Continuing cycles of psychomotor attacks with no recovery of consciousness between automatisms occur during the height of the cycles of electrographic paroxysms. Repeated psychomotor attacks with recovery of consciousness between attacks, on the other hand, is commonly a prelude to psychomotor status. Long-lasting confusion and/or psychotic behavior can be found at the tail end of the episode of psychomotor status. Wieser (1980) has apparently had experiences similar to ours and recently reported transition from repeated discrete seizures, during which his patient remained fully conscious and oriented, to a continuous epileptic clouded state. A second explanation for these two forms of psychomotor status, reported by Gastaut and Tassinari (1975), is that prolonged confusion and/or psychosis and bizarre forms of automatisms may be the main manifestation of psychomotor status epilepticus of extratemporal or presumed frontal lobe origin.

The practitioner must also realize that when frequently recurring psychomotor attacks occur with full recovery of consciousness between attacks, an aura continua may linger in between the periods of loss of consciousness. In such an instance, a fixed and lasting epileptic state is present. In practice, two or three successive psychomotor attacks even with preservation of consciousness between attacks deserve vigorous treatment with intravenous benzodiazepines, because these atttacks usually herald psychomotor status epilepticus. A prolonged state of mental confusion which lasts more than 30 min associated with psychomotor symptomatology and epileptiform ictal patterns on the EEG must be considered a form of psychomotor status and must be treated as such in order to prevent chronic impairment in recent memory (Treiman and Delgado-Escueta 1983; Treiman et al. 1981).

Types of Complex Partial Status

From a purely descriptive point of view, two forms of complex partial status epilepticus may be recognized on the CCTV:

1. Cyclic forms of psychomotor status (Fig. 14.1) where the hippocampus and amygdala are primarily or secondarily involved. Some cyclic forms of psychomotor status have now been proven through stereo-EEG to be hippocampal or hippocampal–amygdalar in origin (see Table 14.5). However, a number of cyclic forms of psychomotor status recently reported by Ballenger et al. (1983) involved mental subnormality and cerebral hemiatrophy and behavioral manifestations of extratemporal complex partial epilepsy, e.g., tonic posture, partial motor and contraversive head and eye movements (cases 5–7). Similar manifestations of complex partial status were reported earlier by Lugaresi et al. (1971), McBride et al. (1981 [case 4]), Heintel (1969), Delgado-Escueta et al. (1974), and Bauer (1976). In a publication by Williamson et al. (1985), some cyclic forms of psychomotor status were proven to be frontal lobar in origin. Thus, it appears that cyclic forms of psychomotor status can be temporal, extratemporal, or frontal lobar in origin.

2. Noncyclic forms of psychomotor status. Most of these forms of psychomotor status display electroclinical characteristics which suggest a frontal lobe origin. Some complex partial seizures are both frontal and temporal in origin and it is conceivable that complex partial status also can be both frontal and temporal in

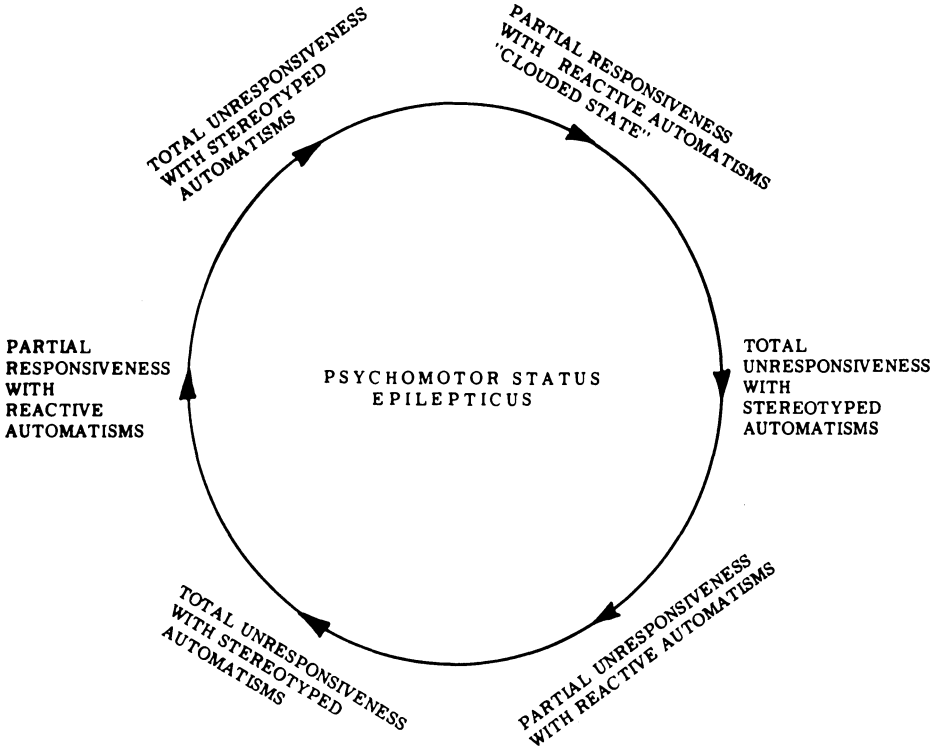

Fig. 14.1. Clinical phases of complex partial status. The patient alternates between total unresponsiveness with stereotyped automatisms (phase I) and partial responsiveness with reactive automatisms (phase II). (Treiman and Delgado-Escueta 1980)

Table 14.5. Criteria for diagnosis of complex partial status epilepticus

1a.	*Cyclic variety*: recurrent complex partial seizures without full recovery of consciousness between seizures, or a continuous "epileptic twilight state," with cycling between an unresponsive state, with oral–alimentary automatisms and stereotyped perseverative gestures or partial motor signs, and partially responsive phases with reactive automatisms
	or
1b.	*Noncyclic variety*: prolonged state of confusion and reactive automatisms with or without partial motor, postural, contraversive head, and eye movements
2.	Ictal EEG with recurrent epileptiform patterns like those seen in isolated complex partial seizures occurring against an abnormal EEG background
3.	A prompt observable effect of intravenous antiepileptic drug on both ictal EEG and clinical manifestations of the status
4.	Interictal EEG with a consistent epileptiform focus, usually in one or both temporal or frontal lobes

origin. The behavioral features of such frontotemporal psychomotor status have yet to be described.

Cyclic Types of Complex Partial Status

a) Psychomotor Status of Hippocampal, Amygdalohippocampal, or Amygdalar Origin.

[Synonyms: status epilepticus in mesial basal limbic epilepsy; primary rhinencephalic psychomotor epilepsy; type I psychomotor seizures of hippocampal origin]

Table 14.5 outlines our criteria for the diagnosis of complex partial status epilepticus. The fundamental characteristic of complex partial seizures of amygdalohippocampal origin, and the characteristic that allows differentiation from complex partial status of frontal lobe origin, spike wave stupor, absence status, and other causes of twilight states, is the cyclicity of clinical behavior observed during complex partial status.

We have observed two separate behavioral phases during complex partial status in 15 patients with proven or presumed hippocampal or amygdalohippocampal epilepsy (Fig. 14.1): (a) a continuous twilight state, with partial and amnestic responsiveness, partial speech or speech arrest, and quasipurposeful complex reactive automatisms, frequently interrupted (b) by the arrest reaction with motionless staring, total unresponsiveness, and speech arrest, or by vocalization, oroalimentary and perseverative gesticulatory stereotyped automatisms. During the motionless, staring phase, unifocal or regional hippocampal and amygdalar ictal 6- to 20-Hz rhythms appear against an abnormal background of the surface scalp EEG. As hippocampal and amygdalar paroxysms spread, surface temporal leads on the lateral and medial surfaces of the scalp show epileptogenic discharges. During the twilight phase with partial responsiveness, the EEG pattern is different from that during the motionless staring phase. In almost all cases, bilateral slow waves appear diffusely and especially posteriorly, frequently intermixed with low-voltage fast activity. Rarely, as reported in one patient, the EEG background is normal, and left anterior-temporal triangular slow waves are seen (Delgado-Escueta et al. 1974).

Clinically and electroencephalographically, the behavioral phases observed in these 15 cases of complex partial status epilepticus were identical with the clinical phases recorded on CCTV–EEG in individual complex partial seizures of amygdalohippocampal origin described by Delgado-Escueta and Walsh (1985) (the arrest reaction with motionless stare, stereotyped oroalimentary automatisms, and reactive automatisms). These observations indicate that complex partial status epilepticus of amygdalohippocampal origin consists of continuously recurring cycles of the clinical phases of individual complex partial seizures. Initially, discrete serial seizures may occur. Eventually, the patient fails to recover completely from the longer state of partial and amnestic responsiveness before the next cycle of arrest staring and oroalimentary stereotyped automatisms begin. At this point the patient should be considered to be in complex partial status. The frequency of the cycles increases until the patient is in a continuous epileptic twilight or fugue state. However, even in the most severe forms of complex partial status of amygdalohippocampal origin, careful observation should allow detection of the clinical phases and concomitant cycling of the EEG patterns. When the repetition of psychomo-

tor seizures slow down, longer periods of confusion without stereotyped automatisms become more apparent, longer intervals between staring and oroalimentary automatisms occur, and a fixed state of confusion is all that is left. The latter is especially common when antiepileptic drugs incompletely suppress psychomotor status.

Complex partial seizures can be purely amygdalar or purely hippocampal in origin. The behavioral manifestations on the CCTV-videotape are identical in both cases. The two forms of complex partial seizure can be differentiated by their initial warning symptoms and signs (aura) elicited at the onset of seizures. Pure hippocampal epilepsy commonly starts with a strange, indescribable feeling and some patients report experiential hallucinations (déjà vu, jamais vu, double consciousness) and interpretative illusions. Pure amygdalar epilepsy frequently shows autonomic symptoms and signs, e.g., pupil, heart rate, and respiratory rate and pattern changes. The patient describes rising epigastric discomfort, nausea, fear, or panic. Most often, epileptogenic paroxysms spread quickly in the amygdalar and hippocampal regions as olfactory and gustatory hallucinations are experienced. However, it is most common to see psychomotor seizures originate from both hippocampus and amygdala. Pure hippocampal seizures are less frequent and pure amygdalar seizures are rare.

In many cases of psychomotor status reported in literature, the cyclic nature of the fixed epileptic state has been adequately documented. Most of the cases, however, appear to have manifestations consistent with complex partial seizures of extratemporal origin, suggesting a secondary invasion of medial temporal lobe structures. Infrequently some patients appear to have clinical manifestations suspicious of hippocampal and amygdalar origin (Markand et al. 1978; McBride et al. 1981 [case 2]; Ballenger et al. 1983 [case 8]). Most of our cases in the last 5 years are of the cyclic variety, perhaps because we have been studying amygdalar and hippocampal epilepsy more intensively during the surgical evaluation process. In the discrete or serial form of complex partial status, as first described by Gastaut and Tassinari (1975), cyclicity can also be easily identified because the patient has a series of complex partial seizures, with partial clearing of mentation between the seizures.

b) Secondary Involvement of the Amygdalohippocampal Regions by Lateral Posterior Temporal Neocortical Epilepsy, Opercular Epilepsy, Occipital–Hippocampal Epilepsy, and Frontal Lobe Epilepsy

Theoretically speaking, psychomotor status can start from the anterior temporal pole, the operculum, the medial occipital–hippocampal regions, and the frontal lobe. Conceivably, these cases of psychomotor status also manifest cyclic phases of total unresponsiveness, arrest reaction with staring, oroalimentary automatisms, stereotyped perseverative and gesticulatory automatisms, and partial responsiveness with reactive automatisms. However, the clinical symptomatology and signs of individual psychomotor attacks and the initial warning signs and symptoms (aura) should distinguish the various sites of origin for the propagating epileptogenic paroxysms. As mentioned above, many of the psychomotor status reports in the literature in fact suggest secondary involvement of the hippocampus and amygdala by propagating paroxysms from the frontal lobe. Only De Pasquet et al.'s 1976 case report suggests an opercular origin. A search for psychomotor status which starts from the anterior temporal pole, the medial occipital–hippo-

campal axis, or the operculum should be conducted to document the existence of such cases.

The important afferent connections of the hippocampus and the amygdala frequently lead to their involvement by propagating epileptiform paroxysms. These propagating paroxysms may produce the arrest reaction with staring, lip smacking, chewing, and gesticulatory automatisms when they invade both hippocampal regions and subcortical way-stations. A review of individual attacks reveals vestibular hallucinations, visual illusions or hallucinations, and unilateral upper limb gesticulatory exploratory automatisms in lateral posterior temporal neocortical epilepsy. Auditory hallucinations, nausea, somatesthetic hallucinations, pupillary and facial color changes, feelings of warmth, and unilateral head and upper limb tonic posture or clonic jerks are observed in opercular seizures. Simple visual hallucinations (dots, scotomata) in the central visual field together signal the start of occipital hippocampal epilepsy. Psychomotor seizures of extratemporal origin frequently show, in the early part of consciousness, partial somatomotor, postural motor changes of head, eyes, or limbs, fencing postures or sudden bizarre bipedal or bilateral arm automatisms, and ambulatory automatisms.

Noncyclic Types of Complex Partial Status

Reports of psychomotor status epilepticus by Mayeux and Lueders (1978), Gastaut et al. (1956), McBride et al. (1981 [patient 4]), and Ballenger et al. (1983 [cases 1–3]) described prolonged confusion or an organic psychosis without delineation of any of the symptoms or signs of amygdalohippocampal epilepsy (arrest reaction, oroalimentary automatisms, gesticulatory perseverative automatisms, and reactive automatisms) or cycles of such symptoms or signs. We have observed such forms of prolonged confusion in five cases of psychomotor status of extratemporal origin, presumably coming from the frontal lobe. In these five cases, we presumed an origin from the orbital–frontal lobe, the frontal pole, or medial regions of the cingulate gyrus because of the presence of somatomotor signs and urinary incontinence. In a forthcoming publication, Williamson et al. provide stereo-electroencephalographic proof that some non-cyclic forms of psychomotor status epilepticus are frontal lobar in origin.

EEG of Complex Partial Status

The ictal scalp EEG patterns reported for complex partial status of hippocampal or amygdalohippocampal epilepsy are essentially those reported for individual complex seizures by Ajmone-Marsan and Van Buren (1958), Wieser et al. (1985), and Delgado-Escueta and Walsh (1985). The specific pattern seen in an individual case appears to be determined by the frequency with which the individual cycles repeat and by the overall duration of the attack at the time of recording. Thus, in most of our 15 cases, in Heintel's cases (1969), and in Engel et al.'s cases (1978), low-voltage fast activity was seen at the start of the cycle, followed by rhythmic buildup of higher amplitude but lower frequency discharges, just as is seen in isolated complex partial seizures. In cases of longer duration before the EEG is recorded, as in another of our cases (Delgado-Escueta et al. 1974), no low-voltage

fast activity is seen, but rather recurrent paroxysms of rhythmic sharp waves from one or the other sphenoidal electrode superimposed on a generally slow background. Still others have described continuous sharp- and slow-wave discharges (Behrens 1980; Lugaresi et al. 1971) or continuous spikes, polyspikes, or sharp waves (Henriksen 1973; Markand et al. 1978; Mayeux and Lueders 1978) from the temporal regions.

There are now four reports of depth electrode recording during complex partial status. Wieser (1980) initially described a 22-year-old woman with medically intractable complex partial seizures who was evaluated for temporal lobectomy with depth electrodes. During the last 2 days of the recording period, she developed "psychomotor status." The episode began as frequently recurring focal seizures characterized by "strange feeling, anxiety, and sometimes ... visceral symptoms" and associated with right hippocampal discharges that usually started in the amygdala. During the focal attacks, the patient remained fully conscious and oriented. The seizures progressed to produce impairment of consciousness and more elaborate psychosensory seizures. When consciousness was clouded, bilateral hippocampal discharges were seen. Ultimately the patient developed continuous electrical status of the right transverse gyrus of Heschl. When the right-sided hippocampal electrical activity became more and more monotonous, it triggered activity of the left hippocampus, and the patient became increasingly anxious and stopped her animated conversation. During more tonic seizure activity, which recurred crescendo-like at the beginning of the continuous status, the patient stared with fixed gaze and frozen face and then usually brought her left hand to her heart and turned her face slightly to the left. The stare and repeated stereotyped automatisms described here may correspond with phases I and II of isolated complex partial seizures previously described by Delgado-Escueta and co-workers (Delgado-Escueta et al. 1977, 1982a; Delgado-Escueta and Walsh 1985). Wieser (1980) suggested that the continuous form of complex partial seizures may best be thought of as a prolonged localized afterdischarge.

Most recently, Wieser et al. (1985) reported three additional cases of complex partial status. These patients provided the opportunity for stereo-EEG study of unilateral left limbic status during gustatory aura continua, the behavioral syndrome described by Geschwind (stickiness, aggressivity, etc.) and impaired lexical decison task performance.

In the last 3 years, we also have had the opportunity to perform stereo-EEG in three patients with hippocampal or amygdalohippocampal epilepsy during psychomotor status epilepticus (see Figs. 14.2–14.4). The findings were essentially similar to the individual psychomotor attacks, with the exception that seizures recurred one after the other in cyclic fashion. The fourth report on stereo-EEG is by Williamson et al. (1985), where both cyclic and noncyclic forms of psychomotor status epilepticus are observed in frontal lobe epilepsy.

In most reported cases of complex partial status epilepticus the interictal EEG has exhibited spikes, spike–waves, or sharp waves from one or both temporal lobes, similar to the interictal epileptiform discharges usually associated with a temporal lobe epileptic focus. A few cases have shown temporal–occipital foci in the interictal EEG after temporal–occipital discharges during the episode of status (Behrens 1980; Henriksen 1973; Lugaresi et al. 1971; Markand et al. 1978; Mayeux and Lueders 1978).

Identification of interictal epileptiform discharges from a region of the brain known to produce complex partial seizures should be considered an essential

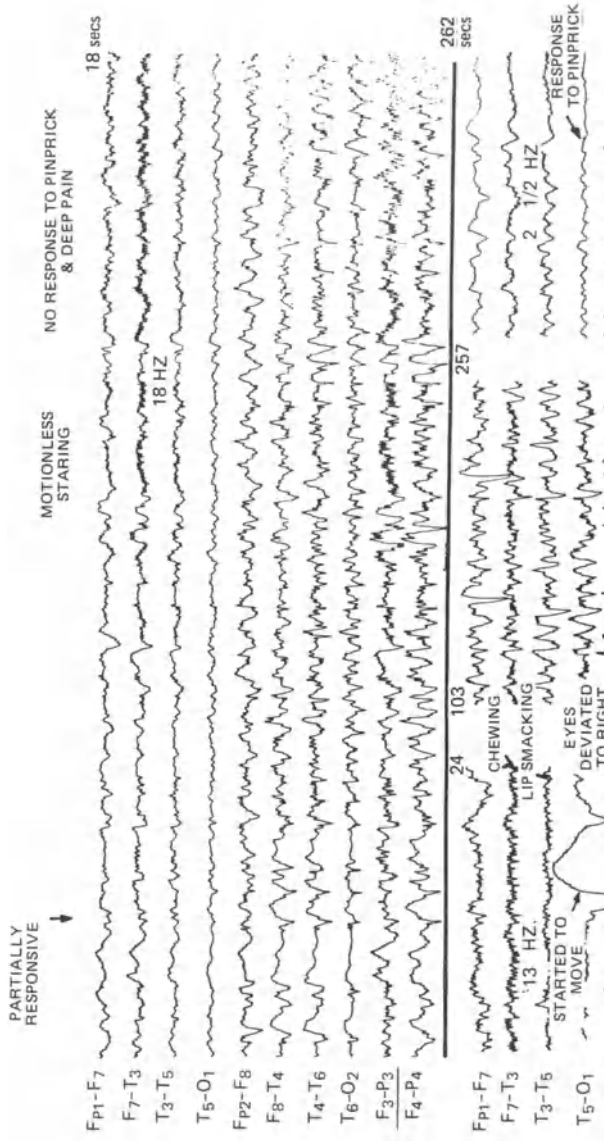

Fig. 14.2. Psychomotor status epilepticus in a 47-year-old woman. 16-Hz rhythms appear in the left anterior temporal region (channels 1–3) at the onset of stare and phase of total unresponsiveness. The phase of partial responsiveness is characterized by chewing, lip smacking, and deviations of the eyes to the right. Rhythmic slow waves are seen on the EEG bilaterally. (Treiman and Delgado-Escueta 1980)

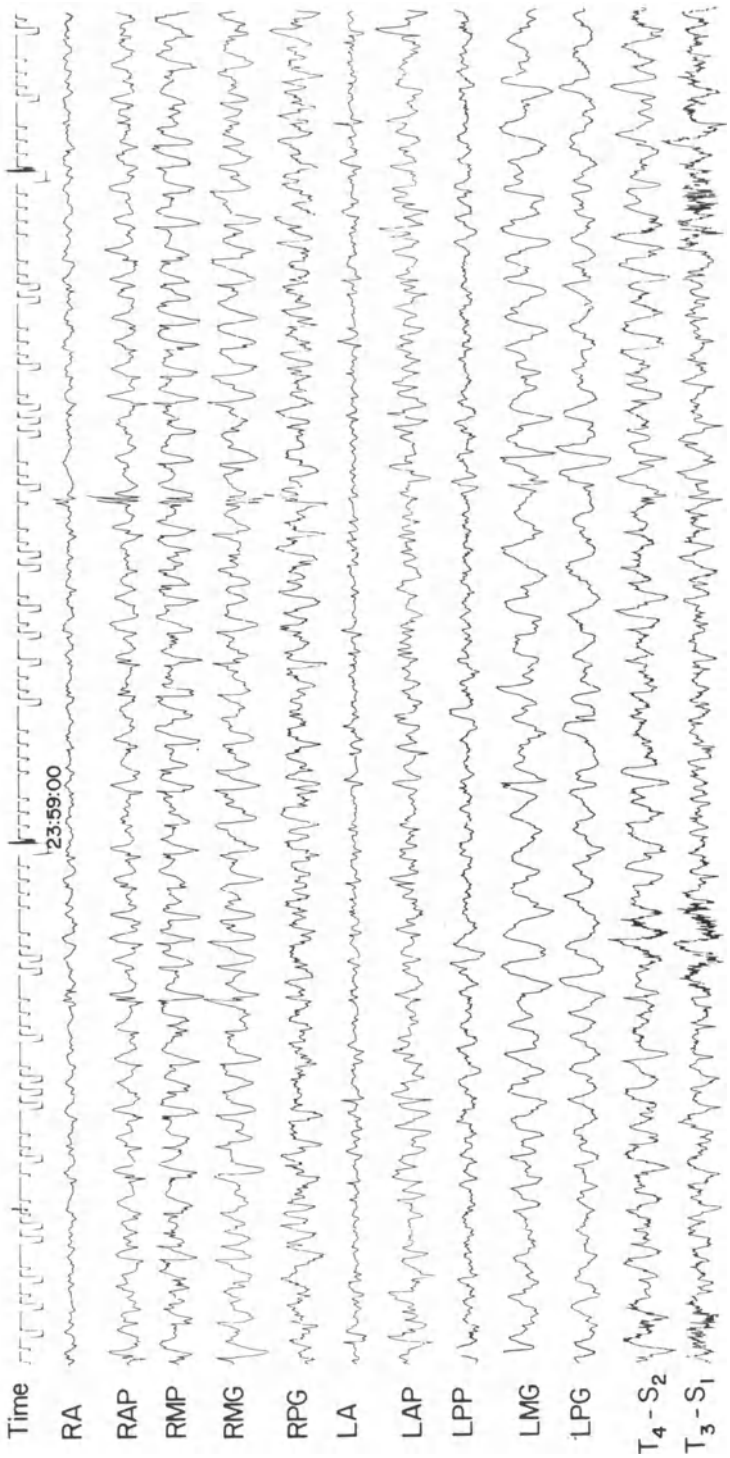

Fig. 14.3a

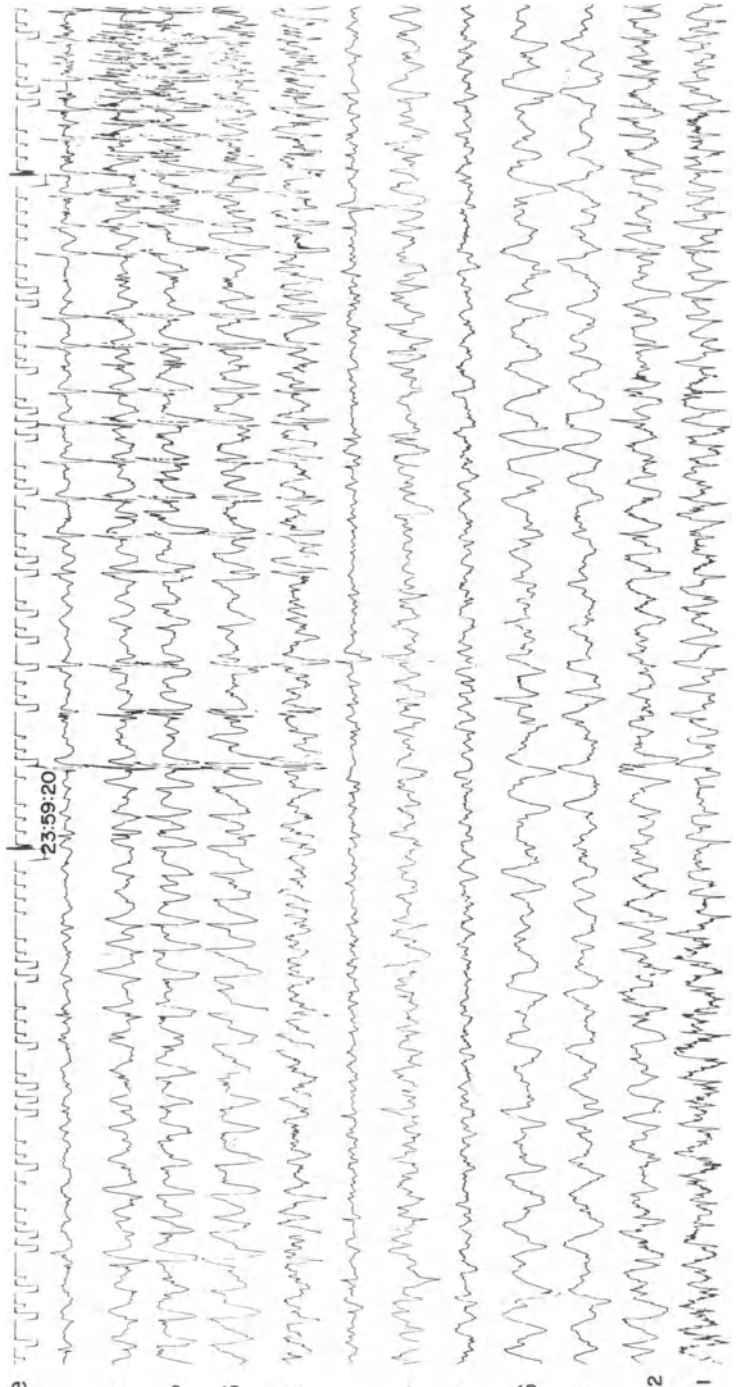

Fig. 14.3b

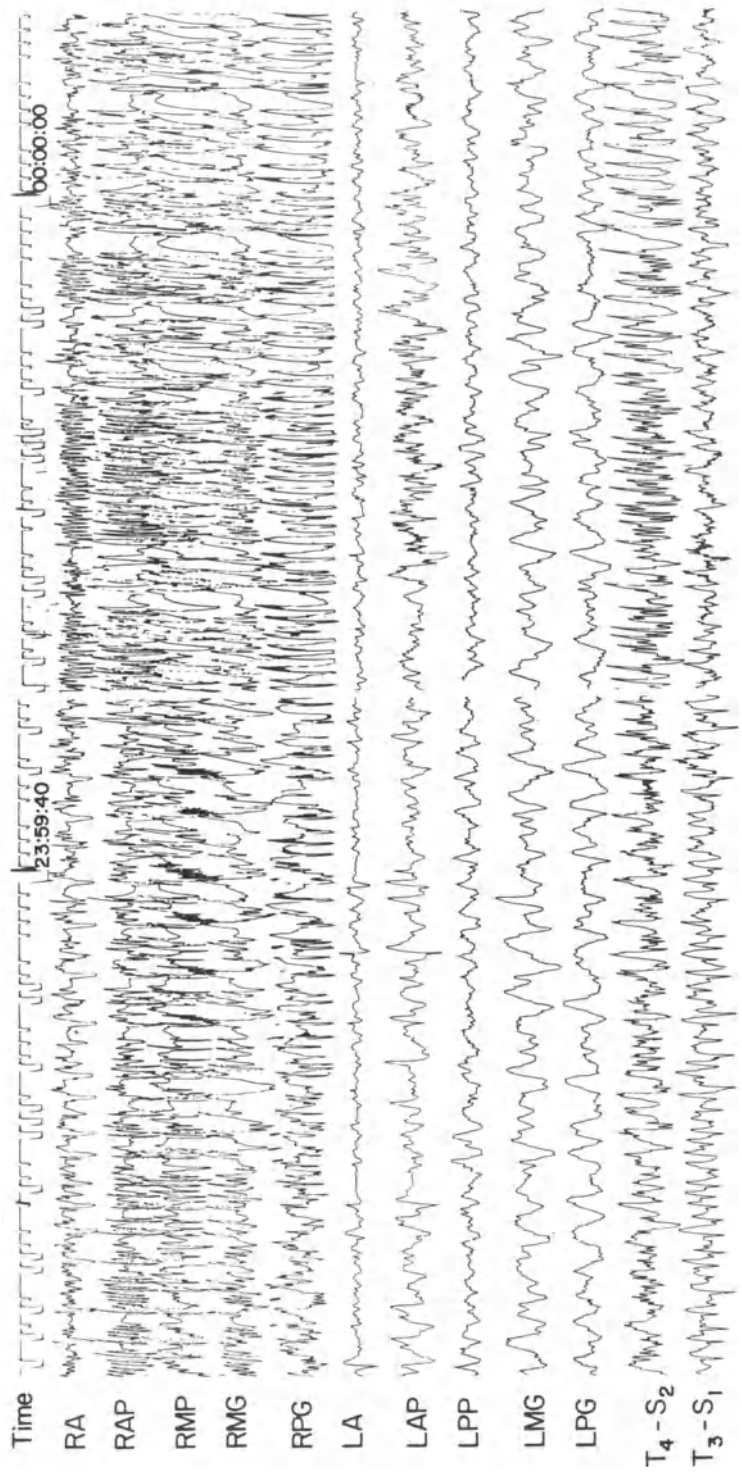
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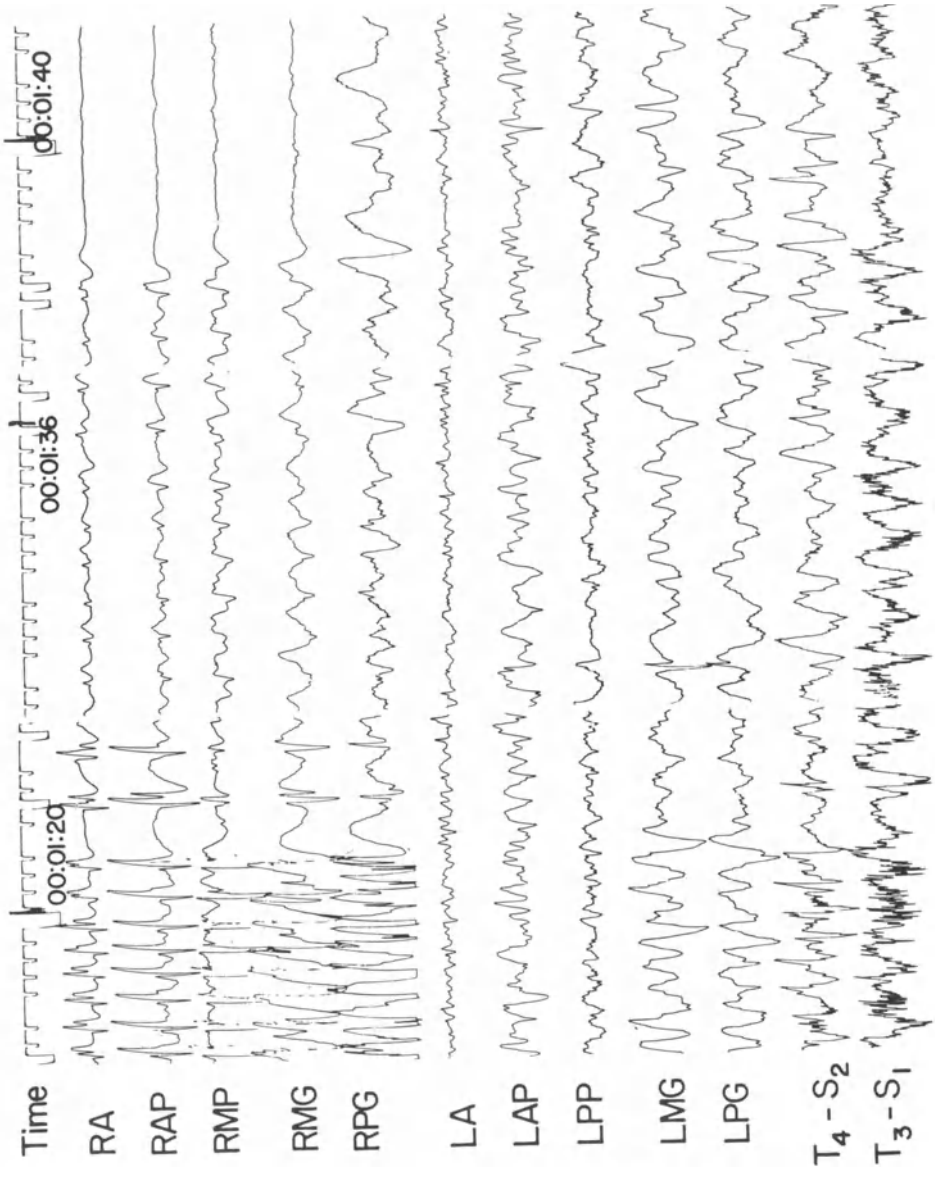
Fig. 14.3c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00:01:36
00:01:40
RA
RAP
RMP
RMG
RPG
LA
LAP
LPP
LMG
LPG
T4 - S2
T3 - S1

Fig. 14.3d

element in the diagnosis of complex partial status epilepticus. However, EEG recording techniques adequate to capture interictal temporal spikes or sharp waves, if they are present, must be used. Delgado-Escueta (1979) observed 3–1200 temporal spikes per hour during prolonged EEG recording in a group of patients with known complex partial seizures when nasopharyngeal or sphenoidal electrodes were used during stage II sleep. Thus, a minimum of 30 min of recording in stage II sleep should result in the recording of at least one temporal lobe discharge to confirm the presence of an interictal temporal lobe focus.

Differential Diagnosis of Complex Partial Status

When complex partial status epilepticus presents as a prolonged twilight or confusional state, there are many conditions with which it may be confused. The differential diagnosis of complex partial status epilepticus is outlined in Table 14.6.

Table 14.6. Differential diagnosis of complex partial status epilepticus (Treiman and Delgado-Escueta 1983)

1. Absence status epilepticus or spike-wave stupor
2. Other "epileptiform" causes of confusion
Prolonged postictal confusion
Delirium in cerebral infarction
Confusion associated with PLEDs
Poriomania
3. Organic encephalopathies
Toxic-metabolic encephalopathies, especially hypoglycemia
Alcohol and other drug intoxication or withdrawal
Transient ischemic attacks
Transient global amnesia
Posttraumatic amnesia
4. Psychiatric syndromes
Dissociative reactions
Hysterical conversion reactions
Acute psychotic reactions

Absence status epilepticus or petit mal status (Aminoff and Simon 1980; Assael 1972; Bohm 1969; Bower 1972; Brett 1966; Doose 1983; Doose and Volzke 1979; Gall et al. 1978; Lennox 1945; Lugaresi et al. 1971; Nakane 1983; Niedermeyer and Khalifei 1965; Patry et al. 1971; Porter and Penry 1983; Pritchard and O'Neal 1984; Sallman et al. 1981) is the most common cause of an epileptic twilight state and may be difficult to distinguish from complex partial status epilepticus.

Fig. 14.3. Stereo-EEG in patient represented in Fig. 14.2 showing bilateral paroxysmal slowing persisting in right pes hippocampi and left hippocampal gyrus as patient remains confused (**a**). Note that the left anterior pes hippocampi show 6–7 Hz rhythms mixed with 4–5 Hz irregular slow waves while the left posterior pes hippocampi show 3–5 Hz activities with superimposed 16–20 Hz faster rhythms. Slowing is also present in the scalp EEG. In **b** high amplitude rapid spikes at 16–20 Hz appear in the right amygdala and hippocampus, increase frequency, and become evident in the scalp EEG (**c**). Rapid ictal rhythms end on the right side (**d**) as abnormal sharp waves and slow waves remain on the left side. Ictal rapid rhythms also started on the left amygdala and hippocampus, precluding surgery.

Table 14.7. Clinical characteristics of prolonged twilight states (Belafsky et al. 1978)

Petit mal status		Complex partial status
	Clinical	
Prolonged state of one attack rather than repeated attacks		Continuous series of repeated attacks
Present	Phase of responsiveness with confusion, disorientation, speech arrest, amnesia, and automatisms	Present
Absent	Phase of total unresponsiveness with stereotyped automatisms	Present
	EEG	
Continuous or noncontinuous diffuse irregular 1.5- to 4-Hz multispike–wave complexes; no patterns are time-locked with automatisms	Phase of partial unresponsiveness and reactive automatisms	1. Low-voltage fast activities with bursts of diffuse slow waves, or 2. Rhythmic bilateral diffuse spokes or slow waves or both most evident anteriorly, or 3. Anterior temporal sharp waves with normal background
	Phase of total unresponsiveness and stereotyped automatisms	1. Correlates with bimedial temporal waves or lateralized to 8- to 20-Hz spikes

However, there are several clinical and electrical characteristics by which these two forms of epileptic twilight state may be differentiated (Table 14.7). As mentioned above, complex partial status epilepticus of temporal or frontal lobe origin is often manifested by recurring cycles of two separate phases, whereas petit mal status appears to consist of only one continuous twilight state with partial responsiveness of variable intensity, merging with total unresponsiveness. Total unresponsiveness is hard to identify in petit mal status, in contrast to the phase of staring, total unresponsiveness, and stereotyped automatisms that recurs in cyclic fashion in most cases of complex partial status epilepticus. Although stereotyped automatisms, such as blinking and chewing, appear in both petit mal status and complex partial status, they last longer in complex partial status and may be somewhat more complex. The EEG of petit mal status is characterized by diffuse spike–wave rhythms of 1–3 Hz, 2½–3 Hz, or 4–6 Hz that may be continuous, intermittent, or irregular in their appearance. There is no exact correlation between variations in the EEG pattern and in clinical behavior. On the other hand, in most cases of complex partial status there is a good correlation between the EEG changes and the cycling between the two clinical phases. During the staring phase, with stereotyped automatisms, EEG patterns like those seen at the onset of individual complex partial seizures, such as rhythmic spikes, sharp waves, or low-voltage fast activity, are always seen. During the twilight state, with partial responsiveness and

Fig. 14.4a–d (pages 371–4). Psychomotor seizure of hippocampal origin in patient 2. In **a**, high amplitude spikes increase frequency in the left anterior pes hippocampi. In previous attacks, an indescribable feeling and abdominal discomfort were described at this period. During this specific seizure, she did not comment. In **b** rapid frequencies fire at high amplitude in the right amygdala and hippocampus as the high amplitude spikes in the left hippocampus turn into rapid rhythmic spikes. From 32:35 to 33:42 (in **a**) she is sitting down playing cards. At 33:45 (**b**), as the right amygdala and hippocampus show rapid frequencies, she shows discrete motions of her head over a backdrop of arrest reaction and staring. At 34:02 (in **c**) the patient remains motionless as bilateral paroxysms fire at higher amplitude and fastest on the right side. At 34:05, she turns her head left. The amplitude of paroxysmal discharges on the left depth structures decrease but rapid rhythmic paroxmal discharges continue on the right side. At 34:48 (in **d**) she moves her head downward while bursts of polyspikes followed by flattening repeat over and over on the right side; the left structures are relatively quiet. At 34:57, the paroxysmal discharges disappear while she seems to continue playing cards.

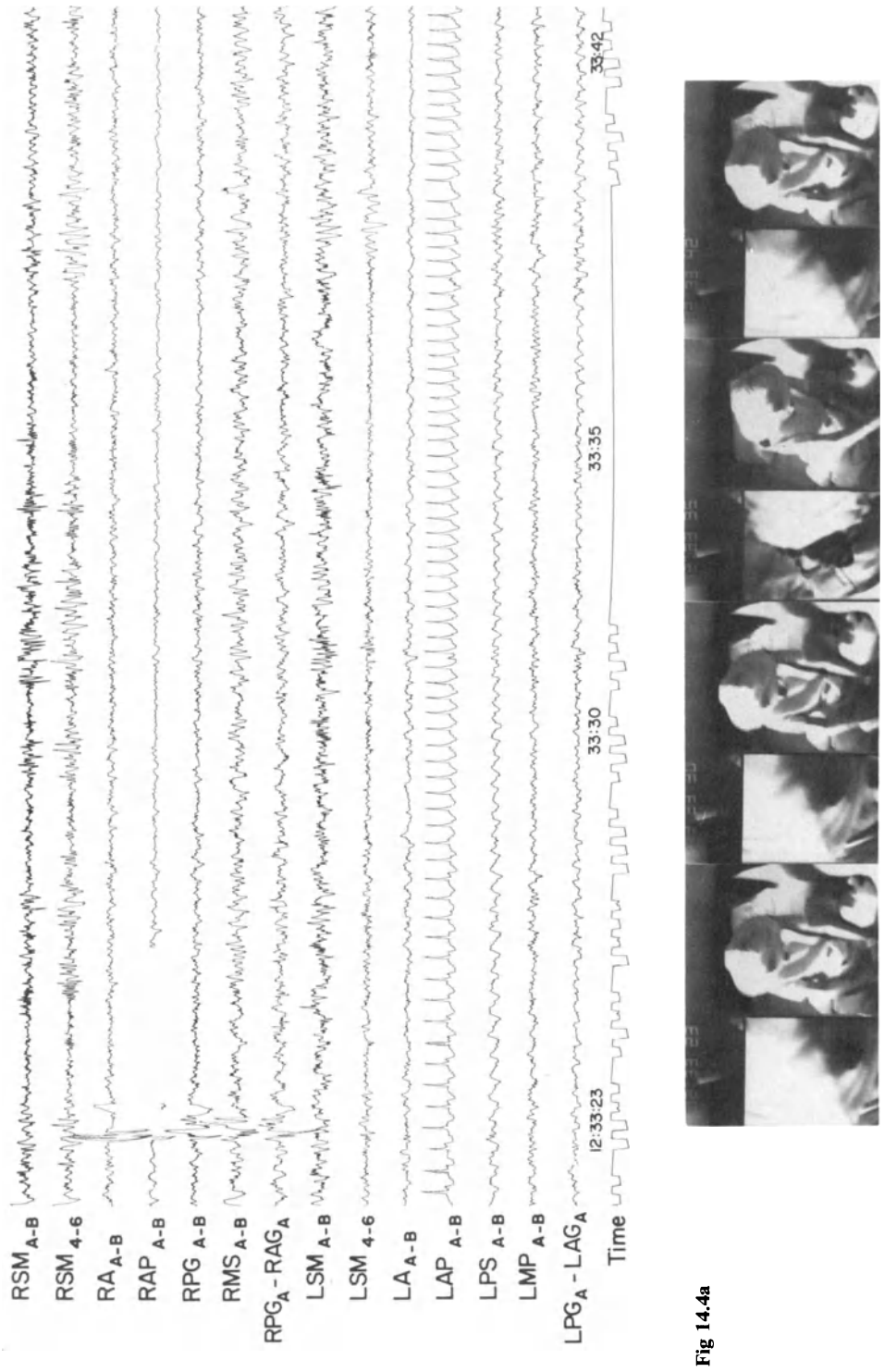
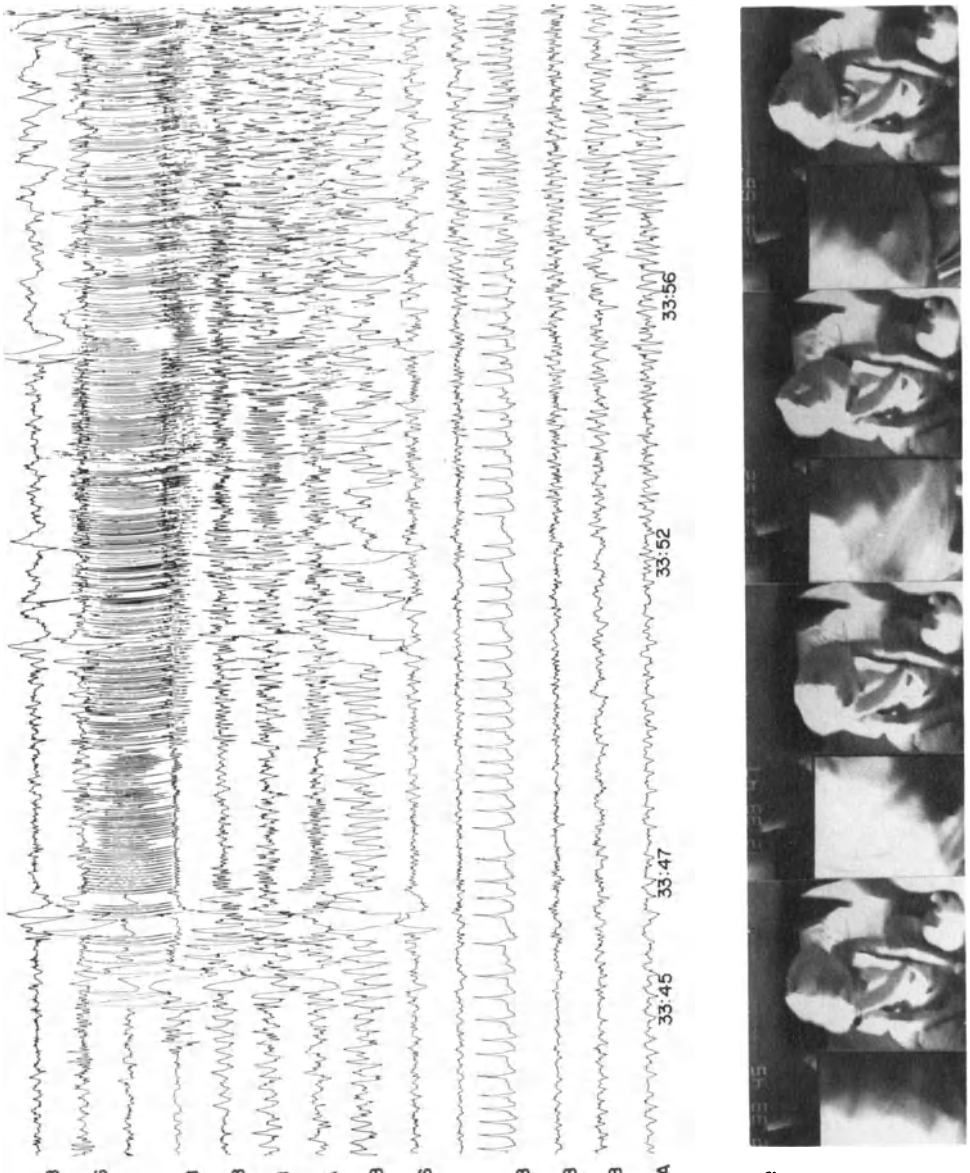

RSM A-B
RSM 4-6
RA A-B
RAP A-B
RPG A-B
RMS A-B
RPG A - RAG A
LSM A-B
LSM 4-6
LA A-B
LAP A-B
LPS A-B
LMP A-B
LPG A - LAG A
12:33:23
33:30
33:35
33:42
Time

Fig 14.4a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RA A-B
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RPG A-B
RMS A-B
RPG A - RAG A
LSM A-B
LSM 4-6
LA A-B
LAP A-B
LPS A-B
LMP A-B
LPG A - LAG A
33:45
33:47
33:52
33:56
Time

Fig. 14.4b

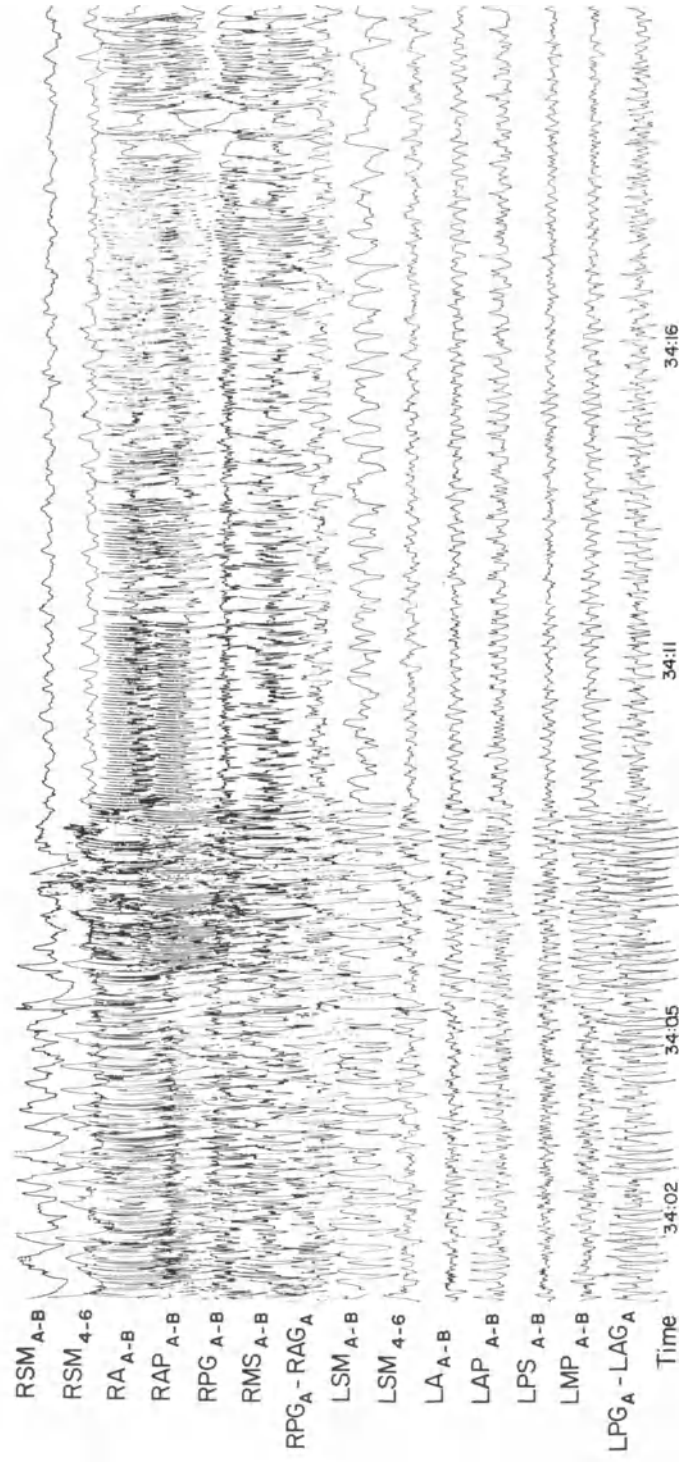
RSM A-B
RSM 4-6
RA A-B
RAP A-B
RPG A-B
RMS A-B
RPG A - RAG A
LSM A-B
LSM 4-6
LA A-B
LAP A-B
LPS A-B
LMP A-B
LPG A - LAG A
Time
34:02
34:05
34:11
34:16

Fig. 14.4c

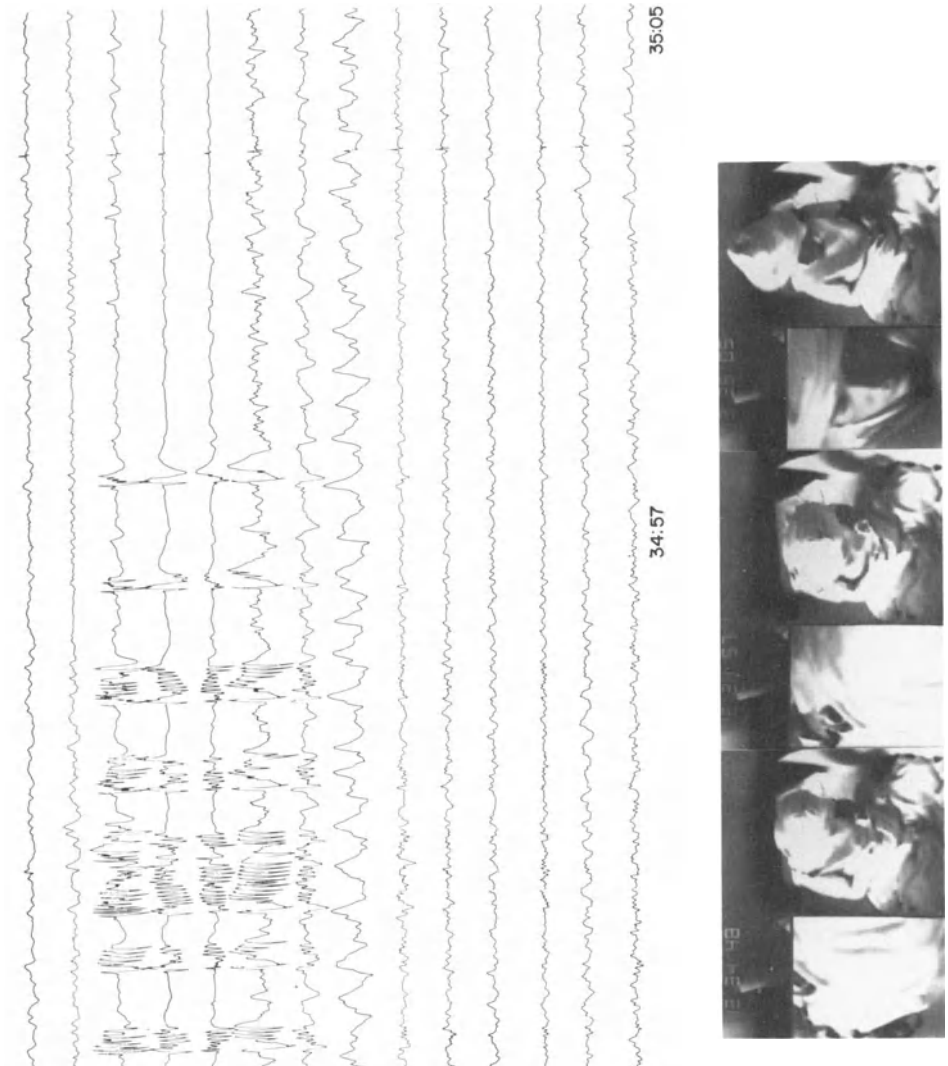
RSM A-B
RSM 4-6
RA A-B
RAP A-B
RPG A-B
RMS A-B
RPG A - RAG A
LSM A-B
LSM 4-6
LA A-B
LAP A-B
LPS A-B
LMP A-B
LPG A - LAG A
34:48
34:57
35:05
Time

Fig. 14.4d

reactive automatisms, there is normalization of the EEG and appearance of various EEG patterns like those seen at the end of an individual complex partial seizure or in the immediate postictal phase (Table 14.7).

When noncyclic types of temporal or frontal lobe psychomotor status are present, it is extremely difficult to differentiate these seizures from petit mal status. The EEG, in these instances, is the only recourse.

Penfield and Jasper (1954) have described prolonged postictal confusional states in which the EEG is diffusely slow. Such cases usually follow a well documented generalized tonic–clonic seizure, and there is no cycling between two clinical phases as in complex partial seizures and no change in the EEG or clinical behavior following administration of diazepam intravenously. Passouant et al. (1957) reported three episodes of confusion, agitation, and disorientation in a 57-year-old woman with general paresis. The third episode, which lasted 2 weeks, did not follow a convulsion and was believed to be an example of complex partial status epilepticus. However, the initial EEG showed rhythmic sharp waves in the left temporal region, which occurred approximately once per second and had the appearance of periodic lateralized epileptiform discharges (PLEDs). PLEDs occur in patients with acute focal cerebral lesions, usually of vascular cause, and frequently are associated with confusion and lethargy; they may superficially resemble other epileptic twilight states (Chatrian et al. 1964; Markand and Daly 1971; Markand et al. 1978). Delirium and confusion may occasionally occur in association with cerebral infarction, even in the absence of PLEDs, but the clinical course following the infarction, the presence of focal or lateralizing neurological abnormalities, and the absence of cycling between two clinical phases should allow differentiation from complex partial status epilepticus without significant difficulty.

A variety of other organic encephalopathies (Boudouresques et al. 1980; Burke et al. 1982; Chatrian et al. 1964; Erokhina and Pashkina 1982; Gastaut et al. 1960, 1963; Giorvani et al. 1985; Karlov et al. 1981; Peters et al. 1984; Pilke et al. 1984) may also give rise to acute confusional states that may occasionally be difficult to distinguish from prolonged epileptic twilight state. Various metabolic encephalopathies, especially hypoglycemia, alcohol abuse, other forms of drug intoxication or withdrawal, and head trauma, all can give rise to prolonged confusional states. Although some waxing and waning of the level of consciousness may occur in these conditions, there is never a clearly cyclical pattern of alternation between partial responses associated with reactive automatisms and total unresponsiveness associated with stereotyped automatisms, as seen in complex partial status epilepticus. Furthermore, the EEG in these conditions is quite different from that seen in complex partial status and does not show periodic ictal discharges, as are associated with the unresponsive phase of complex partial status.

Complex partial status epilepticus must be differentiated from several different psychiatric syndromes. This is especially important in patients with documented preexisting complex partial seizures, because many of these patients also have psychiatric disorders. The observation of interictal temporal lobe spike discharges is not sufficient to prove that a prolonged fugue state is indeed an epileptic twilight state. Apparent confusion due to either psychotic episodes or psychogenic fugue states may occur in epileptic as well as nonepileptic patients. In these instances it is necessary to document ictal epileptiform abnormalities at the time of the fugue in order to establish the diagnosis of an epileptic twilight or fugue state. The diagnosis of complex partial status and its differentiation from absence status are

then, as discussed earlier, based on the presence of clinical and EEG cycling between two distinct phases.

Poriomania represents a special type of dissociation reaction or fugue state that refers specifically to prolonged ambulatory behavior in epileptic patients for which they are amnestic. Mayeux et al. (1979) recently reported three cases of poriomania recurring in patients with apparent complex partial seizures and interictal mesial temporal spike discharges on the EEG. These authors suggested that poriomania is a prolonged postictal automatism and is not psychogenic in origin. Unfortunately, EEGs could not be obtained at the time of attack for any of these three patients. In none of them was cycling between partial and total unresponsiveness described. Poriomania may be a special case of the postictal confusional state, but it should not be considered typical of complex partial status epilepticus unless it can be shown to fulfill the criteria for the diagnosis of complex partial status outlined in Table 14.5.

Pathology of Focal Status Epilepticus, Secondary Tonic–Clonic Status, and Complex Partial Status

Gastaut restricted partial or focal status epilepticus to cases of fixed epileptic states featuring focal seizures without secondary generalization (Gastaut 1983). He emphasized that partial status can occur in known epileptics and in individuals who have never had epilepsy. Passouant et al. (1957) used this same subdivision in analyzing the 50 cases of partial status during the 10th Marseilles Colloquium in 1967. Of 32 patients with chronic epilepsy, motor seizures were localized to the face, eyes, upper limbs, and face and were usually clonic in 21 cases. The sites of origin were frontal, central, or anterior temporal. In the other 11 patients, symptoms and signs were more variable. When partial status occurred in 18 patients who had no history of epilepsy, an underlying disease led to mortality in ten patients. Most commonly, vascular lesions were found (eight cases), while trauma (five cases), metabolic diseases (four cases), and an "encephalopathy" (one case) were also described.

According to Gastaut (1983), when somatomotor status occurs in elderly non-epileptics, "the inaugural episode commonly reflects the existence of metastatic embolus or asymptomatic sylvian ischemia." Gastaut further distinguishes periodic repetition of localized myoclonus involving the proximal part of a limb or one side of a trunk or flank in elderly patients accompanied by PLEDs in the contralateral hemisphere. He suggests that this syndrome is most often related to cerebral infarction and less frequently to metastatic tumor or brain contusions.

The possible causes of "epilepsia partialis continuans of Kojewnikow" have already been discussed. Singh and Strobes (1980) emphasized the importance of considering hyperosmolar nonketotic hyperglycemia to be a cause of this condition. On the other hand, six of our patients with metabolic diseases all had generalized seizures. They were most commonly renal dialysis patients in renal failure with associated electrolyte imbalance. Of seven patients with partial motor status, we observed that two had had acute cerebral infarctions, and two a previous cerebral infarction, being readmitted with PLEDs and electrolyte imbal-

Table 14.8. EEG and clinical patterns and etiology of generalized convulsive status epilepticus (Delgado-Escueta and Enrile-Bacsal 1982)

Clinical and EEG features	Etiology, proven or presumed	No. of patients (total, 50)
Primarily generalized		
Generalized clonic with diffuse 8- to 10-Hz sharp waves	Lafora's disease	1
	Kufs' disease	1
Clonic–tonic–clonic with diffuse 1.5- to 5-Hz spike–wave complexes	Positive family history	1
	Renal encephalopathy	1
	Multiple metabolic disorders	2
Tonic–clonic with diffuse 1.5- to 5-Hz spike–slow wave complexes	Positive family history	3
	Encephalopathy associated with renal disease	3
	Kufs' disease	2
Tonic–clonic with diffuse 16-Hz spikes	No proven etiology but drug noncompliance	1
Secondarily generalized	Diffuse or focal structural lesions	24
Secondary tonic–clonic with focal 12- to 18-Hz spikes spreading diffusely	Diffuse focal structural lesions and drug noncompliance	5
Secondary tonic–clonic with focal 1-Hz spikes spreading diffusely	Focal structural lesion	6

ance. Of the other three patients, one had a subdural hematoma, one diabetes mellitus with hypoglycemia, and one a metastatic tumor.

Table 14.8 lists the proven or presumed causes of convulsive status epilepticus in 50 patients we originally studied. Frequently, a partial onset was present and progressing structural lesions were found, such as meningitis, encephalitis, cerebral metastatic tumors, and glioblastoma multiforme. There were four cases of metabolic disorders, acute cerebral infarctions, and cerebral anoxia secondary to cardiorespiratory arrest.

There have been rare reports on the neuropathology of complex partial status epilepticus. Perinatal complications (Markand et al. 1978), operative trauma (Mayeux and Lueders 1978), perinatal hypoxia (McBride et al. 1981), cerebrovascular disease (Heintel 1969), previous encephalitis, and subdural hematoma have all been cited as presumed causes. Two of our patients with complex partial status, who subsequently underwent surgery, both had hippocampal scleroses on neuropathological examination.

Consequences of Complex Partial Status

The role of the hippocampus in the acquisition of new memories has been well documented. There is increasing experimental evidence that repeated electrical discharges may produce profound neuronal damage, even in the absence of convulsive activity. Siesjo et al. (1983) and Meldrum and co-workers (Meldrum 1983; Meldrum and Brierley 1973; Meldrum et al. 1973) have presented evidence of focal neuronal damage following experimental convulsive status epilepticus.

In the kainic acid model and the kindling model, accumulating evidence supports the concept that sustained seizures confined to the limbic system can cause cell damage in specific cell populations. Local injection of kainic acid induces seizures along synaptically related pathways and in so doing produces damage at distant sites (Ben-Ari et al. 1980; Lothman and Collins 1981; Schwob et al. 1980). In the hippocampus, the rank order of vulnerability was first CA_3 neurons, second CA_2 neurons, third CA_1 neurons, and fourth dentate granule cells. When seizures spread through preferred routes, the amygdala, medial thalamic nuclei, and the pyriform and entorhinal cortex also showed signs of cell damage (Ben-Ari et al. 1980; Lothman and Collins 1981; Schwob et al. 1980). McIntyre et al. (1982) recently demonstrated in rats with a previously established kindled focus that prolonged amygadloid stimulation for 4 h produced CA_1 sector damage of the dorsal hippocampus. Interruption of seizure discharges after 30 min prevented cell loss (McIntyre et al. 1982). In human complex partial status epilepticus we do not know how much neuroexcitation is required to produce irreversible cell damage and whether both types (cyclic and noncyclic) of psychomotor status can produce local cell death. In rats with the kindled foci, seizures of 10–24 h duration and as short as 4 h produced unequivocal damage in the CA_1 sector of the hippocampus, pyriform and olfactory cortex, and amygdaloid and thalamic nuclei.

Complex partial status should, therefore, be stopped in humans as soon as possible, because the molecular events that lead to selective cell death may already be operational during the first two to three cycles of complex partial siezures. We do not know how long psychomotor status in humans has to last before neuronal calcium concentrations rise to toxic levels. Increased Ca^{2+} levels produce a variety of reactions. Arachidonic acid, arachidonoyl diglycerols, prostaglandins, leukotrienes and free radicals, e.g., suproxide and hydroxyl species and hydroperoxide radicals, accumulate to toxic amounts and cause brain edema and cell death in selected brain regions (Meldrum 1983; Meldrum and Brierley 1973; Meldrum et al. 1973; Schwob et al. 1980) (Fig. 14.5).

Engel et al. (1978) described a patient with a prolonged memory deficit following complex partial status epilepticus. We have now seen four patients who developed profound and irreversible memory deficits following cyclic forms of complex partial status which ranged from 76 h to 1 week (Treiman et al. 1981). The following two case reports of psychomotor status of hippocampal–amygdalar origin are given as examples.

The first patient was a 47-year-old woman who worked as a bookkeeper until she had a sudden onset of generalized tonic–clonic status epilepticus. After antiepileptic drug treatment, the status converted to a prolonged epileptic fugue state, during which she exhibited cycling between a clinical phase of immobile staring, with no response to the external environment, and a phase characterized by complex reactive automatic behavior (similar to type I psychomotor attacks). The patient was treated with a variety of anticonvulsant drugs, and finally, after 76 h of psychomotor status, with 2 g of intravenous phenobarbital, which stopped the cycles of complex partial seizures, she awoke with no recent or remote memory. Impaired recent memory continued, as did cycles of psychomotor attacks. In the fourth year of her illness, stereo-EEG was performed. Depth electrode recordings showed a hippocampal origin for the psychomotor seizures, shifting sides from attack to attack. Surgery could not therefore be performed. Mesantoin was added to the regimen, and until the sixth year of her illness the patient had a persistent memory deficit and continued to have intractable complex partial seizures, as

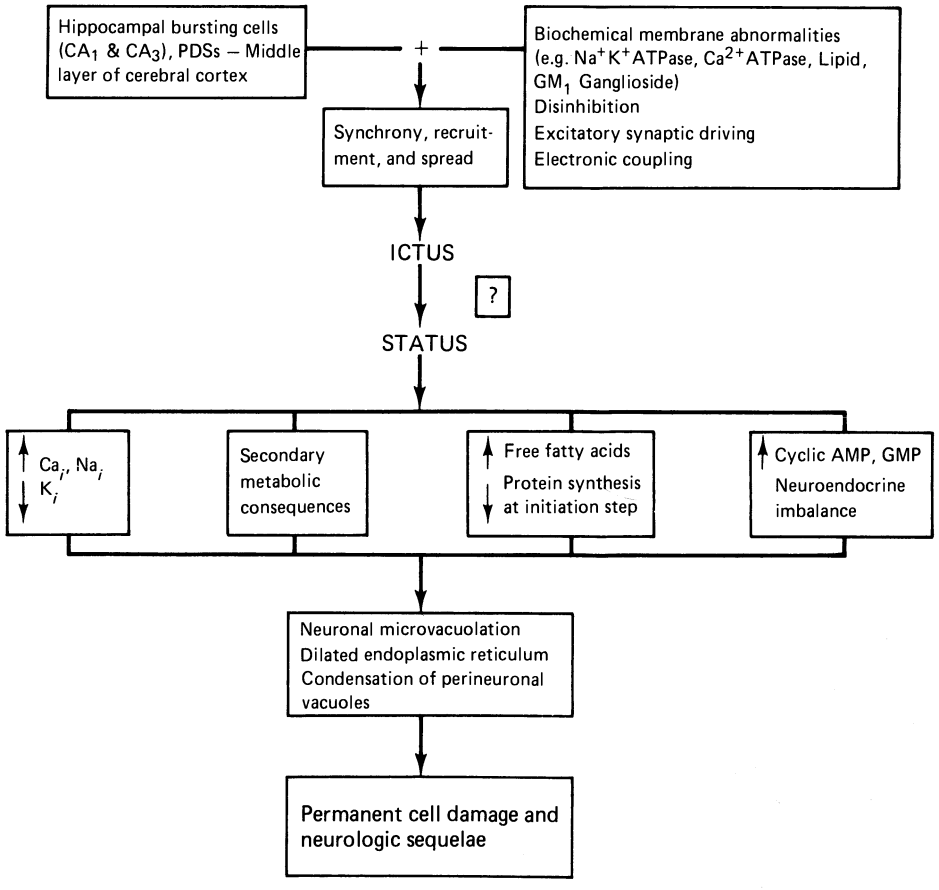

Fig. 14.5. Molecular events that lead to cell damage in convulsive status. Various biochemical membrane abnormalities are postulated to produce bursting behavior in hippocampal and cerebral cortical neurons. Synchrony of neuronal aggregates and recruitment of normal neurons are considered essential for the spread of seizures. The cellular and molecular events that accompany the transformation of a single ictal event to status epilepticus have not been investigated. Convulsive status causes intracellular calcium and sodium to rise, while free fatty acids and prostaglandins accumulate. Neuroendocrine imbalance, impaired protein synthesis, and secondary metabolic complications also result. (Delgado-Escueta and Bajorek 1982)

well as several further episodes of complex partial status epilepticus. By the seventh year, the seizure frequency had fallen to once or twice a month, and between the eighth and ninth year, her recent memory gradually returned to normal.

The second patient was a 31-year-old bankteller. During evaluation for surgical therapy, gradual removal of valproate, mysoline, carbamazepine, and phenytoin induced a change in the length of type I psychomotor seizures of hippocampal origin. Her usual psychomotor attacks were associated with stereo-EEG ictal rhythms lasting an average of 40–70 s and clinical confusion lasting 2–5 min (Fig. 14.4). Seven consecutive cycles of type I psychomotor attacks in a span of 21 h were associated with electrographic paroxysms lasting 1 min and 52 s to as long as 4 min and 42 s. She did not regain consciousness and remained confused between

the cycles of psychomotor automatisms. Intravenous lorazepam stopped the cycles of psychomotor attacks. On regaining consciousness, recent memory functions were absent and she has remained grossly amnesic for 2 years. The cause of this patient's seizures was never ascertained.

Treatment of Partial Status

The indications for vigorous treatment of focal motor status are not yet clear, and the theoretical advantage of stopping focal neuronal epileptic discharges quickly must be balanced against the potential systemic complications of intravenous antiepileptic agents and anesthetics. We would suggest that the patient be treated with intravenous diazepam (one to three bolus injections of 20 mg repeated after 20–30 min) and intravenous phenytoin (slow intravenous push), as outlined in the protocol (Table 14.9). If focal seizures do not stop after a loading dose of 18 mg/kg phenytoin, plasma levels of phenytoin and diazepam should be measured immediately. Phenytoin plasma levels must be kept at 23–25 μg/ml and diazepam should measure 200–400 ng/ml. If partial somatomotor postural seizures persist, the clinician can maintain high plasma levels of phenytoin (23–25 μg/ml) and watch for the disappearance of clinical and/or electrographic signs of focal status over the next 24–48 h. At this interval, a thorough search for the etiology of the focal motor status should proceed. If focal status persists in spite of high plasma levels of chronic phenytoin, the patient should be loaded with intramuscular phenobarbital to produce 35–50 μg/ml.

Table 14.9. Management of secondary tonic–clonic status epilepticus (after Delgado-Escueta et al. 1982b)

Time from initial observation and treatment (min)		Procedure
0	1.	Assess cardiorespiratory function as the presence of tonic–clonic status is verified. If unsure of diagnosis, observe one tonic–clonic attack and verify the presence of unconsciousness after the end of the attack. Insert oral airway and administer O_2 if necessary. Insert an indwelling intravenous catheter. Draw venous blood for anticonvulsant levels, glucose, BUN, electrolyte, and CBC stat determinations. Draw arterial blood for stat pH, PO_2, HCO_3. Monitor respiration, blood pressure, and electrocardiograph. If possible, set up to monitor electroencephalograph.
5	2.	Start intravenous infusion through indwelling venous catheter with normal saline containing vitamin B complex. Give a bolus injection of 50 cc 50% glucose.
10	3.	*Infuse diazepam intravenously* no faster than 2 mg/min until seizures stop or to total of 20 mg. *Also start infusion of phenytoin* no faster than 50 mg/min to a total of 18 mg/kg. If hypotension develops, slow infusion rate. (Phenytoin, 50 mg/ml in propylene glycol, may be placed in a 100 ml volume control set and diluted with normal saline. The rate of infusion should then be watched carefully.) Alternatively, phenytoin may be injected slowly by intravenous push.

Table 14.9 (*continued*)

Time from initial observation and treatment (min)		Procedure
30–50	4.	If seizures persist, *two options are now available: i.v. phenobarbital or diazepam i.v. drip.* The two drugs should *not* be given in the same patient, and an endotracheal tube should now be inserted. *Intravenous phenobarbital option*: Start infusion of phenobarbital no faster than 100 mg/min until seizures stop or to a loading dose of 20 mg/kg. *or* *Diazepam i.v. drip option*: 100 mg diazepam is diluted in 500 cc D5/W and run in at 40 cc/h. This ensures diazepam serum levels of 0.2–0.8 μg/ml.
50–60	5.	If seizures continue general anesthesia with halothane and neuromuscular junction blockage is instituted. If an anesthesiologist is not immediately available, start infusion of 4% solution of paraldehyde in normal saline; administer at a rate fast enough to stop seizures. *or* 50–100 mg lidocaine may be given by intravenous push. If lidocaine is effective, 50–100 mg diluted in 250 cc of 5% D/W D/W should be dripped intravenously at a rate of 1–2 mg/min.
	6.	If paraldehyde or lidocaine has not terminated seizures within 20 min of start of infusion, general anesthesia with halothane and neuromuscular junction blockade must be given.
	7.	If status epilepticus reappears when general anesthesia is stopped, a neurologist who has expertise in status epilepticus should be consulted. Advice from a regional epilepsy center should also be sought in the management of intractable status epilepticus.

Treatment of Partial Status Epilepticus Which Evolves to Secondary Tonic–Clonic Status

Because the ideal drug for treating secondary convulsive status epilepticus does not exist, more attention should be paid to the guiding principles which govern its management (Delgado-Escueta et al. 1982b; Treiman 1983; Treiman and Delgado-Escueta 1980). The first principle of management is the accurate identification of the secondary convulsive status epilepticus. Convulsive status epilepticus requires immediate vigorous treatment.

A second principle requires us to treat and correct the causes and the immediate trigger of secondary convulsive status epilepticus. An immediate search should be made for an acute central nervous system lesion, e.g., acute cerebral infarctions, meningitis, encephalitis, severe head trauma, or a rapidly progressing mass such as a cerebral abscess or neoplasm. If such a lesion is absent, less frequent causes of secondary tonic–clonic status should be considered, such as metabolic and fluid electrolyte disturbances associated with old cerebral infarctions, withdrawal from antiepileptic drugs, metabolic diseases such as renal failure, and cerebral anoxia from cardiorespiratory arrest (Delgado-Escueta and Bajorek 1982).

The third principle is to stop convulsions as soon as possible in order to prevent selective neuronal cell damage and serious secondary metabolic consequences (Brown and Brierley 1973; Brown et al. 1980; Chapman et al. 1977, 1980; Kreisman et al. 1983; Lombroso 1983; Meldrum and Brierley 1973; Meldrum et al. 1973; Oxbury and Whitty 1971a; Richard et al. 1981, 1982). Secondary convulsive status must not be allowed to progress beyond 20 min, the so-called transitional period. If convulsive status epilepticus continues beyond 60 min in spite of antiepileptic drug treatment, the patient should be placed under general anesthesia. Adequate cardiorespiratory function and brain oxygenation must be ensured to prevent selective cell damage in the cerebellum and amygdala and, when present, secondary metabolic complications, such as hypoglycemia, electrolyte imbalance, lactic acidosis, dehydration, and hyperpyrexia, must be corrected (Meldrum and Brierley 1973; Meldrum et al. 1973; Simon 1985; Tawadros et al. 1980; Terrence et al. 1981).

First-Line Drugs

Table 14.9 is a protocol that incorporates these principles of management of secondary convulsive status epilepticus. It is desirable to act deliberately and follow the protocol in a stepwise fashion to avoid unnecessary complications. *To control secondary tonic–clonic status as soon as possible, diazepam is administered intravenously* (Browne and Penry 1973; Delgado-Escueta and Bajorek 1982; Duffy and Lambroso 1978; Fröscher 1979; Gastaut et al. 1965; Prensky et al. 1967; Smith and Masotti 1971; Sorel et al. 1981; Tassinari et al. 1983; Wilder 1983). Intravenous diazepam stops convulsions within 3 min in 33% of patients with status and within 5 min in 80% of patients (Delgado-Escueta and Enrile-Bacsal 1982). Ten to twenty minutes after cessation of intravenous administration, seizures may recur because diazepam is distributed quickly and widely to various organs and tissues. *To prevent recurrence of seizures, phenytoin is given simultaneously* in another intravenous line (Delgado-Escueta and Bajorek 1982; Leppik et al. 1983a,b; Murphy and Schwab 1956; Wallis et al. 1968; Wilder 1983). The slow administration of phenytoin intravenously results in equally slow results. When given as the side treatment, anticonvulsant effects are not evident until 10–20 min after the start of phenytoin infusion (Wilder 1983). Phenytoin stops status epilepticus in 30% of patients after approximately 400 mg has been administered, i.e., about 10 min after the start of its infusion. Maximal anticonvulsant effects appear only after the full dose of phenytoin is administered, i.e., about 10–20 min after the start of its infusion (Wilder 1983). Thus, to terminate convulsions rapidly, intravenous diazepam is administered simultaneously with phenytoin.

Intravenous diazepam and phenytoin stops seizures in more than half (65%) of patients with tonic–clonic status with partial onset. Intravenous diazepam and phenytoin are even more effective in primary epilepsies and stop seizures in nearly all patients with primarily generalized tonic–clonic, myoclonic, and clonic–tonic–clonic status (Browne and Penry 1973; Delgado-Escueta and Bajorek 1982; Duffy and Lombroso 1978; Fröscher 1979; Gastaut et al. 1965; Wilder 1983). Both drugs arrest convulsive status from alcohol and drug withdrawal.

Second-Line Drugs

When intravenous diazepam and phenytoin fail to control secondary tonic–clonic status, a third drug is usually used. The most commonly used third drug is intravenous phenobarbital (Goldberg and McIntyre 1983; Orlowski et al. 1984; Zappoli et al. 1983). However, no prospective study has analyzed the effectiveness of phenobarbital in status epilepticus. Moreover, its use together with or after diazepam should be discouraged, since this drug combination causes respiratory depression. Our experience suggests that a more acceptable option is to administer diazepam by intravenous drip (Delgado-Escueta and Enrile-Bacsal 1982). Others suggest intravenous clonazepam (Gastaut et al. 1971; Singh and Le Morvan 1982; Sorel et al. 1981). Physicians inexperienced with intravenous diazepam drip or clonazepam should not proceed with these drugs and should consider administration of general anesthesia. Whether intravenous phenobarbital, infusion drip of diazepam, or intravenous clonazepam is administered, an endotracheal tube must be inserted as protection against depression. One must understand that to effectively use amobarbital, pentothal, paraldehyde, and even phenobarbital and stop convulsive status epilepticus, anesthetizing dosages must be used.

By the time first-line drugs (diazepam and phenytoin) and a second-line agent (phenobarbital or clonazepam) have proved unsuccessful, secondary tonic–clonic convulsive status will have continued for 60 min. Since these other drugs to be used are administered in anesthetizing dosages, it is safe to have an anesthesiologist administer general anesthesia with halothane and artificial respiration with neuromuscular junction blockade (Delgado-Escueta and Bajorek 1982).

Goldberg and McIntyre reported some success in stopping drug-resistant status epilepticus by pentobarbital coma (Goldberg and McIntyre 1983). Patients received an initial bolus of 5 mg/kg pentobarbital intravenously and sufficient amounts were administered to produce EEG suppression bursts. Infusion was continued at a rate of 1–3 mg/kg per hour for 4 h. After this time, the infusion rate was decreased and the EEG was studied for ictal epileptiform paroxysms. If EEG ictal patterns persisted, the same procedure was repeated for another 4 h. Otherwise the patient was withdrawn from pentobarbital coma over 12–24 h.

Recently, a number of reports on thiopentone treatment of convulsive status have appeared (Burton and Holland 1984; Casaroli et al. 1980; Feneck 1981; Goitein et al. 1983; Goldberg and McIntyre 1983; Young et al. 1980). Burton and Holland (1984) recently reviewed their successful experience with nonanesthetizing doses of thiopental administered intravenously or rectally in 39 patients. One gram of thiopentone in 500 cc normal saline was administered at 2 mg/min for 30 min and was then reduced to 1 mg/min if seizures stopped. Several reports have shown that anesthetizing doses of thiopentone can successfully stop drug-resistant status. Thiopentone is metabolized to pentobarbitone which can reach CSF levels between 15% and 40% of serum levels. The potential for decreasing intracranial pressure, cerebral hypoxic damage, and metabolism in addition to stopping convulsive status epilepticus warrants further investigation of barbiturates for status epilepticus.

Third-Line Drugs

While waiting for the anesthesiologist, alternative drugs considered third lines of defense, such as paraldehyde (Browne 1983), chlormethiazole (Harvey et al. 1976; Lingum et al. 1980; Miller and Kovar 1983), or lidocaine (Browne 1983), can be used. According to Browne, evidence of efficacy of paraldehyde in status epilepticus consists of 36 case reports in two uncontrolled trials and two widely quoted testimonials by Obrador's group in 1949 and Wechsler in 1940. These reports suggest that paraldehyde can control secondary convulsive status in adult and pediatric patients when other agents fail. It must be understood, however, that comparison of paraldehyde with other agents for status epilepticus has never been done in a controlled trial.

Improper storage of paraldehyde results in depolymerization to acetaldehyde and the oxidation by air of the latter to acetic acid. As little as 7 ml of decomposed paraldehyde containing 40%–98% acetic acid has proved fatal. Thus, only properly stored pure paraldehyde from freshly opened containers should be used. If given intravenously, paraldehyde must be diluted to 4% and infused slowly. Only glass syringes should be used since paraldehyde will decompose plastic syringes and tubings in less than 2 min. Following intravenous injection, anesthesia ensues within less than 2 min. Plasma concentrations of 12–33 mg% produce anesthesia. The plasma concentration of paraldehyde necessary to control convulsive status is not known. The practicing physician must remember that 10% paraldehyde injected intravenously can produce apnea, coughing, cyanosis, hypotension, and pulmonary edema. A less optimal method of administration of paraldehyde is by the intramuscular route; 5 ml is injected deep into each buttock. Sterile abscesses and sciatic nerve damage sometimes occur. Slow absorption of paraldehyde through the rectal mucosa makes this route undesirable for treatment of convulsive status (Browne 1983).

Browne reports that the evidence of the efficacy of lidocaine in status epilepticus is derived from 148 cases contained in eight reports. In almost every case, patients received multiple drugs in addition to lidocaine. These studies did suggest that lidocaine may control secondary convulsive status when diazepam, phenytoin, phenobarbital, and paraldehyde fail. The antiepileptic effects of an intravenous bolus of lidocaine is rapid; seizures decrease in 20–30 s. Treatment can be started with a single dose of 2–3 mg/kg administered intravenously not faster than 25–50 mg/min. If seizures stop and then recur, lidocaine can be infused at a rate of 3–10 mg/kg per hour. Constant EKG and blood pressure monitoring are necessary to detect cardiovascular complications. Evidence for proper usage in children is limited (Browne 1983).

Probable Replacement of the Diazepam–Phenytoin Combination by Lorazepam

There remains a need to develop an ideal drug for treating secondary tonic–clonic status—one that will promptly stop status, remain long enough in the brain to prevent recurrence of seizures, and yet be free from undesirable side effects such as deep coma, hypotension, and respiratory depression (Treiman 1983).

Lorazepam, a 5-hydroxy,1,4-benzodiazepine, is similar in structure to diazepam

and approximately five times more potent in stopping status in experimental animals. Early clinical studies suggest it effectively stops tonic–clonic status in humans and has relatively little effect on cardiac or respiratory function.

Lorazepam tissue distribution is less rapid and less extensive than diazepam, and its elimination half-life is 12–16 h. The clinical effects of an intravenous bolus injection would therefore be more prolonged than those of diazepam.

Clinical studies suggest it is effective in the acute treatment of status epilepticus in humans. Six open studies have thus far been reported and have included a total of 113 adults and 75 children (Greenblatt and Divoll 1983; Griffith and Karp 1980; Homan and Walker 1983; Levy and Krall 1984; Ruelius 1978; Treiman et al. 1985; Walker et al. 1979). Lorazepam was successful in stopping status in 88% of children. Sorel compared lorazepam and clonazepam in his group of hospitalized chronic seizure patients in an open, nonrandomized study and concluded that improvement in the EEG manifestations of status was greater with lorazepam whereas the clinical symptoms of status responded more completely to clonazepam. One double-blind comparison of lorazepam with diazepam in the treatment of status has recently been reported (Leppik et al. 1983b). Seventy episodes of status epilepticus were treated, 37 with lorazepam and 33 with diazepam. For the partial seizure group, diazepam was effective 70% of the time while lorazepam was effective 86% of the time. This was not statistically significant, possibly because of the relatively small number of episodes treated (20 with diazepam, 22 with lorazepam). In addition, intravenous phenytoin was administered within 30 min of the onset of treatment, thus obscuring the expected differences between the two benzodiazepines as regards duration of action and frequency of recurrence. There is a rapid redistribution to other tissues after intravenous administration of lorazepam, and maximum tissue concentrations are reached within 15–30 min after injection (Greenblatt and Divoll 1983). The mean distribution half-life in man appears to be between 3 and 10 min depending on dose and rate of intravenous infusion, whereas the elimination half-life is 12–16 h (Greenblatt and Divoll 1983). However, Greenblatt and Shader (41) have suggested that in comparison to diazepam, lorazepam tissue distribution is less rapid and extensive, thereby prolonging the clinical effects of an intravenous bolus injection.

Lorazepam has been thought to be less likely to produce respiratory depression than diazepam (Walker et al. 1979). This was not confirmed in the double-blind comparison study cited above, as the same number of patients developed respiratory depression with lorazepam as with diazepam. However, all patients who developed respiratory difficulties with lorazepam had a history of respiratory problems, while none of the diazepam group had such a history. Walker et al. (1979) reported one case of respiratory depression following treatment of status epilepticus with lorazepam in a patient who had no history of respiratory difficulties. A total of five episodes of respiratory depression have occurred in 266 reported patients treated with lorazepam for status epilepticus.

Lorazepam has not yet been approved by the Food and Drug Administration for use in status epilepticus and this prevents us from recommending the drug as a replacement for diazepam–phenytoin combination. Moreover, at the present time, a nationwide, cooperative study involving 11 medical centers is evaluating in a blind, randomized fashion which method of treatment is best: phenobarbital alone vs diazepam–phenytoin combination vs phenytoin alone vs lorazepam. The results of these studies hopefully will tell us which drugs are first choice and which agents are second best.

Treatment of Complex Partial Status

Responses to treatment have only infrequently been described in reports of complex partial status, and the details have frequently been lacking. Lugaresi et al. (1971) reported that continuous sharp-and-slow wave discharges in the right temporal–occipital region disappeared when the clinical episode of complex partial status ended, but they did not comment on treatment. Intravenous diazepam has been most frequently mentioned in those reports that have discussed treatment at all, but it has only sometimes been successful in stopping status at the dosages used. Wolf (1970), in his first case, reported that diazepam improved both the clinical and EEG manifestations, but he gave no further details. Engel et al. (1978) reported a transient interruption of continuous temporal–occipital epileptiform EEG abnormalities after administration of diazepam, but only gradual improvement after phenobarbital and phenytoin. In Wieser's cases (1980, 1985) diazepam produced a decrease in the frequency of the recurrent tonic and clonic discharges. Wolf, in his second case, and more recently, Behrens (1980), reported improvement the next day after treatment with diazepam or with diazepam and phenytoin.

Only two recent reports have documented definite responses to diazepam. Mayeux and Lueders (1978) administered 2 mg diazepam, which promptly stopped the epileptiform discharges on EEG, after which the patient slept for 5 min and then awoke alert and able to follow commands. Markand et al. (1978) also reported that administration of diazepam promptly stopped both the clinical and the electrical manifestations of status.

The ease and rapidity of responses to intravenous anticonvulsant medication may be partially determined by the duration of status at the time of treatment. We saw a 57-year-old man who had been in a stuporous twilight state for 8 days after cardiac surgery. The EEG showed continuous epileptiform discharges from both temporal regions. Four milligrams of diazepam promptly normalized the EEG but full recovery of mental alertness required several days. If complex partial status is sufficiently prolonged before adequate treatment, permanent changes in mental status may occur, as described earlier.

Two patients with complex partial status, who were studied in our unit, have undergone anterior temporal lobectomy and have experienced no further seizures.

The need for rapid and vigorous treatment of complex partial status epilepticus has only recently been recognized. In the past, the assertion was made that complex partial status need not be treated with the same urgency as generalized tonic–clonic status. More recently, Williamson has claimed that complex partial status epilepticus of frontal lobe origin is not followed by impaired recent memory. We do not believe this is the case in psychomotor status epilepticus of hippocampal–amygdalar origin. Experimental evidence has amply demonstrated that profound hippocampal damage can occur as a result of prolonged electrical discharges in the perforant pathway or as a result of repeated electrical seizures in a previously kindled animal. Moreover, there is accumulating evidence that psychomotor status of hippocampal–amygdalar origin, when left abated for days and weeks, can produce chronic impairment of recent memory. We therefore recommend that psychomotor status with either primary or secondary engagement of the hippocampal–amygdalar complex be treated as quickly as possible to prevent chronic neuronal damage. However, in order to avoid inappropriate administration of large doses of potentially toxic drugs, it is essential to establish the diagnosis of

complex partial status epilepticus prior to initiating treatment. In the cases of nonconvulsive status, the choice of drugs will be influenced by whether the epileptic fugue represents absence status, spike–wave stupor of late age onset, or complex partial status. Thus, a patient suspected of having complex partial status should be observed under EEG control sufficiently long to identify the clinical and EEG patterns described earlier. Treatment should then be initiated with intravenous diazepam and phenytoin. Intravenous diazepam should be given at a rate no faster than 2 mg/min until the status stops or to a total dose of 20 mg. Simultaneously or immediately after the diazepam is given, infusion of phenytoin should be initiated at a rate no faster than 50 mg/min to a total dose of 18 mg/kg.

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