THE PROGNOSIS OF PATIENTS WITH EPILEPSY

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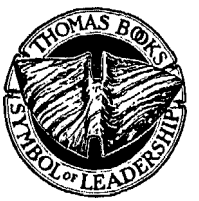

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FOREWORD

When I was asked to write this book, I had initially considerable doubts whether the topic would indeed merit extended discussion. My misgivings were based, in part, on the currently accepted view that epilepsy is not a disease but a symptom of a variety of different illnesses. They were also related to the feeling that seizure control should no longer be a great problem in the majority of patients, if they receive expert medical management.

If epilepsy is only a symptom, the prognosis would obviously depend upon the course of the basic illness, and to write a book on the prognosis of a symptom would be anachronistic to say the least. In regard to treatment, new anticonvulsants are steadily produced, and one gains the feeling that any results that are reported may soon be hopelessly outdated.

The reason for accepting the task, in spite of these considerations, lay in the opportunity to review the actual progress that has been made in the medical and surgical treatment of seizure patients and to delineate the characteristics of patients who respond to treatment as opposed to those in whom treatment results are, at present, unsatisfactory. The third, and possibly most important aspect was the hope that one might find some clues about pathophysiologic mechanisms underlying this disorder. Prognosis obviously means prediction. If we can predict accurately the course of a given patient's illness and the factors that will influence it, we may be a step closer in the understanding of the condition. The book presents, therefore, a statement of where we stand today in our concepts about this ancient disorder, the achievements that have been accomplished during the

past six to eight decades, and it also points out the areas where progress has been lacking.

The personal investigations that are reported here mark a departure from classic scientific methodology. Traditionally one forms a hypothesis on the basis of existing data and subsequently puts it to the test. I have purposely refrained from making any hypotheses in order to proceed in as unbiased a fashion as possible. The various steps in the data collection and workup resulted primarily from statistical considerations, rather than from the intention to prove or disprove a given point. The statistically significant results of each step of the investigations dictated the further course of data workup, Although these studies dealt only with seizure patients, the methodology can, of course, be applied to any other condition one may wish to study and is likely to become increasingly useful for medical research in the future.

In contrast to other publications which emphasize that epilepsy is the "hopeful disease," this book will concentrate on those areas where current results are unsatisfactory. This is not due to an inherent pessimism of the author but results from the conviction that a realistic rather than an optimistic outlook is called for. Baseless optimism can seriously hinder future medical research because the problem that is to be investigated does not attract its proper attention as a result of wishful thinking. Hope has always and will always be with us, and a paragraph such as the following reads strangely modern: ". . . and the present generation has witnessed an advance in the treatment of these diseases equalled in perhaps no other branch of therapeutics. Thanks to the influence of one drug and its combinations, hundreds of epileptics have been cured, and thousands are leading useful lives who would otherwise have been incapacitated by the disease. Although the condition of many sufferers is still gloomy enough, it is not without hope, and to them also, we may surely trust, the progress of the recent past is the dawn of a brighter day."

The "drug and its combination" is not Dilantin,® but salts of bromide, and the words were written by Gowers around 1880. All of us who have been treating chronic seizure patients in the

1960's will be aware of cases whose condition "is still gloomy enough." By pointing out the areas where our efforts have not been very successful, it is hoped that more interest may be stimulated in regard to this fascinating disorder of the central nervous system and that this will eventually lead to the eradication of the condition. As has been mentioned previously, the results of the studies presented here may soon be obsolete, but if some of the ideas and suggestions that are contained in the following pages can contribute to their obsolescence this book will have served its purpose.

ACKNOWLEDGMENTS

A book of this type is obviously not the work of one person, and I am indebted to a number of people for their continued help.

For the statistical procedures I am grateful to Doctor J. Grisell, head of the Computing Laboratory of the Lafayette Clinic, and his able assistants: Mr. R. Gudobba, Mrs. P. Levin, Mrs. R. Bendiner, Miss K. Lennox, and Mr. J. Porzak. They have worked with me step by step and I am most happy to gratefully acknowledge their efforts. I would also like to express my thanks to the staff of the Neurology Division of the Lafayette Clinic, especially nurses and attendants. They have made it possible to take care of some severely regressed—and sometimes psychotic —patients who had been living for years behind closed doors in various state hospitals. These patients had to be integrated on an open ward with other patients from the community who had a variety of different neurological illnesses. This was a major accomplishment for which the staff deserves full credit. Special thanks are also due to my EEG technicians, Mrs. E. Davenport and Mrs. B. Brown, who have been exceedingly helpful by obtaining top quality records from some very severely disturbed patients, and who were always willing to schedule an extra patient at a moment's notice whenever I felt that a special study would be helpful at that particular time.

The manuscript itself, however, could not have come about without the unceasing efforts of the staff of the Michigan Epilepsy Center under the direction of Doctor R. D. Dennerll, and its office manager, Miss J. A. Cheek. The librarians, Mrs. M. Hagstrom and Mrs. C. Perliss, kept procuring literature from

numerous sources; the EEG technicians, Mrs. P. Scerpella and Mrs. B. Pachucki, were not only instrumental in recording the patients involved in the follow-up studies and the VRA Project, but also helped in collation of EEG data. A special vote of thanks is due to Miss J. Smith who worked long and hard in typing, retyping, and typing again the manuscript, assembling the bibliography and proofreading part of the material with other members of the staff. For typing the major portions of the final copy, I am grateful to Mrs. E. Lessnau. The final proofreading was accomplished with the dedicated help of Mrs. M. M. Bryan and Mrs. C. Perliss.

I would also like to thank Mr. A. E. Hearron, Jr., of the Health Statistics and Evaluation Center of the Michigan Department of Public Health, for sending me the data on the patients who had died. Doctor W. Dickerson, Superintendent of Caro State Hospital (now retired), was most cooperative in arranging transfers of his patients to the Lafayette Clinic, and it was a pleasure to have had the opportunity to work with him. To Doctor V. Samuel, I am grateful for his help in arranging the transfer of patients from Pontiac State Hospital, and to Doctor C. Chen, for sending us some of his patients from Northville State Hospital.

It is also a pleasure to thank Doctor J. Gottlieb, Director of the Lafayette Clinic, for allowing me complete freedom of action in the pursuit of these investigations. Doctor R. D. Dennerll, Director of the Michigan Epilepsy Center, has been most helpful in sponsoring the follow-up projects and by putting all the resources of the Center at my disposal in the preparation of the manuscript. I am grateful to him also for reviewing the manuscript, and making valuable suggestions. Doctor J. Grisell, and my wife, Doctor M. Rodin, were likewise drafted into the process of manuscript review and I am happy to acknowledge their help.

While numerous people collaborated in data collection, data workup, presentation of results, and preparation of the manuscript, the fact that this book was written at all is due to the initiative of one person only, Mr. Payne Thomas of Charles C Thomas, Publisher. He suggested that I consider writing a de-

tailed exposition of the problem after I had presented some of the data of the follow-up studies at the Pan-American Medical Society meeting in May, 1965. It was indeed a pleasure having had the opportunity of working with him and his staff.

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PART ONE
REVIEW OF THE LITERATURE

Chapter 1

RESULTS OF FOLLOW-UP STUDIES AND GENERAL PROGNOSTIC CRITERIA

A statement that is frequently quoted to the lay public as well as to the medical profession is as follows: "With current medical therapy approximately 80 to 85 per cent of all cases can be controlled" (Forster, 1960), or "Treatment of epilepsy with anticonvulsants results in control of seizures in approximately 80 per cent of the cases" (Fabing and Barrow, 1954). This would suggest that seizure control is a problem in only a small minority of patients. It is apparent, however, that the statements contain nothing in regard to what constitutes "control" of seizures. When one reviews the literature and stipulates that a minimum of one year must have elapsed without the occurrence of a seizure before the patient is placed in the "controlled" group, one obtains a somewhat different impression. Results of studies spanning more than sixty years are shown in Table 1. Only those studies were included where patients had been followed for at least one year. It can be seen that the highest percentage of complete freedom from seizures for a two-year period prior to last examination of the patient was obtained by Trolle, 1961, and it is only 37 per cent. It is apparent, therefore, that approximately two-thirds of all patients with epilepsy are likely to have a chronic seizure disorder in spite of modern medical treatment. Surprisingly enough one can also see that modern drugs have not brought about a substantial change in long-term remission rates. Turner, with bromide medication in 1907, achieved seizure control for a two-year period in 33 per cent of his patients. If one were to doubt Turner's figures as to the efficacy of bromide medication, we can

point to Stone and Arieff, who reported in 1940 that they brought about remissions as a result of bromide treatment in 78 per cent of ninety-eight patients treated at the Epilepsy Clinic of Northwestern University School of Medicine. Attacks were stopped from the beginning of treatment in 38 per cent of patients and remissions ranged from six months to eight years. A remission of at least six months prior to last visit occurred in 48 per cent of their patients. By 1951, Arieff reported even higher six-month

TABLE 1

PERCENTAGES OF TERMINAL REMISSIONS GIVEN IN THE LITERATURE FOR ADULTS WITH EPILEPSY

	Minimum Duration of Terminal Remission (in years)	*Percentages of Patients Remitted*	*Number of Patients Examined*
Habermaas, 1901	2	10.3	937
Turner, 1907	2	32.0*	87
		33.6**	125
Grosz, 1930	10	10.99	91
Kirstein, 1942	3	21.8	174
Alstroem, 1950	5	22.0*** (approximately)	897
Kiorboe *et al.* 1958 (Short duration, onset after age 17 years)	4	32	130
Strobos, 1959	1	38	228
Probst, 1960	2	31	83
Trolle, 1961	2	37	799
Juul-Jensen, 1963	2	32.1	969
Lorgé, 1964	2	34	177

* Positive family history for epilepsy

** Negative family history for epilepsy

*** Group U 29.2%, Group P 22.7%, Group K 14.2%

Note: Studies containing follow-up of less than 1 year were omitted.

remission rates; 83 per cent of 140 patients treated only with bromides, and 80 per cent of ninety-one patients treated by phenobarbital only. Total remission rate, regardless of drug used, was given as 68 per cent. These figures are presented merely to point out the problem one is confronted with when evaluating the effectiveness of new anticonvulsant medications; length of follow-up of the patient is the all-important variable.

But let us return to the quotation that "80 to 85 per cent of all patients with epilepsy can be controlled." Where did these figures originate? They are probably taken from a paper published in 1952 by Yahr *et al.* who stated in their summary that "The use of diphenylhydantoin (Dilantin) sodium and phenobarbital in this group of 319 patients resulted in 79 per cent control or improvement of seizures regardless of causation. The addition of other anticonvulsants added 6 per cent, giving an overall rate of 85 per cent improvement or control." The attentive reader will note immediately that there is an important qualification in this statement. The authors did not talk about control only, but also about improvement. When we examine the breakdown of the 85 per cent figure, we find 48 per cent completely controlled and 37 per cent improved. When we look for the duration of complete control we find the criterion "complete absence of seizures for periods varying from less than six months to five and one-half years." The paper does not contain a breakdown in regard to the number of patients who were seizure-free for less than six months as opposed to the number of patients who were free from seizures for several years. Inasmuch as the group apparently contains a number of patients whose follow-up period was relatively short, an overall figure of 48 per cent control is not surprising. It agrees, as a matter of fact, with Stone and Arieff's bromide treatment results.

The fact that control of seizures is inversely related to the period of follow-up is important to remember and can be demonstrated whenever follow-up data spanning several years are available. One of the clearest demonstrations of this phenomenon is recorded by Bridge, 1949, and his figures are reproduced in Table 2.

Long-term follow-up studies are quite difficult to perform, especially in the United States due to the mobility of its population, but Alstroem (1950) had the opportunity to examine 897 epileptic patients during the years of 1945 to 1950 who had been originally diagnosed during the period of 1925 to 1940. He divided the total group into three subgroups, depending on presumed etiology of seizures. One group, U, consisted of patients where the etiology of seizures was unknown; in the second group,

TABLE 2

DURATION OF THE PERIOD FREE FROM SEIZURES AT TIME OF FOLLOW-UP STUDY ON 472 EPILEPTIC CHILDREN AS GIVEN BY BRIDGE, 1949*

Period of Freedom	*Number of Cases*		*Per cent*	
5 years or more	81		17	
4 years or more	101		21	
3 years or more	134		28	
2 years or more	161		34	
1 year or more	187		40	
6 months or more	218		46	
1 month or more	264	264	56	56
All others living		147		31
Dead		45		10
Unknown		16		3
Total		472		100

* From *Epilepsy and Convulsive Disorders in Children* by E. M. Bridge. Copyright McGraw-Hill Book Company, Inc., New York, 1949. Used by permission of McGraw-Hill Book Company, Inc.

P, etiology was probably known, and in group three, K, etiology was known. Percentages of recovery were calculated separately for males and females in these groups. A +3 result referred to freedom from seizures for five years or more; and a +2, freedom from seizures for at least three years or an appreciable decrease in the frequency or severity of seizures. Patients who had not changed or who had shown only slight improvement or deterioration were placed in a ± category, while patients who had shown a considerable and distinct exacerbation of seizures were classified as −2 or −3. Table 3 is a reproduction of Alstroem's Table 6. If we concentrate on the +3 group (i.e. freedom from seizures for five years) and calculate the percentage for the total group, we arrive at a figure of approximately 22 per cent.

Alstroem proceeded, subsequently, to calculate the probability of an epileptic becoming seizure-free at varying intervals after the manifestation of the disease. He found considerable differences between patients who showed mental changes and those who were mentally unaffected. He observed that within five years after the onset of the illness approximately 20 per cent of the mentally healthy patients had recovered. The correspond-

TABLE 3

PERCENTUAL DISTRIBUTION OF FOLLOW-UP RESULTS BY ALSTROEM, 1950*

		U (unknown)			*P (probable)*			*K (known)*		
	Seizure Prognosis	M	F	M + F	M	F	M + F	M	F	M + F
+3	Freedom from seizures for five years or more	29.7	28.7	29.2	25.0	19.0	22.7	9.6	23.4	14.2
+2	Freedom from seizures for at least three years	18.3	19.7	19.0	18.5	20.7	19.3	9.6	6.4	8.5
±1	Some improvement or exacerbation	49.3	49.0	49.2	48.9	55.2	51.3	64.9	55.3	61.7
−2 and −3	Considerable and distinct exacerbation in respect of the nature or frequency of seizures	2.6	2.7	2.6	7.6	5.2	6.7	16.0	14.9	15.6

* Reprinted with permission from Alstroem, Carl H.: A study of epilepsy in its clinical, social and genetic aspects. *Acta Psychiatrica et Neurologica, Supplementum 63*, 1950.

ing figure after ten years was almost 30 per cent. The incidence of recovery thereafter fell rapidly and did not reach 35 per cent even after several decades of observation. The mentally unaffected group had, according to Alstroem, the best prognosis; nevertheless, it is clear from his figures that two-thirds of this group had remained chronic seizure patients. For the mentally affected patients the prognosis was poorer still. Even after twenty years of observation the incidence of recovery did not reach 10 per cent. If we take the liberty of combining the two groups of Alstroem (the mentally healthy and the mentally affected) to form one large group of all epileptics, we can see that the incidence of recovery from seizures after twenty years of observation would be only 20 per cent. In other words, 80 per cent of all patients with epilepsy are likely to have a chronic seizure disorder. This does not rule out short-term remissions or changes in seizure patterns, it merely reemphasizes that epilepsy should be regarded as a chronic condition with remissions and exacerbations.

From the data presented so far we can now formulate the next question, Are there any criteria that would reliably differentiate the patient who is likely to show a complete recovery from one who will continue to go on with seizure activity in spite of adequate therapeutic efforts? A review of the literature showed that this is not possible at the present time, but there are certain indices which lend themselves to a better general prognosis, while others tend to be associated with an unfavorable course. Let us now go through a number of variables that have been investigated in the past and examine the various opinions given.

Sex has not been shown to affect prognosis appreciably although Gowers (1885) felt that males had a slightly better prognosis than females, but this view could not be confirmed by others (Turner, Guttmann (1929), Alstroem, Kirstein (1942), Trolle, Strobos (1959)).

As far as age of onset is concerned there is considerable evidence that the earlier the condition manifests itself, the more refractory it tends to be to treatment. It becomes, however, quite difficult at times to decide what one should regard as the age of onset of epilepsy because a number of children may have one or

several febrile or nonfebrile seizures during the first few years of life, but the chronic seizure disorder may not make its appearance until puberty or even later. The question whether the first convulsive seizure should be taken as age of onset, or the time at which recurrent seizures developed remains unanswered. Most studies reported in the literature do not make this distinction. Nevertheless, the general consensus is that seizure disorders starting in childhood or adolescence have less frequent permanent remissions than those starting after age twenty (Grinker *et al.* (1960), Guttmann, Himler, and Raphael (1945), Merritt (1963), Brain (1951), Turner, Selbach (1953), Lempp (1964)). One opinion to the contrary comes from the distant past: "those cases of epilepsy which come on before puberty may undergo a change, but those which come on after twenty-five years of age for the most part terminate in death" (Hippocrates). Habermaas (1901), as well as Grosz (1930), did not feel that age of onset allowed any statement about prognosis. While onset in childhood has been stated to carry a relatively unfavorable prognosis, those cases which start during the first year of life tend to have the poorest prognosis of all (Kiørboe (1961), Hedenstroem and Schorsch (1963), Strobos). This aspect of the problem will be dealt with further in Chapter 2.

While early onset tends to have a poorer prognosis, there are several papers available that deal specifically with "late onset epilepsy," but again the definitions of "late onset" vary. Furthermore, there is frequently no way of knowing whether or not patients who start with seizures for the first time in adult life have had febrile or nonfebrile convulsions in infancy. Hyllested and Pakkenberg (1963) defined late onset seizures as starting after the age of forty-five and found the prognosis to have been quite good unless the disorder was caused by a brain tumor. A follow-up of four to fourteen years showed that nineteen of fifty-nine patients had died, but of the remaining forty individuals, thirty-five had no, or only rare, seizures. Woodcock and Cosgrove (1964), studying patients at the Montreal Neurological Institute in cases where seizures came on after the age of fifty, commented that "in many of the nontumor group, the seizures are chiefly nocturnal, easily controlled by anticonvulsants and not a major

problem to the patient." The relatively good prognosis of patients with late onset epilepsy is also probably a factor in the prognosis of posttraumatic seizures which will, however, be discussed separately. Serafetinides and Dominian (1963) defined late onset as starting after twenty-five years of age, and 70 per cent of their cases started having seizures under the age of forty. Their data can, therefore, not be directly compared with the previous two studies. With a minimum follow-up of four years, they found that 56 per cent were improved, but only 37 per cent seizure-free for at least one year. This figure is, therefore, similar to the other figures listed in Table 1.

In regard to duration of the illness, prior to start of therapy and its relation to prognosis, we have the same difficulty that was mentioned under age of onset. What definition should we use: the very first seizure, or time of onset of recurrent attacks? A definition is even more important here than in the previous paragraphs because it is well known through family histories that individuals may have one or two seizures which never recur. The inclusion of these patients in a drug treatment group will undoubtedly raise the percentage of cases that are "completely controlled by medication" when in fact the patients would not have had further seizures anyway. Nevertheless, the literature shows remarkable unanimity on this point. Practically all studies point out that the shorter the duration of the illness prior to treatment, the better the prognosis. Gowers found that with less than one year duration, 83 per cent of patients could have their seizures arrested. If the illness had lasted ten years or longer, only 24 per cent had their seizures arrested. Similar opinions were voiced by Turner, Alstroem, Habermaas, Oppenheim (1908), Brain, Muskens (1928), Kiørboe, and Trolle.

Somewhat related to duration of illness is the number of seizures the individual has experienced prior to treatment, and it likewise tends to show a direct relationship to prognosis. The fewer seizures the individual has had, the better the chances for remission (Grinker *et al.*, Gowers, Turner, Frantzen (1961), Juul-Jensen (1963), Merritt, Perkins, and Laufer (1947), Probst). Strobos did not find this relationship in regard to major seizures, but noted it to hold true for minor attacks.

The severity of the illness as expressed by the frequency of occurrence of seizures also shows a definite relationship to results of anticonvulsant treatment. The milder the disorder, the easier it is influenced by medication (Gowers, Lennox (1960), Frantzen, Lorgé). Yahr *et al.*, as well as Ranheim *et al.* (1965), did not find such a relationship. A history of recurrent status epilepticus was regarded as an unfavorable prognostic sign by Grosz and by Lennox.

As one might expect, the relationship of seizure types to prognosis has been investigated intensively. The general conclusion seems to be that grand mal, if uncomplicated by other seizures, has the best prognosis; and psychomotor seizures, especially when present in addition to grand mal, have the poorest outcome in regard to complete arrest of attacks (Gowers, Turner, Grinker *et al.*, Arieff, Frantzen, Juul-Jensen (1963), Kiørboe, Hedenstroem and Schorsch (1963), Strobos, Muskens, Probst). A comparison of the percentages of remissions obtained by various authors in grand mal seizures and psychomotor seizures is shown in Table 4. The duration of follow-up varies considerably among authors; nevertheless, the findings do not differ appreciably. It is obvious that in all instances patients with psychomotor seizures enjoyed fewer remissions than those with grand mal. Lennox pointed out that patients who have amnesia for their psychomotor attacks have a poorer prognosis than those in whom this is not the case.

In regard to these series of psychomotor patients one should remember, however, that all of the series probably contain a number of individuals who not only have psychomotor attacks

TABLE 4

COMPARISON OF REMISSION RATES OF PATIENTS WITH PURE GRAND MAL VERSUS PATIENTS WITH PSYCHOMOTOR SEIZURES

	Grand Mal Only		*Psychomotor Seizures*	
	%	N	%	N
Yahr and Merritt, 1959	59	290	20	85
Frantzen, 1961	55	165	34	76
Kiørboe, 1961	58	64	21	28
Trolle, 1961	56	147	35	159
Juul-Jensen, 1963	63	318	20	44

but also, on occasion, grand mal seizures; they suffer therefore from two different seizure types. A combination of different seizures, regardless of specific types, represents a prognostically poorer outlook, as we will see later. This may affect the statistics adversely, and one would theoretically have to treat the data from the patients with pure psychomotor seizures separately. Although this is theoretically desirable, it is frequently impossible to do because patients who have only psychomotor attacks without ever having had a grand mal seizure are relatively infrequent, and it is therefore difficult to get a large enough sample for statistical purposes. A further point of interest with respect to the difference in prognosis for psychomotor versus grand mal seizures is that even Gowers, as well as Turner and Muskens, commented that grand mal seizures are more responsive to treatment than minor seizures and "equivalents."

The opinions concerning petit mal are divided and will be taken up in a separate chapter. Infantile myoclonic seizures will also be discussed later. The prognosis of adult patients with other seizure types tends to fall somewhere between the two extremes of grand mal and psychomotor seizures, except for akinetic and/or myoclonic seizures which are quite difficult to control by medication (Yahr and Merritt, 1959).

It has already been mentioned that the presence of more than one distinct seizure type in the same patient carries an unfavorable prognosis as to complete cessation of all attacks. This has been pointed out by Turner, Arieff, Juul-Jensen (1963), Lempp, Lorgé, Selbach, Strobos and Yahr *et al.* The usual course of events in these cases seems to be that the major seizures tend to show a decrease in frequency and intensity, but minor seizures are likely to continue (Juul-Jensen (1963), Lorgé, and Yahr *et al.*).

Hedenstroem and Schorsch in 1963 reported a study that dealt specifically with the question of why some institutionalized patients respond to anticonvulsant medication, while others remained refractory in spite of maximal efforts. There could be no question about optimal medical treatment for their patients. It was again observed that even in the hospital situation the therapy refractory cases contained significantly less grand mal (25%) and significantly more psychomotor seizure patients (54%).

The conclusion seems inescapable that our drug armamentarium is still quite inadequate for minor seizures even under optimal circumstances.

The relationship of seizures to the sleep-waking cycle was also investigated, in regard to ultimate seizure cessation, by a number of authors. Gowers felt that the prognosis was better when seizures occur in one state only (either waking or sleeping) than if they occur in both of these states. Turner, on the other hand, felt that attacks occurring only during daytime (which included the early morning awakening seizures) had a better prognosis than seizures which occurred during sleep. A poorer prognosis for nocturnal seizures was also reported by Probst. Although they tend to improve in time, their complete cessation occurs rarely. Kiørboe reported that seizures occurring mostly in sleep in children have a good prognosis. No relationship between wakefulness versus sleep and prognosis was noted by Hedenstroem and Schorsch (1963) as well as Strobos. Janz (1962) has recently prepared an extensive review of clinical and electroencephalographic differences between patients whose seizures occurred during sleep only, during the waking state only, and in both states. As it is a cross-sectional study, it does not cover prognosis, but it should be consulted by anyone who is interested in the cyclic manifestation of the epilepsies. As far as menstrual cycle is concerned, no difference in seizure prognosis was found by Strobos.

In regard to etiology of epilepsy and its relationship to prognosis, the literature is far from unanimous. This is, in a way, not surprising because the ultimate cause of epilepsy is unknown and all of the causes that are listed in the literature are in all probability contributory elements rather than the primary etiology. Alstroem's work has already been commented upon, but it bears repeating that he found epilepsy of unknown etiology to have the best prognosis; cases with probably known etiology stood in the middle, and those with definitely known etiology fared the worst. Other authors who have tried to group their seizure patients into *symptomatic* and *idiopathic* did not find this relationship (Arieff, Kiørboe, Trolle, Kirstein, Yahr *et al.*).

Although Juul-Jensen (1963) found the best prognosis in pa-

tients with epilepsy of unknown cause, he qualified his statement by saying, "if cases who had temporal lobe epilepsy were excluded." In view of our previous discussion, this is obviously an important qualification. When he subdivided his material of symptomatic epilepsies into "cerebrovascular disease, head injury, infantile encephalopathy, meningoencephalitis, oxycephaly, multiple sclerosis, etc.," he found the best results in cerebrovascular disease and meningoencephalitis, the poorest in head injuries. The poor result in posttraumatic epilepsy is at variance with other reports, but inasmuch as there is such extensive literature available on this topic it will be taken up in a separate chapter. The view that patients who had an organic etiology for their seizures did worse than those in whom no such etiology was present was also put forth by Habermaas, Lennox, and by Strobos.

As far as the influence of a positive family history of epilepsy on the prognosis of the condition is concerned, Gowers felt that positive heredity histories "lead to easier cessation of seizures but also to a greater chance of relapse and therefore a permanent cure is not easily achieved." Turner did not find a difference as far as arrest of seizures was concerned between hereditary and nonhereditary cases. Lorgé observed that patients with a positive family history did poorer than did those with symptomatic epilepsies, and Hedenstroem and Schorsch (1963) noted in their institutionalized sample that there was also a tendency for hereditary cases to be more resistant to treatment, but the finding did not reach statistical significance.

While etiology presents considerable classification difficulties, no such problems are encountered when one relates seizure prognosis to neurological examination, mental state, and intelligence of the patient. There is considerable agreement between authors that an abnormal neurological examination, an abnormal mental state, and/or low intelligence, carries a poor prognosis with respect to long-term outcome; while patients who have a normal neurological examination, no psychiatric difficulties, and average or above average intelligence tend to do well in general (Gowers, Habermaas, Oppenheim, Muskens, Brain, Arieff, Himler and Raphael, Alstroem, Lorgé, Strobos). Again, one is re-

minded of one of Hippocrates' aphorisms: "in every disease it is a good sign when the patient's intellect is sound." Apparently, however, there are important exceptions to this general rule as far as the intactness of the neurological examination is concerned. Hedenstroem and Schorsch (1963) found this an unimportant variable in their institutionalized patients concerning seizure control, and a similar observation will be commented upon in Chapter 6. On the other hand, dementia was found, even in Hedenstroem and Schorsch's (1963) sample, significantly more frequently in patients who were refractory to treatment. In regard to cerebral atrophy, as demonstrated by pneumoencephalography, no difference was found between this variable and the course of the illness by Hedenstroem and Schorsch (1963), and also by Kiørboe. Juul-Jensen (1963) observed that slight cortical or ventricular atrophy had no influence on clinical prognosis and 51.4 per cent of patients were completely or nearly seizure-free, while this was the case in only 33.6 per cent of patients who had considerable ventricular or cortical atrophy.

The laboratory examination that would appear the most closely related to the epileptic state is, of course, the electroencephalogram and one might expect that it would be a good indicator of a patient's prognosis.

One of the earliest papers on the relationship between the electroencephalogram and treatment results was by Hoefer *et al.* (1947). Ninety-six patients were investigated and it was noted that "In adequately treated cases the EEG becomes more normal. Incidence and duration of paroxysmal bursts are diminished first in the basic run and eventually also during overventilation. Furthermore, the basic activity tends to approach that in normals of the same age group. However, abnormal activity does not fully disappear in most instances." Out of forty patients whose seizures were abolished by treatment (length of time not specified) the EEG became normal in nine; in the other thirty-one, some paroxysmal activity persisted and became even worse in four instances. The opposite phenomenon (namely, EEG improvement in face of persistent seizures) was noted in three cases. Perkins and Laufer found that 53 per cent of thirty-four patients who had a normal EEG by the time of discharge from an army hospital

had no further seizures. The EEG was normal in 21.7 per cent of forty-six patients whose seizures continued subsequently. Follow-up evaluations ranged between four and nineteen months. Toman (1949), in discussing the neuropharmacology of anticonvulsant medication, stated his opinion as follows: "The correlation between clinical and EEG improvement varies widely from patient to patient. At one extreme are the frequent cases of complete suppression by trimethadione of spike and wave discharges with concomitant freedom from seizures. An intermediate group is found in which a diffuse dysrhythmia disappears under diphenylhydantoin treatment, leaving a focal dysrhythmia which may previously have gone unnoticed. Finally, there are the occasional cases in which the focal or diffuse EEG signs continue unabated while the patient enjoys complete freedom from seizures. The latter effects, like changes in severity of seizures, probably represent the ability of anticonvulsant drugs to prevent convulsive activation of normal areas by a primary focus."

Ever since electroencephalography became a clinical tool, investigators have been confronted by the problem that a number of patients with known epilepsy have normal EEGs. The percentages given vary widely between authors, mostly because of differences of opinion as to what is a normal EEG, but regardless of the actual numbers involved the fact remains that normal EEGs are observed in patients with known seizure disorders. For this reason Abbott and Schwab (1948) investigated the meaning of the normal EEG in a patient who has epilepsy. From a total material of 193 cases the authors selected forty patients with normal EEGs who were then matched for age with a group of thirty-eight patients who had abnormal EEGs. Comparing the two groups it was found that the normal EEG group had a later age of onset of the disorder, fewer different kinds of seizures, less frequent seizures, a greater response to medication, more remissions while off medication, more frequent seizures during sleep rather than during the waking state, and a greater ability to work. Patients with abnormal records were found to have had spells during infancy, head injuries or other encephalopathy, and a positive family history of epilepsy. For these reasons it was felt that patients with a normal EEG have a better prognosis.

The papers mentioned so far cover, in essence, experiences that were accumulated subsequently. Most authors now subscribe to the feeling that an EEG which is initially normal, or has become normal as a result of treatment, is significantly more frequently encountered in patients whose seizures cease for some time than in those where they persist (Frantzen, Hedenstroem and Schorsch (1958), Juul-Jensen (1963), Kiørboe *et al.* (1958), Landolt (1957), Messina and Ragonese (1965), Serafetinides and Dominian). The comment is also frequently made that clinical improvement precedes EEG improvements sometimes by several years. While normalization of the EEG tends to herald a good prognosis, the opposite (namely, continuing EEG abnormality) is not necessarily an indication that seizures will remain uncontrolled (Juul-Jensen, 1963). A lack of correlation between EEG and seizure outcome was especially evident in patients with grand mal, according to Frantzen.

Greenstein (1953) found that patients with a family history of epilepsy rarely showed a normal EEG, and that an earlier onset of seizures was associated with more abnormal EEGs. No relationship was found concerning time of day of seizures, frequency of attacks, or duration of the illness.

Probst limited himself to a comparison of patients who had a normal versus a nonspecifically abnormal EEG. No statement was found in the paper whether or not the patients were on anticonvulsant medication at the time of the EEG recording. Probst found no overall difference in regard to prognosis between the two groups. A statistically significant difference was observed, however, when the seizure type was taken into account. Patients with focal seizures and a normal EEG had a poorer prognosis than patients with a normal record and centrencephalic seizures. In contrast to this a nonspecific dysrhythmic record in a focal seizure patient was associated with a better prognosis than when it occurred in a patient with centrencephalic epilepsy.

Juul-Jensen's (1963) series is one of the largest follow-up studies, covering 720 patients. He concluded that abnormal background rhythms in the initial pretreatment EEG suggested a poorer prognosis, but paroxysmal activity in the initial EEG

did not seem to predict a poorer outcome. Improvement of the EEG during treatment was related to a better prognosis, but no definite relationship could be established between deterioration of the EEG and prognosis. Most important for future prognosis was the appearance of the EEG background during treatment. Patients who had "nearly no seizures" showed normal background rhythms in 59.7 per cent, while this was the case in only 14.3 per cent of patients with severe epilepsy. Bilaterally synchronous paroxysms occurring during treatment were not significantly related to prognosis. The group of focal symptomatic epilepsies could be subdivided into mild and severe groups. The mild group did better as far as seizure control was concerned when there was no EEG focus. The presence or absence of an EEG focus was of no importance in the severe group. No relationship was found between the various types of EEG foci and prognosis.

In regard to the likelihood of recurrences of seizures after medication withdrawal, Juul-Jensen (1964) noted that the presence of slow wave foci or bilateral paroxysms increased the risk of recurrence. Landolt also observed that the EEG does not allow definitive conclusions as to the time when anticonvulsant treatment can be reduced. He felt that anticonvulsant treatment should be continued as long as the patient showed seizure discharges in his electroencephalogram, but he also knew of several cases where the patient had become seizure-free, had gone off anticonvulsant medication, and continued to show focal seizure activity in his recording. Furthermore, he noted that, in some instances, patients who had a normal EEG would show immediate recurrence of seizures if the medication was reduced even slightly. In this connection one might point to Hedenstroem and Schorsch's (1958) observation on four patients who had been seizure-free for a considerable period of time, but showed a relapse soon after an electroencephalographic examination. The tracings had not shown any indication of the impending recurrence of seizures in these cases. Kiørboe *et al.* emphasized the point that the initial EEG is not as important for prognosis as the changes that occur while the patient is undergoing treatment. In a group of patients who had no seizures

during the year immediately prior to reexamination, significantly more normal EEGs were encountered than in the group of patients with seizures in the year in question. As far as specific EEG abnormalities are concerned, it was noted that patients with independent bitemporal foci hardly ever became seizure-free for at least one year. Messina and Ragonese felt that age was an important variable in the relationship between EEG and the prognosis of epilepsy. The agreement between electroencephalographic and clinical improvement was found to have been poorer in younger individuals.

Wakana *et al.* (1964) followed one hundred patients for three years after an initial pretherapy EEG. It was found that the EEG can provide prognostic criteria if one looks at specific features of the tracings rather than at a global rating of abnormality. Three groups were formed, namely, normal EEGs, dysrhythmic EEGs, and slow EEGs. As far as the normal EEG was concerned, patients whose seizures started before age fifteen had a poor outcome, while those who had a normal EEG and started after the age of fifteen years did well. In the dysrhythmic group the opposite was the case: patients with early onset did better than those who had started after age fifteen. In the group with predominantly slow activity there was no relationship between age at time of onset of seizures and outcome.

The studies mentioned so far mostly contain heterogeneous groups of seizure patients as far as seizure types are concerned. Ulrich (1961) made a specific effort to deal only with patients who had clinically focal motor or sensory seizures. He found that EEG foci were encountered relatively infrequently in these patients, and for practical purposes all types of EEG findings could be elicited. It was also observed that definitive prognostic statements could not be made on basis of the appearance of the electroencephalogram.

It is apparent, therefore, that the relationships between the clinical seizures and the interictal EEG are, for the most part, indirect. Precise prognostic statements cannot be made on basis of the electroencephalogram alone, in the majority of cases. The exceptions to this general rule will be taken up later.

At this point we may now address ourselves to the problem:

How long should a patient, who is completely controlled on anticonvulsants, remain under this treatment, and what are the chances of recurrence of seizures if treatment is stopped, either on the patient's own account or as a result of the physician's recommendation? It is remarkable that there is not much information available on this obviously important question. Yahr *et al.* decreased anticonvulsant medications gradually in twenty-six patients who had been seizure-free for two years or more. Complete withdrawal of medications without recurrence of seizures could be accomplished in five patients only. Nine had a "significant reduction of medication without recurrences of seizures," and twelve had recurrences during the period of medication reduction. No correlation with type, frequency, or causation of seizures and success of withdrawal of medication could be found. The length of follow-up after complete withdrawal was accomplished was not mentioned in the paper. Strobos reported that forty-one out of eighty-six completely controlled patients attempted gradual reduction of medication; nineteen of these experienced a recurrence; sixteen were still proceeding with gradual reduction while his paper was written; the remaining six tolerated discontinuation of anticonvulsant medications well. Again, the length of follow-up was not stated. He commented that patients who had bilateral synchronous abnormalities in the EEG, which became normal during drug treatment, seemed to tolerate withdrawal better. Juul-Jensen (1964) studied the recurrence of seizures in two hundred patients who had been seizure-free for at least two years and 35 per cent showed a recurrence of seizures within two years after anticonvulsant drugs were discontinued. The recurrences occurred in 50 per cent in close relation to the attempted discontinuation of medication; 33 per cent showed recurrence during the first year and the rest during the second year. It was found that the length of the period during which medication withdrawal took place (ranging between one month and three months) had no influence on the frequency of recurrence. Clear criteria for patients in whom withdrawal did not result in a recurrence of seizures could not be found, but the presence of slow wave foci and bilateral paroxysms in the electroencephalogram increased

the risk of recurrence. The risk increased with higher age at time of onset, and epilepsy of known pathogenesis also had a slightly increased risk of recurrence. Type of seizure, its severity, and the presence of atrophy in the pneumoencephalogram were of no importance. It was also pointed out that when seizures recurred after withdrawal of drugs, they could usually be brought under control again by reinstitution of medications and the patients were subsequently not more difficult to treat.

Reviewing this material the reader will probably be left with a sense of bewilderment. There is agreement in the literature on some points and considerable disagreement on others. It may be best, therefore, to summarize those findings on which the majority of authors agree:

1. Approximately one-third of all epileptic patients are likely to achieve a terminal remission of at least two years.
2. The percentage rises to between 50 and 60 if one considers only those patients who have grand mal seizures without associated minor attacks.
3. It drops to approximately 20 to 30 per cent if one deals with patients who have psychomotor seizures.
4. The percentages of patients who are regarded in terminal remission stand in marked indirect relationship to the length of follow-up.
5. The longer the illness has lasted, the less likely will control be achieved.
6. The more seizures the patient has experienced prior to his first visit to the physician, the less likely will be complete control.
7. The more different seizure types a given patient has experienced, the less likely control.
8. The more abnormal the neurological examination, mental status examination, and the lower the IQ, the more difficult will it be to control the patient.
9. The younger the patient at the time of onset of the illness, the less likely will complete control be achieved; but there are some authors who feel that age at time of onset is not a good prognostic indicator.
10. The initial EEG is of limited value for prognosis, but a

persistently abnormal EEG during treatment tends to be associated with poor seizure control.

Opinions are more divided between authors on the importance of heredity, other etiological factors, nocturnal versus diurnal seizures, and sex.

In regard to the question of drug withdrawal after seizure control has been established for a number of years, the literature contains only a few studies and further investigations of this important area are needed.

Chapter 2

CHILDHOOD EPILEPSY

The majority of patients with epilepsy have their first seizure before ten years of age, and a considerable amount of literature exists that deals specifically with childhood epilepsy and its prognosis.

Let us first consider some general statements that have been made about epilepsy starting in childhood, which would allow a comparison with those made about adult epileptics.

Livingston wrote in 1961: "The medical treatment for epilepsy today is effective in the control of seizures in about 60 per cent of cases. The number of seizures in another 25 per cent can be cut down until they are hardly a handicap. In the remaining 15 per cent, the seizures are refractory to all of the available forms of therapy." Breg and Yannet stated in 1962, ". . . a satisfactory degree of seizure control and social adjustment can be achieved in at least 85 to 90 per cent of mentally normal children. But only 50 per cent can be expected to become completely seizure-free with anticonvulsant therapy during childhood." It is important to point out the qualification that was contained in the statement, namely, "mentally normal" children. We can note again that the meaning of the word "control" is not defined. Remission rates obtained through actual follow-up studies conducted by various authors are shown in Table 5; they range between 16 and 55 per cent. Monrad's two series are of interest because the 1932 report contains nearly twice as many patients in the seizure-free group as the 1923 report. It is not quite clear why this marked change in figures has occurred except, possibly, that the patients in the 1923 report had been treated, for

TABLE 5

PERCENTAGES OF TERMINAL REMISSIONS GIVEN IN THE LITERATURE FOR CHILDREN WITH EPILEPSY

	Minimum Duration of Terminal Remission (in years)	*Percentages of Patients Remitted*	*Number of Patients Examined*
Monrad, 1928	3	28	43
Monrad, 1932	3	50	84
Clemmesen and Moltke, 1935	2	33	76
Faxén, 1935	3	15	95
Wilkins, 1937	1	23	200
Keith, 1937 (Ketogenic diet)	1	36	160
Keith, 1947 (Ketogenic diet)	4	35	190
Bridge, 1949	5	17	472
Lennox, 1951	1½	24	680
Hess, 1958	3	16	228
Kiørboe, 1961	1	41	136
Lundervold and Jabbour, 1962	1	32	100
Fukuyama *et al.* 1963	"complete control" (length of time not specified)	30	801
Lundervold, 1964	2	55	78

the most part, with bromides and borax while the patients mentioned in the 1932 report had also received phenobarbital. A similar phenomenon of marked increase in the number of patients who are controlled, when reported by the same author, can be seen in Lundervold and Jabbour's (1962) data. In 1962, 32 per cent of patients were reported seizure-free for *one* or more years, while in Lundervold's study in 1964, 55 per cent were free from seizures for *two* years or more. The patient populations were different in these two studies; one being conducted in the United States of America, the other in Norway, but this is not likely to account for the discrepancy. The reasons may lie, at least in part, in the fact that the Minnesota sample was drawn from an outpatient clinic, while the patients in the Oslo series were returned from the community for study five or more years after their initial evaluation. The possible importance of

such differences in methodology will be amplified later on. It is, of course, interesting to note that Lundervold's 1964 figure, which is the highest in the table, does not differ appreciably from Monrad's 1932 figure of 50 per cent. This is even more obvious when one considers the fact that Lundervold's remission rate was based on seizure freedom for at least two years, and Monrad's on freedom from seizures for at least three years. We can see again that there has not been the long-awaited breakthrough as a result of new drugs in the past thirty years. Keith's figures, as far as treatment with the ketogenic diet is concerned, have remained constant over a ten-year period; 36 per cent of patients were regarded as seizure-free in 1937, and 35 per cent in 1947. The 1947 report deals with remission rates spanning four to twenty-two years of follow-up.

In 1934 Clemmesen and Moltke reported on seventy-six children treated for epilepsy, twenty-five of whom were regarded as cured, which meant freedom from seizures for two years. This would amount to 33 per cent, as listed in the table. However, the series includes one case of narcolepsy and six cases of isolated seizures, and when these are removed, the remission rate would drop to 26 per cent. One of the lowest figures in the table, namely, 16 per cent remissions reported by Hess (1958), requires further comment. He noted that maximum efforts had been made in this group of 228 patients, but he pointed out that his material probably contained a negative selection because seizure-free patients frequently did not come for control observations and could therefore not be followed. This explanation would, however, not apply to Faxén's (1935) study which was a questionnaire type of follow-up study of patients who had been seen at least three years earlier.

The paper by Fukuyama *et al.* published in 1963 presents a rather typical example of potentially misleading information. The paper is entitled "Medical Treatment of Epilepsies in Childhood: A Long-Term Survey of 801 Patients," and it is stated in the summary: "The authors have reviewed their therapeutic results in 801 epileptic children, all of whom were followed up for a long period. Complete or nearly complete control of seizures was obtained in about 55 per cent of patients, while a smaller

proportion (12%) of the patients demonstrated intractable resistance to medication." From the title and the summary one would gain the impression that the authors want to emphasize that they had a large number of patients available who had been followed for a long period of time and that their results are therefore authoritative. When the paper is examined in detail, one finds the following: out of 1,800 cases of infants and children suffering from chronic recurrent epileptic attacks, 801 were selected who have attended the clinic regularly for a period of *over half a year* at least. Complete control of seizures was obtained in 243 patients (30%), suppression of over 90 per cent of seizures in 182 (23%), 50 to 89 per cent suppression of seizures in 180 (23%), 10 to 49 per cent suppression in 103 (13%), and no significant change or aggravation of the condition was observed in 93 (12%). The authors concluded that ". . . medical therapy was more or less effective in 708 cases (88%) in total; whereas no significant changes or even some aggravation of symptoms were observed only in 93 cases (12%)." If we look at the length of follow-up one finds the following statements: "Patients were followed by the authors during various periods which were distributed in the following manner: 203 cases (25%) for seven to twelve months, 259 cases (32%) for one to two years, 159 cases (20%) for two to three years, 71 cases (9%) for three to four years, 58 cases (7%) for four to five years, and 51 cases (6%) for over five years." As mentioned before, a genuine long-term survey would mean a follow-up of at least three years and hopefully five years, but 77 per cent of the authors' patients were followed for a period of time less than three years, and only 6 per cent of the cases were followed for more than five years. There is also no statement in the paper regarding the length of time the patients had to be completely seizure-free in order to qualify for inclusion in the completely controlled group. But even if we assume that this means a remission rate of at least one year, the 30 per cent figure is not particularly high.

Wilkins found in 1937 that forty-six out of two hundred children (23%) were seizure-free for at least one year. Trying to find criteria which would allow a prediction of good outcome, he

noted that a better chance for remission existed in those patients who had seizures less frequently than one a month. Remissions were also more frequent in patients who had a fewer total number of seizures spaced at long intervals. If the illness started after the age of four years, chronological age was not important for outcome. There was, however, only one child out of the forty-six with freedom from seizures who was under four years of age at the time of initial evaluation. This would suggest that children whose seizures start under age of four are not likely to have long remissions. As far as duration of illness was concerned, most remissions were encountered in patients who had had attacks for less than five years. Patients with normal intelligence and/or normal neurological examination also had a better outcome. Spontaneous remissions, without the children ever having been treated, were also noted but usually in milder cases. However, this was occasionally seen in severe disorders.

Bridge (1949) found the following variables *unrelated* to seizure remission: heredity, personality maladjustment, environmental strain, and duration of illness. Comparing eighty-one cases who had been seizure-free for five years or more with the rest of the sample, he found no differences in regard to age of onset, seizure type, single or multiple seizure types, duration of illness, or intensity of illness. In regard to seizure type there was only one exception: he found akinetic seizures particularly difficult to control and these were not represented in the sample of eighty-one seizure-free patients. Brain injured children were also significantly less common in this sample than in the rest of the group. Investigating the circumstances around cessation of seizure activity in these eighty-one children, he found that in about one-half of the group no reason for cessation could be found; for the other half the reasons were varied, but medication such as bromides, phenobarbital or ketogenic diet accounted for seizure arrest in only 27 per cent of the group.

Lennox (1960) reported the remission rate for more than five years as only 6 per cent of his patients. Probably we have here the same problem that was discussed in regard to Hess's figure in Table 5, when one is forced to calculate the percentages from current outpatient files. Lennox further states: "If a patient, as a

result either of treatment or the kindness of nature, has a reduction to 5 per cent or less of his former attacks (from twenty to one a day, or from once a week to twice a year), he has experienced arrest or approximate cure of his illness. . . . Whether the cause or the result of epilepsy, structural abnormality of the brain is a definite hurdle in the path of full recovery. . . . Presumably the more widespread the lesion, the higher the hurdle—for example, a diffuse encephalitis versus a localized cicatrix . . . petit mal, . . . has by far the best prognosis. . . . Control of generalized convulsions follows control of petit mal at a distance, and is followed in turn by control of focal convulsions and of attacks of temporal epilepsy. Recurrence of status epilepticus is especially foreboding. Frequency of convulsions or psychomotor seizures, particularly if the patient has amnesia for them, clouds the prognosis. . . . Even if all the factors named are in the patient's favor, attacks may persist. On the other hand, if chances of relief seem against him, seizures may greatly diminish or even vanish." With all the experience that Lennox had accumulated in a lifelong effort to understand the nature of epilepsy, the last sentences strike one as particularly sad. They had to be written because they correspond to the facts, but they are also testimony to our abysmal ignorance in regard to the true nature of the disorder.

Yannet (1949) approached the problem of prognosis from a somewhat different aspect and he stated: "While there has been much written on the subject of prognosis in epilepsy, it is difficult to evaluate adequately. The primary reason for this is that the surveys, as a rule, were concerned almost exclusively with the effect of treatment on the incidence of seizures alone. Unfortunately, this fails to take into consideration the many other factors that determine whether an epileptic child is living a relatively normal life in his community. It is conceivable that an emotionally well adjusted child having three to five spells a year is infinitely better off than the child having only one spell a year but seriously handicapped by personality deviations resulting from untreated tensions in the home directly related to the epileptic state."

Yannet reported subsequently on a follow-up study, carried

out at New Haven, on children who were seen at least one year after therapy was instituted and in whom accurate records of seizures, school progress, adjustment at home and community, as well as adequate clinical studies were available. A good result was defined as ". . . less than five spells per year (grand mal); completely satisfactory adjustment in school according to the mental ability of the child; relatively normal community life in line with the age of the child, and satisfaction on the part of the parents as regards to the epileptic state." A poor result was defined as ". . . relatively serious behavior and personality disorders including home, school, and community; seizures occurring five or more times per year, and relative disappointment on the part of the parents as to the progress of the child in reference to the epileptic state." Ninety-nine cases with grand mal seizures were studied and with these criteria in mind the following observations were made. Eighty-three per cent of idiopathic cases had a good result; all cases with positive family history had a good result as compared to only three-quarters of the cases with a negative family history; children with congenital cerebral defects had a good result only in 30 per cent; most of these children were also mentally retarded; about 64 per cent of the birth trauma group had a good result. Little difference was found between the response of those children whose spells began prior to one year of age as compared to those whose spells started later (80% versus 88% good results), and a good response was obtained in 87 per cent of children in whom treatment was started within one year after the onset of spells as compared to 71 per cent good response when treatment was started more than one year after onset. Yannet felt that this difference was probably not significant.

The statement that idiopathic epilepsy responds better to treatment than symptomatic seizures was also made by Fukuyama *et al.* Chao (1958) too, felt that ". . . epilepsy of genetic etiology has a better prognosis for mental and motor development than epilepsy of symptomatic cause. Of the idiopathic group, petit mal absence carries the best prognosis. Most of the patients outgrow their seizures before adolescence and maintain normal to superior intelligence. The majority of patients with

grand mal seizures of idiopathic origin outgrow their seizures in early adult life. The prognosis is less favorable, with respect to complete seizure control and mental development, for mixed seizures of the idiopathic type with either two or three types of petit mal or with petit mal and grand mal seizures. The prognosis is extremely variable in patients with symptomatic epilepsy, varying from extremely good in children with seizures of unifocal origin to extremely grave in cases of multifocal or diffuse encephalopathy. Multifocal and generalized seizures are usually less responsive to treatment than are unifocal seizures . . . prognosis in all cases is further darkened if there are persistent and prolonged seizures, particularly generalized seizures with cyanosis, because of the possibility of the seizures themselves adding insult to injury and causing further deterioration."

Frequently one finds in the literature "idiopathic epilepsy" being equated with "genetic epilepsy." This is unfortunate because in a considerable number of instances of "idiopathic epilepsy" no evidence for a positive family history of epilepsy can be elicited. On the other hand, one can sometimes find a family history of epilepsy in cases with clearly "symptomatic" seizure disorders. This confusion between terms probably beclouds the issue further whether true genetic epilepsy has a good or a bad prognosis, or whether heredity makes no difference at all in regard to seizure control.

No difference in the incidence of family history of epilepsy in regard to seizure control was obtained by Bridge, and by Lundervold and Jabbour, but Craig and MacKinnon (1965) stated that the prognosis of patients with a family history of epilepsy is better than that of those whose seizures are probably related to undisclosed organic lesions. A study group reporting to the World Health Organization on Juvenile Epilepsy in 1957 also expressed the opinion that ". . . except for the babies dying in early infancy, the prognosis of the types of epilepsy in which genetic factors predominate is better than the other types as regards the number of fits, their responsiveness to treatment, and the infrequency of undesirable psychological changes."

In regard to age of onset, Monrad found it not to be significant. This was also the opinion of Lundervold and Jabbour. On

the other hand, Fukuyama *et al.* stated that the younger the age of onset, the worse the result of treatment. Complete control or suppression of over 90 per cent of seizures was obtained in 46 per cent of patients whose seizures started under one year and in 75 per cent of cases who started between twelve and fourteen years. Hess found terminal remissions infrequently in patients whose seizures started between birth to four years (17%). The most frequent terminal remissions occurred in patients whose seizures started between five to nine years (30%), and they were the least frequent when seizures started between ages ten to fifteen (5%). The complete disagreement between Fukuyama *et al.* and Hess in regard to the outcome of patients who started with seizures after ten years of age should be noted. Wilkins' observation on the rarity of remissions when seizures start before four years of age has already been mentioned, but it is repeated here because it agrees with the findings of Hess.

As far as focal seizures are concerned, Hess observed that if these started early in life there are significantly more frequent remissions than in centrencephalic seizures. The later the onset of the illness, the worse the prognosis for focal seizures, and if they started after nine years of age there were no remissions.

Craig and MacKinnon (1965) felt that seizures in babies occurring between the ages of one and six months are usually due to brain damage and carry a poor prognosis. Keith (1964) noted that out of fifty-six children who had convulsions during the first month of life, eighteen had died (32%) and of the survivors 68 per cent became seizure-free. In regard to neonatal convulsions, Burke (1954) found that out of forty-eight cases who had seizures during the first fifteen days of life, eighteen (37.5%) died within a few days. Twenty-seven of the survivors could be followed for periods of time ranging between six months and four and one-half years; five were severely retarded mentally (18%), but only two had had further convulsions (7%). There was close agreement in the mortality rates of Keith and Burke. The disagreement between the number of patients becoming seizure-free may be due to the longer follow-up (10 to 14 years) in Keith's cases. These figures are also of theoretical importance. If epilepsy is caused by birth injury and symptomatic epilepsy

has a bad prognosis, one would expect that children who convulsed within a few days after birth would show a very serious and intractable form of epilepsy. The data on hand do not confirm this concept; they show, on the contrary, that only one-third of the survivors have a chronic seizure disorder. This would suggest, therefore, that the differentiation between symptomatic and idiopathic, as far as birth injury is concerned, is not very fruitful for prognosis in regard to seizure control.

As far as some other prognostic characteristics are concerned, Bergemann (1936) found herself in agreement with Muskens (1928) as well as Grosz (1930) that personality changes in the beginning of the illness represent an unfavorable prognostic sign, but Bridge felt that personality maladjustment made no difference in seizure control. Lundervold and Jabbour reported that no significant differences were found in regard to the incidence of mental retardation, prenatal insults, abnormal birth, birth presentations, birth weight, or postnatal cranial injuries, and the response to treatment. Histories of infection of the central nervous system, including viral and bacterial meningoencephalitis were, however, obtained in 30 per cent of their unimproved group in contrast to 15 per cent of those clinically free from seizures. A combination of low IQ, abnormality of speech, behavioral disturbances, and developmental retardation was observed twice as frequently in the unimproved group as in the other two groups. Cases with more frequent seizures were more difficult to control. In his 1964 study Lundervold found no significant correlation between frequency of attacks and clinical outcome, but cases with more severe and long-lasting seizures were found to be more difficult to control. Faxén noted that among epilepsies with organic etiology, cerebral malformations and birth trauma had the poorest prognosis.

In regard to specific seizure types, there tends to be agreement that grand mal seizures are the easiest to influence by treatment (Chao; Craig and MacKinnon; Fukuyama *et al.*; Hess; Keith). Monrad, on the other hand, found the prognosis to have been the same for grand mal, petit mal, and mixed seizures, but a part of this contradiction appears to reside in what constitutes petit mal, and this will be taken up subsequently in further detail.

There is virtually unanimous agreement that infantile myoclonic seizures have the worst prognosis, but this will also be discussed in greater detail later on. Psychomotor seizures also tend to be somewhat more resistant to treatment as reported by Fukuyama *et al.;* Hess; Livingston and Petersen (1956); and Lundervold and Jabbour. The observation that a combination of different seizure types has a poorer prognosis was reported by Chao and by Keith, but Bridge did not find this to be the case in his sample.

The critical reader will note that criteria which have been implicated as being of good or of poor prognostic significance in childhood epilepsy also have been advocated for the prognosis of the adult patient. Although remission rates for children (as shown in Table 5) are slightly higher than those shown in Table 1 for adults, this is possibly offset by the shorter follow-up in most instances.

Two other conditions peculiar to childhood also should be mentioned briefly. Seizures characterized predominantly by tonic manifestations are often refractory to treatment according to Gastaut *et al.* (1963). The other condition is "acute infantile hemiplegia of obscure origin" (Ford). This is not infrequently encountered although precise figures are lacking. Children, usually under the age of three years, suddenly develop a severe convulsive seizure or status epilepticus which has focal features. This is followed by hemiplegia. The hemiplegia, although improving later on to some extent, tends to remain permanent and some deformity contracture of the extremities, especially of the hand, is usually present later on. The children nearly always show on follow-up some mental retardation and frequently have behavioral difficulties as well as epilepsy. Prognosis as to recovery from the acute condition is good, but quite poor for all the sequelae that have been mentioned. A considerable proportion of these children tend to become inmates of state hospitals. Although the clinical course of the condition is usually quite similar, the etiologies may be diverse. Vascular causes (i.e. venous sinus thrombosis) are listed as most prominent in the literature, but infections and toxic processes also have been assumed, and precise information about the nature of the condition is still not

available. A classic description of this illness is contained in Gowers's book (1885), and he also noted that hemiplegia is more frequently found on the left than on the right side. Gastaut *et al.* (1960) recently have restudied this condition in great detail and have suggested the term H.H.E. syndrome (i.e. Hemiconvulsions-Hemiplegia-Epilepsy). The initial episode was followed by further convulsions within one year in 82.6 per cent of 150 cases. Psychomotor seizures appeared after more than three years in one-half of the patients.

To what extent can the EEG help in the prognosis of childhood seizures? Livingston (1954), although usually on the optimistic side, paints a rather gloomy picture in this regard. "There is no definite relationship, in many cases, between the degree of abnormality in the electroencephalogram and the severity of the epileptic state. Some patients who present marked electroencephalographic abnormalities have fewer and milder seizures than those who have minimal changes in their brain wave patterns. There is also no specific correlation between the clinical course of a patient's seizure and the pattern of subsequent electroencephalograms. In some patients, repeat electroencephalograms present more numerous abnormalities in spite of the fact that the clinical seizures have been controlled with anticonvulsant medication. In other patients the seizures will become more frequent and more severe, and a repeat electroencephalogram will show a marked improvement in the brain wave pattern. . . . The only type of electroencephalographic abnormalities which disappear, in most cases, from the electroencephalogram concurrent with clinical improvement attained by medical therapy are (1) the three per second spike and wave forms such as are seen in the electroencephalograms of patients with petit mal . . . and (2) the petit mal variant forms such as are seen in the electroencephalograms of patients with minor motor epilepsy who are treated with the ketogenic diet."

Chao *et al.* (1958) had a considerably better opinion about the prognostic capabilities of the EEG than Livingston. Inasmuch as they provide a great deal of specific information, their statements will be quoted extensively.

"The original electrographic findings have prognostic signifi-

cance in terms of the outcome for the patient in relation to the number of seizures, in the ease with which such seizures may be controlled, and in the evaluation and differentiation of non-progressive from progressive pathology. In children, the possibility of predicting future mental and motor development will be greatly influenced by the original and subsequent electrographic findings. The following may be considered reliable factors of prognostic evaluation in these terms: (1) A normal electroencephalogram in the patient, whether child or adult, with known convulsions or epileptic symptoms may be considered a good prognostic sign, in that, statistically, patients presenting with normal electroencephalograms show less in the way of neurological deficit, generally show a better response to medication, and rarely show progressive deterioration or deficit. (2) Demonstration of the classic three per second spike and wave pattern against a normal background in a patient with the classic absence seizures may be considered a good prognostic sign, in that such findings rule against the presence of palpable cerebral pathology. The outlook for mental and motor development is generally good. While the control of seizures may be difficult initially, there is a strong chance for spontaneous remission as the child reaches his teens or early adulthood. (3) Demonstration of slow-spike and wave diffuse patterns is a prognostically poorer sign, both in terms of control of seizures and in terms of motor and mental development. (4) If interpretation and evaluation are based largely upon the natural history of such cases, the fourteen and six per second positive spike pattern may be considered to have a relatively good prognostic significance. It has been demonstrated that, although such patients are sometimes refractory to drug therapy and require considerable experimentation in order to find an effective agent for the control of attacks, if this is their sole electrographic abnormality they usually do not have evidence of other neurological abnormality and do not develop any. When this pattern is present in children, both the pattern and the clinical symptoms generally will disappear before adolescence or in the adolescent period. (5) In infants and young children, the demonstration of hypsarhythmia is a poor prognostic feature in that it is almost inevitable that there will

be some degree of mental and motor retardation; however, the spontaneous remission of seizures in later childhood is not uncommon in this group. (6) Circumscribed focal abnormalities in otherwise normal electroencephalograms have a better prognostic significance than all other forms of electroencephalographic abnormalities, with the exception of fourteen and six per second positive spikes and the classic three per second spike and wave pattern. Indeed, in children, the demonstration of a focal slow-spike abnormality in the midtemporal region may constitute the most benign, in terms of its natural history, of any symptomatic finding known. In these children, the seizures are generally easy to control, and the abnormality and seizures usually disappear in late childhood or early adulthood; the incidence of temporary or persisting neurological deficit is relatively low. (7) Focal abnormality existing against a background which is diffusely abnormal is a poorer prognostic finding than the purely focal record and is often a sign of both diffuse and focal involvement of the brain. However, it is possible in certain instances for the focal discharge to disrupt the total activity of the brain so that when and if the focal discharge is curbed through the use of surgery or medication the generalized disturbance will subside, thus indicating that the essential abnormality was primarily focal. (8) Paroxysmal slow activity against a normal background may be a relatively good prognostic electrographic finding; however, this evaluation is much less assured than that given above for the other types of abnormality.

"Perhaps the greatest error of electrographic evaluation is the one of trying to equate the dramatic character of an electrographic abnormality with the severity of the patient's symptoms. Thus, a monorhythmic dysrhythmia—by which we mean, for example, an electroencephalogram consisting of little except low voltage five to six per second rhythmic waves—may have a much greater significance in terms of clinical abnormality and underlying pathology than does a record in which there is a dramatic demonstration of numerous high voltage three per second spike and wave bursts. This is because such a finding may be a sign of deterioration and, therefore, in spite of its undramatic character, a sign of a diffuse encephalopathy of severe degree. Thus, it is

almost impossible to equate the degree of (nonspecific) dysrhythmia as such with the severity of the epilepsy or even of an underlying encephalopathy."

Several points deserve to be emphasized—while a normal EEG tends to be associated with a good prognosis a summary statement that an "abnormal" EEG is prognostically poorer would be a gross oversimplification. The distinctions made by Chao *et al.* between focal abnormalities, appearance of background rhythm, and presence of paroxysms are important because they represent different, and in part, independent phenomena with different prognostic value. Focal abnormalities in form of spikes and/or sharp waves carry different significance in children. They do not necessarily represent the fixed atrophic lesions that we are used to finding in adults with these patterns. Extensive work on this problem has been carried out by Gibbs *et al.*, who reported in 1954 on the disappearance and migration of epileptic foci in childhood. Follow-up studies were obtained on forty-five children above the age of nine who had shown, prior to that time, an occipital focus of seizure activity: 40 per cent of them had normal tracings on follow-up and were seizure-free; 23 per cent had an occipital focus and about one-quarter were seizure-free; in 18 per cent the occipital focus had disappeared and was replaced by a temporal occipital focus and about one-quarter were seizure-free; in 14 per cent the focus had shifted to the midtemporal area, and about one-third were seizure-free; 5 per cent had fourteen and six per second positive spikes, and approximately one-third were seizure-free. Recalculating all figures, one finds approximately twenty-six children seizure-free, that is, about 57 per cent. Ninety-eight patients who had a midtemporal focus were restudied after the age of fifteen: 53 per cent had normal EEGs and all were seizure-free; in 15 per cent the focus had shifted to the anterior temporal area and none were seizure-free; 23 per cent had fourteen and six per second positive spikes, and one-half of them were seizure-free—when the figures are recalculated there are approximately sixty-five patients seizure-free (66%). Gibbs *et al.* concluded that ". . . the evidence indicates that the discharging lesion and the structural lesion are distinct and independent. Unlike the structural lesion, the dis-

charging lesion can migrate, and it commonly heals completely. Healing of the discharging lesion appears to depend on some as yet unknown processes that are intimately related with growth and development. Experience with the present group of cases suggests that when a focus has disappeared and the electroencephalogram has remained normal for one year it is safe to discontinue medication."—No figures were given to support this opinion—"However, when phenobarbital or other barbiturates are employed, they should be discontinued gradually over a period of two weeks to avoid flare-up that sometimes occurs as a result of sudden barbiturate withdrawal. . . . Present experience suggests that it is wise to continue anticonvulsant medication until one year after the last seizure in cases in which a previously abnormal EEG has become normal awake and asleep. Normalization of the EEG is evidence of a recovery process that probably has carried the patient out of danger of further seizures. In order to play doubly safe, however, medication can be continued for another year; a second normal electroencephalogram awake and asleep at the end of that time indicates that no relapse has occurred and gives added assurance that medication can be discontinued without a recurrence of seizures." No statement was made in regard to the length of follow-up of these children in this paper.

The study was continued further by Gibbs and Gibbs, and in 1960 they reported on the good prognosis of midtemporal epilepsy. Seven hundred and thirty-nine persons who had midtemporal spikes but no other seizure activity were investigated. It was found that these foci were increasingly common up to the age of eight years. Their occurrence fell rapidly between eight and fifteen years, and thereafter a pure midtemporal spike focus was rare. A follow-up study of ". . . 120 children whose seizures began after the age of five and who had a spike focus in the midtemporal region and no seizure activity elsewhere revealed that by the age of eighteen years, 85 per cent of such children had no symptoms clearly identifiable as epileptic. In 55 per cent of the eighteen-year-olds the electroencephalogram had normalized and all epileptic symptoms had ceased. Thirty per cent developed fourteen and six per second positive spikes by the age of

eighteen; half of these were asymptomatic and half complained of headaches, dizzy spells, paresthesia, or visceral and vegetative symptoms. Ten per cent developed a negative spike focus in the anterior temporal region, and 5 per cent continued to have negative spikes in the midtemporal region. All patients with negative spikes continued to have convulsions or, in the case of patients with an anterior temporal spike focus, trance-like attacks or confusional episodes. Only this last mentioned group (the 10% with an anterior temporal spike focus) had a residual, seriously handicapping disorder, which can be considered more or less permanent."

Gibbs summarized his feelings about the prognostic importance of certain EEG features in 1954 as follows: Infantile spasms —hypsarhythmia (commonest, ages one to three years) has a bad prognosis. Petit mal variant (commonest in ages two to five years) is only slightly less malignant than infantile spasms. Petit mal (commonest in ages six to twelve years) has a relatively good prognosis; it tends to subside in late adolescence and it is rarely associated with brain damage or intellectual impairment. Occipital focus (commonest in ages three to five years): by nine years of age, 48 per cent of patients cease to have seizures. Midtemporal focus (commonest in ages between seven and ten years): 50 per cent of patients when restudied after age fifteen had normal EEGs and were seizure-free. Fourteen and six per second positive spikes (commonest in late adolescence and young adults) is a relatively benign type of epilepsy; it is easily controlled by drugs and tends to subside with increasing age. Anterior temporal lobe focus—psychomotor epilepsy (commonest in adults): it is less likely to clear up with increasing age and is commonly resistant to medication.

Hess likewise found that EEG foci in children are inconstant, but focal clinical features tend to remain constant. It was also observed that, in general, normalization of the EEG occurred only several years after clinical freedom from attacks. In a subsequent study, Isler and Hess (1960) pointed out that in about one-third of epileptogenic foci, regardless of location, the EEG became normal or nonspecifically abnormal later on. In another third the focus persisted in the same area but showed occasion-

ally more spread into adjacent regions and in the rest of the patients the focus was replaced by generalized abnormalities. No significant correlations between location of EEG focus and seizure outcome were noted. It was felt that the topographic localization of the epileptogenic focus does not seem to be important prognostically in regard to cessation of seizures, persistence of attacks or change to generalized seizures. These results are, of course, contrary to those of Gibbs and Gibbs, but it is conceivable that the length of follow-up might have been important. Approximately two-thirds of Isler and Hess's cases had been followed for two to five years and the rest for more than five years. The length of follow-up in the Gibbs' series is not specified in the 1954 paper and reported as ranging between two and sixteen years in the 1960 study. There was no breakdown provided which would allow one to calculate the average length of follow-up of the Gibbs' cases. Hess also found that patients with normal EEG or nonspecific abnormalities had the strongest tendency towards remission, those with typical spike and wave patterns the least.

Lundervold and Jabbour reported that patients with a normal or nonspecific abnormal EEG had the best prognosis. In his second series Lundervold noted the same phenomenon but added that improvement of a previously markedly abnormal EEG is likewise indication of a good prognosis. Fukuyama *et al.* stated that the outcome was better in patients who had no spikes in their initial EEG than those who did, but no further details were given.

Courjon and Cotte (1958) felt that children under three years of age who have an abnormal EEG several days or several months after the first seizure manifestation have a poorer prognosis than those with a normal tracing.

Yannet *et al.*, using the classification described previously, found no difference in regard to good or poor outcome whether the EEG was normal or abnormal.

Lamontagne and Fischgold (1965) noted considerable correspondence between EEG and clinical improvement but they also stated that they did not know the degree of probability of a permanent cure if the EEG had normalized and they also did

not know the probability of recurrence of seizures in a patient whose EEG had remained abnormal.

The importance of the EEG as a prognostic tool after the very first convulsive seizure was stressed by Aass *et al.* (1956) ". . . an abnormal EEG . . . indicates far greater possibility for recurrent seizures." Of thirty-nine children with a normal EEG after the first seizure, five (13%) had recurrent convulsions within two to five years, but this was the case in forty-six of sixty-one children (75%) who had an abnormal tracing.

As far as the prognosis of children with neonatal convulsions and the electroencephalogram is concerned, Harris and Tizard (1960) followed thirty-one babies for at least one year. Birth weight, age at time of onset of seizures, age at cessation of seizures, clinical diagnosis and type of seizures, as well as rhythmic slow wave activity, focal sharp waves or spikes, repeated stereotyped sharp waves or wave complexes, gross asymmetry, small amplitude, sharp waves during episodic sleep activity, fast activity, and type of EEG pattern during the seizure did not show any definite relationship to the findings at follow-up. The only statistically significant finding was that out of seven children with unilateral EEG abnormalities other than "simple flattening," six were clinically normal and only one abnormal at age of one year or more. Out of twelve children with bilateral abnormalities, two were clinically normal at age one, eight were abnormal, and two had died. The authors pointed out that even more important for prognosis was the duration of the seizures in the neonatal period. Of ten children who convulsed for less than two days, nine were normal and one abnormal at follow-up; while out of ten who convulsed for more than two days, only two were normal and eight abnormal.

One of the most recent reviews of this problem is by Tibbles and Prichard (1965). Of 135 children recorded during the first month of life, 126 were traced; of these, 106 were alive at time of follow-up. Seventy-five of the survivors were examined in the department of pediatrics and the rest followed through the mail. The length of follow-up is not stated in the paper. It was found that 70 per cent of children with normal EEGs had at follow-up normal intellect and no handicap; while in the abnormal EEG

group, 33 per cent had normal intellect and no handicap. The previous suggestion of Harris and Tizard about the prognostic differences between unilateral and bilateral abnormalities was not commented upon by Tibbles and Prichard.

Although not dealing with prognosis, the study of Passouant and Cadilhac (1962) should be mentioned because it demonstrates the pleomorphism of clinical and EEG features that result from different stages of cerebral maturation. The paper points out the difficulties one can encounter when one tries to relate clinical to electroencephalographic features in infancy and early childhood.

A specific investigation regarding discontinuation of anticonvulsant medication when children had been controlled for some time was performed by Zenker *et al.* in 1957. Out of 117 children who had become seizure-free for periods ranging between one-half and nine years, twenty-five showed relapse after anticonvulsants were either decreased or discontinued. Relapse was more common in children who had intellectual defects or personality changes. It was also more frequently seen around puberty regardless of age of onset of the illness and in children who had had infrequent seizures while on medication. Duration of seizure freedom prior to discontinuation of medications seemed unrelated to relapse rate. Hereditary factors were also unimportant in this respect. As far as the EEG was concerned, relapses were not observed when the EEG had markedly improved or become normal under treatment. When the EEG had remained abnormal in spite of anticonvulsant treatment, relapses occurred in twelve out of thirty-three patients; when the EEG had shown moderate improvement, relapses were noted in three out of sixteen patients.

Having given a general review of the problem we can now proceed to examine in detail three conditions that are peculiar to childhood, namely, febrile convulsions, petit mal, and infantile spasms—hypsarhythmia. Breathholding spells will not be discussed because they are clearly nonepileptic. Those episodic conditions that present with headaches, abdominal pain, dizziness, or other manifestations, and that are variously diagnosed as "epileptic equivalents" or "borderland of epilepsy" will also be

omitted because I am not sure that the diagnostic criteria of different authors are uniform enough to allow for meaningful comparisons.

To summarize the information that has been presented in this chapter, we may state that the percentages for terminal remissions in children have been reported to range between a low of 15 per cent and a high of 55 per cent. Similar to the situation in the adult, there exists agreement that patients who have only grand mal seizures tend to respond best to medication while those with psychomotor seizures fare poorer in this respect. There is less agreement in the literature on other prognostic factors. The importance of heredity, other etiological factors, age at time of onset of the illness, and personality adjustment are controversial. As far as the EEG is concerned, there tends to be agreement that patients who have a normal tracing, or those whose EEG normalized during treatment, are likely to have a better outcome. It needs to be emphasized, however, that the term "abnormal EEG" is a gross oversimplification, and different types of EEG abnormalities tend to carry different prognostic information. Reviewing the material one also gains the feeling that there is less agreement on firm prognostic criteria when it comes to children than when one is dealing with adults.

Chapter 3

FEBRILE CONVULSIONS

Accurate information about the incidence of febrile convulsions is not available at the present time, but the following observations may serve as guidelines. Patrick and Levy (1924) found that 4.2 per cent of 752 unselected infants and children who were seen at "better baby conferences" had suffered from convulsions at one time or another. Thom (1942) reported that 6.7 per cent of 3,461 children coming from a "fairly typical cross section representing the working class" of the city of Boston had convulsions. Cooper reported in 1965 that out of 4,779 children born in 1946 and subsequently kept under observation, 107 had experienced convulsive seizures by two years of age (2.2%). These figures, however, refer to all forms of convulsions and not to febrile seizures only. W. Lennox (1960) estimated that ". . . something like 2 per cent of children in the community have one or more febrile convulsions in their first five years, or perhaps 2.5 per cent at any age." Friderichsen and Melchior (1954) found that out of 1,507 children admitted to the pediatric department of Sundby Hospital with fever over 37.6 degrees centigrade, 171 had febrile convulsions (11.3%).

Being confronted with a child who has just had a febrile seizure and assuming that the patient does not suffer from an overt infection of the central nervous system, one would like to know the answers to several questions. These could be listed as follows:

1. Will the patient develop further febrile convulsions?
2. If he does, will this lead to brain damage?
3. Is this convulsion the first indication of future epilepsy?

4. Can anything be done to prevent further recurrences?

In regard to the first question, Table 6 lists some recurrence rates that have been given in the literature. They range from a low of 22 per cent (Frantzen *et al.*, 1964) to a high of 71 per cent (Peterman, 1941). Frantzen's figure was based on a preliminary report of a short follow-up period and may therefore be unduly low. According to Herlitz's (1941) calculations the risk of recurrence of febrile convulsions after the first seizure is 34.9 per cent ± 2.5 per cent, after the second seizure 46.5 per cent ± 4.4 per cent, and after the third, 60.0 per cent ± 6.3 per

TABLE 6

RECURRENCE RATES OF FEBRILE AND AFEBRILE SEIZURES AFTER INITIAL FEBRILE CONVULSIONS

	Febrile Seizures (%)	*Isolated Afebrile Seizures* (%)
Herlitz, 1941	see text	
Ekholm and Niemineva, 1950	15	
Peterman, 1952	71	
Melin, 1954		10.4
Livingston, 1954	52	
Millichap *et al.* 1960	54	17.0
Frantzen *et al.* 1964	22	3.4

cent. If there was a history of seizures in childhood in one of the parents, the risk for recurrence after the first seizure increased to 62.5 per cent.

The second question, whether brain damage is likely to result, is very difficult to answer because appropriate studies are not available. Zimmerman (1938) as well as Fowler (1957) have demonstrated anoxic changes in the brains of children which they regarded as having been caused by the seizures. The results of these studies are somewhat difficult to apply to the clinical situation because we do not know what the state of the brain was before the seizures occurred. The children reported in these two studies were of course all severely ill, and in most instances the convulsions were merely an added complication rather than

the sole cause of the condition. This problem could be studied much better in the animal. From a clinical point of view Ekholm and Niemineva (1950) observed in their follow-up study of sixty-six children with "infectious convulsion" that forty-seven (71%) were normal in all respects after seven to twenty-nine years. Mental development was "more or less retarded" in four (6%). Friderichsen and Melchior had five children in their series of 282 (1.7%)who were found to be mentally defective or retarded at follow-up. Margaret Lennox (1949), comparing the mental development of epileptic children with those who had only febrile seizures, found no difference between the groups in this respect. There were 21.6 per cent abnormal patients in the febrile convulsion group and 22 per cent in the group of epilepsies. These figures are also difficult to evaluate. One cannot say with certainty whether some retardation had been present prior to the onset of febrile seizures, or if it was brought on as a result of the convulsion. Fukuyama (1963) felt that "minor syndromes such as behavior disorders, speech disorders, et cetera, could be frequently encountered." Marked "psycholability" was also encountered in many of Zellweger's patients (1948). Again, we do not know if convulsions in these instances were merely an incidental added complication or if they were causally related. Therefore, we have at the present time no definitive data that would allow a firm conclusion in this respect. On general grounds, we could probably say that the seizures are obviously of no benefit to the subsequent mental and emotional development of the child; but the extent to which they are harmful remains as yet to be determined. One could easily expect considerable individual variation depending upon several different features of past history, as well as frequency and intensity of the convulsive episodes.

As far as the third question is concerned, in regard to the chances for epilepsy to develop, we are on somewhat firmer ground. Table 7 gives some figures from the literature. As one can see, the percentages reported are quite low. The authors that are listed in this table have all carried out longitudinal studies of febrile convulsive patients. The numbers, therefore, are not artificially inflated like those obtained if one tries to deter-

mine how many epileptics have had febrile convulsions in infancy or childhood. Herlitz felt that a definite statement about the risk of future epilepsy cannot be given because of short follow-up periods, but it should in all probability not exceed a small per cent. In order to get this low incidence, one has to be careful in the diagnosis and must differentiate between "simple febrile convulsions" and "epilepsy triggered by fever." The clear-

TABLE 7

INCIDENCE OF EPILEPSY AFTER FEBRILE CONVULSIONS

	Duration of Follow-up	*Percentages of Patients who Developed Epilepsy*	*Number of Patients Examined with Febrile Convulsions*
Frantzen *et al.* 1964	Several months to 2 years	1.9	206
Horstmann and Schinnerling, 1963	Few months to 12 years	9	108
Millichap *et al.* 1960	Six months to 2 years	4	107
Friderichsen and Melchior, 1954	1 year to 15 years	2.4	282
Faxén, 1935	More than 3 years	5	238
Herlitz, 1941	More than 3 years	2.5	424
Zellweger, 1948	More than 4 years	14.3	105
Ekholm and Niemineva, 1950	7 to 28 years	6	66
Livingston, 1954	More than 10 years	2.9	201

Note: Arranged by length of followup.

est demonstration of this difference was given by Livingston (1954). Out of 498 children, who were followed for at least ten years after an initial febrile seizure, 282 (56.5%) subsequently developed epilepsy. When the groups were divided into 201 patients with typical febrile convulsions and 297 patients with atypical febrile seizures, it was found that six (3%) of the first, and 276 (93%) of the second group had developed epilepsy. These striking differences point to the importance of accurate diagnosis at the time of the first seizure.

Twelve criteria, which have been cited by various authors as being important for the differential diagnosis, are rank ordered

in Table 8. The order was based on the number of different authors who felt a particular criterion to be important.

Ad-1: A focal convulsion always argues for the occurrence of future epilepsy, while a benign febrile convulsion has to be generalized and symmetrical (Friderichsen and Melchior; Fukuyama; Horstmann and Schinnerling (1963); M. Lennox; Patrick and Levy; Prichard and McGreal (1958); Peterman; Livingston; W. Lennox; Chao *et al.* (1958); Jennings (1954); Melin (1954); Zellweger (1958)).

TABLE 8

CRITERIA GIVEN IN THE LITERATURE FOR DIFFERENTIATING BENIGN FEBRILE CONVULSIONS FROM EPILEPSY TRIGGERED BY FEVER

1. Type of seizure nonfocal versus focal
2. Age at time of first febrile convulsion
3. Normal versus abnormal EEG
4. Duration of the actual seizure in minutes
5. Family history of benign febrile convulsions versus family history of epilepsy.
6. Number of recurrences of febrile convulsions
7. Absence or presence of preexisting external causes
8. Type of findings during postictal state
9. Absence or presence of neurological deficit either preexisting or after the seizure
10. Intelligence
11. Sex
12. Responsiveness of the convulsion to medication

Note: Arranged by frequency with which finding is cited by various authors.

Ad-2: In regard to age of onset, benign febrile convulsions tend to occur mostly between six months and preschool age. Patrick and Levy felt that the six-month to eighteen-month period is the most common for benign febrile convulsions, but most other authors extend the upper limit to four, five, or six years (Friderichsen and Melchior; Fukuyama; Horstmann and Schinnerling; M. Lennox; Prichard and McGreal; Chao *et al.*). Onset under one year of age was felt to favor future epilepsy by Pache (1954); Melin, and Hrbek (1957).

Ad-3: A normal EEG several days after the seizure argues for benign febrile convulsions; an abnormal EEG for epilepsy (Friderichsen and Melchior; Fukuyama; Horstmann and Schinnerling; M. Lennox; Prichard and McGreal; Peterman; Livingston;

W. Lennox; Chao *et al.;* Jennings). This area is, however, not too clearly delineated in regard to specific features such as type of EEG abnormality and—even more important—the speed with which a record should become normal after a febrile convulsion. Doose *et al.* (1966) felt that a combination of focal and centrencephalic abnormalities had an especially poor prognosis in regard to the development of future epilepsy.

Ad-4: A long seizure argues for epilepsy; a brief one is in favor of benign febrile convulsions. Different authors disagree in regard to how long is "long," but most of them regard the maximum duration of a benign febrile convulsion as thirty minutes (Friderichsen and Melchior; Patrick and Levy; Prichard and McGreal; Peterman; Jennings). Hrbek allows fifteen minutes and Fukuyama gives twenty minutes; but Livingston and Horstmann and Schinnerling allow up to one hour for benign febrile convulsions. These are obviously vast differences and more data will have to be obtained to settle this question.

Ad-5: A family history of benign febrile convulsions is favorable; a family history of epilepsy is unfavorable (Friderichsen and Melchior; Fukuyama; Horstmann and Schinnerling; M. Lennox; Patrick and Levy; Peterman; Livingston; Jennings).

Ad-6: Frequent recurrence of seizures (more than six, Livingston; more than three, Horstmann and Schinnerling) or a series of seizures in a short period of time favor epilepsy (Horstmann and Schinnerling; M. Lennox; Jennings; Hrbek; Zellweger).

Ad-7: Preexisting external causes, like birth injury, have been regarded as favoring subsequent epilepsy (Fukuyama; Horstmann and Schinnerling; M. Lennox; Patrick and Levy; Hrbek).

Ad-8: Sustained postictal coma or Todd's paralysis suggests future epilepsy (Fukuyama; Patrick and Levy; W. Lennox; Jennings).

Ad-9: A neurological deficit, either preexisting or after the seizure, is in favor of subsequent epilepsy (Doose *et al.;* Fukuyama; Prichard and McGreal; Chao *et al.*).

Ad-10: Normal IQ is in favor of benign febrile convulsions; low IQ favors epilepsy (Fukuyama; Horstmann and Schinnerling).

Ad-11: Female sex favors epilepsy (Horstmann and Schinnerling; M. Lennox).

Ad-12: Failure of the individual seizure to respond to adequate medication favors epilepsy (Friderichsen and Melchior).

As far as height of fever is concerned, Prichard and McGreal accept a temperature of over 100 degrees Fahrenheit for benign febrile convulsions, while Chao *et al.* and Jennings require 103 degrees or more.

Reviewing these criteria we can see that they actually boil down to the assumption that a brief self-limited, but generalized, seizure in a child with an otherwise healthy central nervous system, occurring no sooner than six months and no later than six years of age, is not likely to be followed by a chronic seizure disorder. The literature also emphasizes that the likelihood of future epilepsy increases in proportion to the number of unfavorable prognostic indices that are present in a given case. It is, of course, interesting to note that most of the criteria that are given for distinguishing benign febrile convulsions from epilepsy have also been advocated to distinguish between epileptic patients who have a good prognosis as against those who have a poor one. This would strengthen the belief that benign febrile convulsions represent one of the mildest forms of epilepsy rather than being a completely separate entity. One could therefore visualize a continuum of intensity of seizure activity in childhood with benign febrile convulsions on the one extreme and infantile spasms—hypsarhythmia on the other. The other forms of childhood epilepsy would fall prognostically somewhere in between.

This brings us to the fourth question, To what extent can further seizures be prevented after the initial episode? Apart from fever reduction, two courses of action have been advocated. One consists of the continuous treatment of the child with regular anticonvulsant medication to the same extent as if the patient had proven epilepsy (M. Lennox; Peterman); the other of intermittent treatment with phenobarbital at the time of a febrile illness only (Prichard and McGreal). If the first seizure was a typical benign febrile convulsion, Chao *et al.* recommend continued anticonvulsant medication after the second seizure; Jennings after the third; and Livingston *et al.* (1947) after more than four seizures per year. All authors agree that patients with atypical febrile seizures should go on regular anticonvulsant medication immediately. As far as duration of treatment is con-

cerned, it is usually given as one to two years after the last seizure and after the EEG has normalized. It should be pointed out at this time that all these recommendations are based purely on clinical intuition; nevertheless, they are at times propounded in a rather evangelistic manner. Shanks (1951) stated, for instance, in a paragraph entitled Epilepsy as a Preventable Condition: "It cannot be too strongly emphasized, however, that there is a very real possibility that epilepsy under favorable conditions may be preventable. There can be no doubt that convulsions beget convulsions and that uncontrolled convulsions lead in themselves to progressive mental impairment. It follows that no child or adult should be allowed to have repeated fits without the most energetic attempts to control them in the shortest possible time. It is better to use phenobarbitone unnecessarily than to await until repeated fits have confirmed the diagnosis. A confirmed epileptic is an incurable epileptic." The last sentence of the paragraph is especially impressive because it takes care of over 2,000 years of "medical progress" representing a delayed echo of Hippocrates. In his treatise on the sacred disease one can find ". . . it is curable no less than the others, unless, when, from length of time, it is confirmed, and has become stronger than the remedies applied." Addressing oneself to the other parts of the paragraph one would assume that there ought to be an abundance of data by now, showing that epilepsy can indeed be prevented. It is therefore astonishing to find that there is a remarkable lack of controlled studies which deal with actual attempts to find out whether either of the two courses of prophylactic treatment that have been advocated is of any value.

Livingston *et al.* treated sixty-three children with daily doses of anticonvulsants after the first febrile seizure. Attacks recurred in thirty-three (52%). Of thirty-one patients who received no or irregular treatment, fifteen had further seizures (49%). Treatment with anticonvulsants was therefore of no help in preventing further febrile seizures in this group of patients. Millichap *et al.* (1960) compared the results of continuous versus intermittent treatment with phenobarbital in nineteen and twenty-one patients respectively. Seizures recurred in 43 per cent of the continuously treated, and in 53 per cent of the intermittently treated group. Although the numbers of patients involved in these two

studies are relatively small, the results are in essential agreement.

The most extensive investigation to answer the question of preventability of seizures by continuous anticonvulsant medication is being conducted at the present time by Frantzen *et al.* in Denmark. Only a preliminary report is available so far, but even these results are of considerable interest. I am indebted to Doctor Frantzen for the translation of the manuscript into English. Two hundred and twenty children, admitted to the pediatric department of Copenhagen County Hospital after their first febrile convulsion, were extensively studied from the neurological and general medical point of view. All children were under seven years of age and none had had afebrile attacks before. The temperature had been higher than 37.5 degrees centigrade during the febrile illness in all instances; EEGs were obtained twice, on the third or fourth day after admission and on the tenth day. Prior to being discharged from the hospital, the children were divided into two groups, one group comprising children born on odd days, and another containing children born on even days. The group born on odd days was placed on Dilantin (5 mg/kg). The children were then followed as outpatients initially at three months, six months, twelve months, and then once a year. General medical and EEG examinations were made at each follow-up visit. Follow-up information was available on 206 children. Approximately one-half had been followed for one to two years, one-fourth for more than two years; the rest were presumably followed for less than one year, although this is not specifically mentioned in the paper. Out of these 206 children, thirty-eight had developed further febrile convulsions (18%), seven children had one or several afebrile attacks (3%), but only four developed recurrent afebrile seizures, i.e. epilepsy (1.9%). These percentages differ slightly from those given by Frantzen *et al.* in their summary because I based them on the 206 patients that were followed rather than on the original group of 220. As far as recurrence rate of febrile seizures was concerned, it was found to have been 20 per cent for the treated and 23 per cent for the untreated group. A major point of interest was the observation that, of the seven children who had developed afebrile seizures, only one belonged to the treatment group; the other six were

found in the control nontreated group. In contrast to other reports in the literature, family history, birth pathology, and nature as well as duration of the initial seizure, were of no prognostic value in regard to the occurrence of subsequent nonfebrile convulsions. These latter findings agree with the most recent observations by Doose *et al.* (1966).

Taking the three studies of Livingston *et al.*, Millichap *et al.*, and Frantzen *et al.* together, the evidence seems to indicate that there is no reason for the belief that continued, or intermittent, administration of anticonvulsant medication can prevent the occurrence of further febrile seizures. Although this negative result is regrettable, the observation by Frantzen *et al.* that the treated group did, for the most part, not develop nonfebrile seizures is of importance. If this result can be substantiated on a larger sample of patients with a longer follow-up, it might yet show that long-term chronic epilepsy can be avoided in a number of cases.

In summary we may say that the incidence of febrile convulsions in the general population is not known at the present time, but it is estimated to lie around 5 per cent. Recurrence rates of febrile seizures after the first convulsion have been reported to range from a low of 22 per cent to a high of 71 per cent. Occurrence of isolated afebrile seizures after the first febrile convulsion has been given between 3 and 17 per cent. Chronic epilepsy occurred between 2 and 14 per cent of patients who had initially a febrile convulsion.

Criteria were given to differentiate between "benign febrile convulsions" and "epilepsy triggered by fever." These criteria resemble markedly the ones that have been advocated to differentiate between epileptic patients with a good versus poor prognosis. This would seem to lend strength to the belief that febrile convulsions are one of the mildest forms of epilepsy.

There is no evidence to date that continued or intermittent treatment with anticonvulsant medication can prevent the recurrence of further febrile seizures, but there is preliminary suggestive information that it may prevent the occurrence of afebrile seizures or chronic epilepsy. Further controlled studies in this important area are urgently needed.

Chapter 4

PETIT MAL

In regard to the prognosis of petit mal, one cannot readily compare the old literature with present day follow-up studies, because the term has acquired a very specific meaning as a result of EEG studies. At present, it is limited to attacks which are characterized electroencephalographically by diffuse, high voltage, bilaterally symmetrical and synchronous three cycles per second spike wave activity lasting several seconds. The clinical expression of this electrical disturbance is either pure unresponsiveness and staring on the part of the patient, or additional blinking of eyelids, or minimal jerking of the arms or head, or very slight automatic movements of the tongue, lips, or extremities. A history of "staring spells" may sometimes be noted in patients with psychomotor seizures, and this can cloud the diagnostic classification, but an EEG examination during the seizure will usually clarify the picture. We will initially limit ourselves to the discussion of the pure form of petit mal and leave the other two members of Lennox's (1960) "petit mal triad," namely, myoclonic and akinetic seizures, until later. However, we have to mention one other term which overlaps the present day use of petit mal and that is "pyknolepsy." Friedmann (1906) has been given credit for the earliest description of this condition (Adie, 1924; Pohlisch, 1923). When one reviews Friedmann's paper, one finds that the cases which were reported in detail do not form a well-defined group from the present day point of view. Five patients were adults, the attacks had started during adult life, and they lasted up to several minutes. The four reported children do correspond to today's concept of petit

mal. Friedmann regarded the condition not as epilepsy but as narcolepsy, and tried to differentiate it from epileptic petit mal by the following features:

1. The disturbance in consciousness is only a partial one.
2. It is easily provoked and easily suppressed.
3. The individual attacks come about as a result of sudden excitement, certain situations, or momentary stimuli.
4. Mental concentration or other external stimuli when properly timed may inhibit the onset or terminate the existing attack.
5. Apart from prolonged bed rest, they are uninfluenced by drug treatment.
6. The entire abnormality represents a relatively mild defect, is compatible with an otherwise healthy nervous system, and does not result in damage to the mental development even if it occurs in childhood.

Although Friedmann is being credited with describing the condition, the term "pyknolepsy" was coined by Schroeder and appeared for the first time in a paper by Sauer in 1916. The paper contains a very detailed description of eight children with a variety of different seizure phenomena. Seven of the patients were regarded as having suffered from pyknolepsy. It is of historical interest to review these cases because they should, of course, be the prototype for this diagnosis.

CASE 1. Sixteen-year-old boy, head injury at age eleven, unconscious for five minutes. A few days later became dizzy, stated it got dark before his eyes, raised both hands, and fell. Attacks recurred for three to four weeks about five times a week, duration two to three minutes. In addition, milder seizures consisting only of momentary dizziness. Subsequently, some remissions and exacerbations in the condition. Description of attacks as seen in hospital: sits up in bed, kicks with hands and feet, twitching of facial musculature, duration approximately thirty seconds. Occurred during day and night, on one occasion during the night did not awaken with seizure, snored, grabbed the nightstand, threw it over, face was cyanosed. Psychiatrically: became increasingly irritable, aggravated other patients and nursing personnel, used vile language. Attacks improved, patient was discharged, no follow-up.

CASE 2. Seven-year-old female, age two and one-half onset of seizures, got up from chair, went down to floor, and crawled around in a circle, duration of seizure not quite a minute, up to twenty-five attacks daily. Stopped after three months. Four years later different seizure type. Twitching of right hand, runs to mother and hangs on to her. Takes a deep breath. Afterwards tired and yawns. Three to four attacks per day and similar frequency during the night. Once a major seizure, the patient fell to the ground was unconscious and twitched. Description of attack witnessed in hospital: jumps up, becomes red in face, grabs mother with hands and feet. Releases mother after about fifteen seconds, moves hand over head and face, sits down in chair again as if nothing had happened. During the attack, while hanging on to mother, rhythmic to-and-fro movements of head and trunk. Three years later second visit to hospital. Attacks had remitted after initial hospital visit but had returned three months before second visit. Seizures seen in hospital: child gives a frightened shout, grabs mother with arms around the waist, makes restless movements of the trunk, encircles the mother's legs with her own, proceeds to climb up on mother and hangs there. Duration fifteen to twenty seconds. Does not respond immediately afterwards, then becomes tearful and says, "Just had one." School performance good. Child was still having seizures at the time paper was published.

CASE 3. Six-year-old female. Minor seizures since age two, since age three falls and has frequently injured herself but gets up immediately afterwards as if nothing had happened. Seizure observed in hospital: duration ten to fifteen seconds, eyelids close slowly. With longer attacks some twitching of eyelids, eyes deviated upwards, arms limp. Generally does not fall, keeps objects in hand and continues playing immediately afterwards, four to six attacks per hour. Occasionally some swaying and knees become limp. Falls at times but gets up again right away. Still having seizures when discharged from hospital.

CASE 4. Eleven-year-old male. Three months prior to visit onset of seizures, head drops, stares straight ahead, "funny expression of eyes." Duration few seconds, initially one to two per day. Attacks observed in hospital: patient stares vacantly, face expressionless, slight drooping of eyelids, no motor manifestations. Does not drop objects he holds in his hand. Duration one to two seconds. Immediately afterwards says, "It happened again." Thirty to forty attacks per day, normal Binet IQ. Readmitted one year later, attacks only one to two per day, no personality or intellectual change. No further follow-up.

CASE 5. Nine-year-old male. Onset of seizures, age eight. Stops playing, drops objects, stares vacantly, arms tremble somewhat, resumes playing after a few moments as if nothing had happened. Sei-

zures as seen in hospital: patient runs away as if trying to hide at onset of seizure, stands slightly bent forward, head drops, eyes deviate upwards. Duration approximately twelve to fifteen seconds, occasional loss of bladder control, up to one hundred or more attacks a day. At last contact still having seizures but less frequent.

CASE 6. Seven-year-old male. Age three fell from couch, three days later first seizure, becomes completely red in face as if he couldn't get air, then shakes head, duration momentary only. Has never fallen, did not even stumble or stop while running upstairs during attacks. In beginning was supposed to have had them every minute. This lasted seven weeks, then complete freedom from attacks for three years. Seizures returned at age seven. Observation in hospital: sits up in bed, cries out, kicks bystanders with arms and legs, grinds teeth, pupils unreactive during seizure, reacts defensively to pinpricks. After the seizure deep sleep, hardly can be awakened. Attacks repeat every fifteen minutes. Attacks disappeared after patient was placed in isolation. Initial diagnosis: hysteria. Readmission two years later, up to 104 attacks counted per day in the hospital. During seizure face shows furious expression, patient is irritable, talks in angry tone of voice, in beginning of seizures does not answer but later on swears to himself. Towards the end of the seizure answers in irritated tone of voice and later on does not remember what he had said, no amnesia for attacks. Behavior pleasant when not having attacks. Other attacks on different admissions: pulls blanket in front of face, turns onto stomach, goes into knee-elbow position, subsequently kneels in bed, throws himself forward then turns with throwing and kicking movements onto back, lies rigidly for approximately one minute. At last contact still having seizures.

CASE 7. Twelve-year-old male. Age six starts yelling during onset of sleep, can hardly be aroused. When awakened does not know that he had cried. During daytime, momentary attacks of initially few absences, later on started dropping objects, head and body turns to right, eyes deviate upwards and to the right, sometimes smacking movements of the lips, up to forty attacks per day. Every three to four weeks there is one day when the attacks are innumerable. Follow-up: attacks frequent but occur in cyclic fashion with maximum every four weeks. Patient has then hundreds of attacks per day, every few seconds and attacks last several seconds; has only short clear moments, may be incontinent of feces during that day, is completely incompetent mentally that day. This state improves on the second day. Patient is completely well on the third day. Attacks themselves are always exceedingly brief, momentary loss of consciousness, slight turning of the head, and then attack is over. At last contact was still having daily seizures but the "bad days" much less frequently. Able to attend high school.

Sauer concluded that patients should be regarded as having pyknolepsy when there is no evidence of mental or intellectual deterioration in spite of exceedingly frequent attacks which show periodic remissions and exacerbations, and which probably cease around puberty. It was also felt that the most pronounced difficulty in making the diagnosis remains in a definitive separation of this group from the group of epilepsies.

There are several rather interesting features in this paper. From today's point of view we would probably regard cases 1, 2, and 6 as having suffered from psychomotor seizures and cases 3, 4, 5, and 7 as pure petit mal absences. Case 3 also had akinetic attacks and case 7 contains a typical description of petit mal status. Of considerable interest is the statement in regard to probable cessation of attacks around puberty. All of Sauer's cases still had seizures at the time of last hospital visit, and the paper mentions cessation of seizures more as a hope than as a fact. Nevertheless, as we shall see in the subsequent literature review, this particular feature became one of the main characteristics for diagnosis of pyknolepsy.

Pohlisch reviewed the concept and established the following criteria which differentiated pyknolepsy from "genuine" epilepsy: disappearance of the attacks without the production of epileptic personality change; uselessness of anticonvulsant drugs; frequent seizures from the start; duration, in general, from early school age to puberty; only rarely interrupted by short pauses; monotony of seizure type; absence of generalized convulsions and epileptic equivalents. He found pyknolepsy to be rather rare. He subsequently reported thirty-two personal cases of whom he regarded twenty-six as pyknolepsy; the others, as epilepsy or questionable epilepsy. He regarded as characteristic the frequency of seizures from the very first day: five to ten attacks per day are regularly found, and a smaller number should lead one to consider "genuine" epilepsy. Attacks are more frequent immediately after arising and in the forenoon than in the evening. Of seventeen children treated with phenobarbital, temporary improvement was seen in six. He felt that the condition was separable from epilepsy and was not narcolepsy.

In 1923, Adie gave a report to the section of neurology of the Royal Society of Medicine and characterized the condition as: "A disease with an explosive onset between the ages of four and twelve years, of frequent short, very slight, monotonous minor epileptiform seizures of uniform severity, which recur almost daily for weeks, months or years, are uninfluenced by antiepileptic remedies, do not impede normal mental and psychical development, and ultimately cease spontaneously never to return. At most, the eyeballs may roll upwards, the lids may flicker, and the arms may be raised by a feeble tonic spasm. Clonic movements, however slight, obvious vasomotor disturbances, palpitations, and lassitude or confusion after the attacks, are equivocal symptoms strongly suggestive of oncoming grave epilepsy, and for the present they should be considered as foreign to the more favorable disease." He did regard it as a form of epilepsy in children, but felt that it is distinguishable by its clinical features and the prognosis is always good. During the ensuing discussion he admitted, however, that major attacks have occurred in some of the cases ". . . in fact there seemed to be every gradation from pyknolepsy to ordinary epilepsy."

Rosenthal (1935) gave a review of the literature and history of the condition up to 1935. He concluded from his own cases, as well as those from the literature, that pyknolepsy represents an intermediate condition which contains the elements of two groups of diseases without being identical with either one of them. He regarded it as an intermediate between a specific autonomic disturbance on the one hand and epilepsy on the other. He rejected the opinion that the condition was narcolepsy, but

	Cured	*Changed to Epilepsy*	*Chronic Cases*
44 pure cases which had few symptoms associated with the attack	56.5%	30.0%	13.5%
33 atypical cases, those which had a greater variety of symptoms during the attack	40.0%	40.0%	20.0%
25 mixed cases, which had features combining pure as well as atypical features	20.0%	32.0%	48.0%

he emphasized that some cases changed to grand mal epilepsy in the second or third decade. He felt that females had a somewhat poorer prognosis for seizure cessation than males. When he compared the outcome of the illness after several decades, he distinguished the three groups shown on page 59.

If one considers these three different subgroups as one total group, 102 cases are obtained, and when percentages are calculated one finds that 42.1 per cent were regarded as cured, 33.3 per cent had changed to epilepsy, and 24.5 per cent had continued with minor seizures. These figures can be compared with one of the most recent reports by Kuhlo (1965) on seventy-six patients, thirty-one (40%) of whom had enjoyed a terminal remission of at least two years; twenty-seven patients (35%) had changed to grand mal epilepsy, and petit mal persisted in eighteen (24%). The close correspondence of these figures is, of course, striking.

The concept of pyknolepsy being a separate disease entity was again reviewed by Janz in 1955. He concluded that pyknolepsy constitutes a form of petit mal epilepsy. He investigated ninety-eight cases, eighty-eight of whom had started with pyknolepsy and ten who developed pyknolepsy after the first major seizure. This represented 7.7 per cent of all patients with epilepsy seen in nine years (total number 1,272). Studying the outcome of 163 cases he found that spontaneous cure (i.e. seizure freedom for at least two years, ten to fourteen years after onset of the illness and with the patient not on medication) had occurred in only 16 per cent. Thirty-one per cent were still pyknoleptic and 53 per cent had developed major seizures. The few spontaneous remissions occurred on the average after four years but were also seen as late as ten years after onset of the illness. Transition into grand mal usually occurred after five years, but could be seen as late as twenty-two years. He concluded that spontaneous arrest is therefore not the rule but the exception and pyknolepsy appears to be a prelude of later grand mal epilepsy.

American authors have never been impressed with pyknolepsy being anything else than petit mal, and Bridge (1949) does not even mention the term. The reason for the existence of the term

was its supposedly good prognosis. It was, therefore, essentially a retrospective diagnosis. As Lennox (1960) pointed out, a ". . . classification that permits diagnosis only in retrospect is hardly a useful one. . . . The term is welcomed by parents because it connotes something different from epilepsy. However, physicians should not allow paths of thought to be confused by mislabeled signboards." Lennox also pointed out that the first description of classical petit mal he had come across in the literature was contained in a book by Tissot, the observations being dated September, 1769. The beautiful description of the case in Lennox's book is well worth reading.

Inasmuch as the term pyknolepsy was based on a misconception in the first place, it serves no purpose to continue its use. The subject was dealt with in some detail here to point out that it should be regarded as a historical curiosity rather than as a distinct disease entity. Inasmuch as pyknolepsy is petit mal, I will, in the subsequent discussion of the literature, use this term only.

Bridge found that petit mal epilepsy ". . . runs a course with less fluctuations than the predominantly convulsive form. Daily seizures continue to recur year after year with some variation in frequency but rarely with intervals of freedom. After adolescence, seizures that have been frequent for several years may gradually diminish and disappear spontaneously. . . . While the outlook for cessation of seizures may be uncertain, the outlook for essentially normal living is good. . . . Seizures themselves fade in importance both to him and to others of his associates." As far as incidence is concerned, he found that petit mal, either alone or in combination with other forms, comprised approximately 12 per cent of the cases seen at the Epilepsy Clinic.

As to the likelihood of patients with petit mal developing grand mal, Lennox (1960) noted that the older the individual at the time of onset of petit mal, the greater the likelihood that some other seizure type besides petit mal will develop. He found from his patient material that if petit mal began during the first five years of life, 42 per cent had major attacks later on; if it developed between five and nine years, major seizures

occurred in 50 per cent; and if petit mal started at ten years of age or later, 76 per cent of the patients developed other forms of seizures, usually grand mal. In total, out of 404 patients 54 per cent later developed grand mal or psychomotor seizures.

Paal (1957) who followed thirty-nine cases with typical petit mal for periods ranging between six and seventeen years found that they could be divided into three groups: 36 per cent were completely free from seizures for at least two years; 32 per cent had developed grand mal seizures in addition, and another 32 per cent continued to have petit mal only. The group of patients in whom grand mal appeared along with petit mal was predominantly male, those in whom petit mal persisted unchanged tended to be predominantly female, and the group in whom petit mal disappeared was also predominantly female. It was impossible to arrive at specific prognostic criteria in regard to the three courses from the clinical picture or from the electroencephalogram. Heredity had no influence on the course of the illness and patients with organic cerebral damage, or increased incidence of seizures in the early hours of the morning, did not have a more unfavorable prognosis. However, all patients who had an aura later developed major seizures. A greater frequency and spontaneous occurrence of petit mal in the EEG was not an unfavorable prognostic sign. In the clinically seizure-free group the EEG did not show typical three cycles per second spike waves at the time of remission, but it was not always normal. Atypical spike wave bursts could still be seen up to seventeen years after cessation of petit mal.

Holowach *et al.* (1962) reviewed the histories of eighty-eight children with petit mal and, like others, found the condition to be uncommon. Out of 1,054 patients at the seizure clinic of St. Louis Children's Hospital only sixty patients had petit mal. Twenty-eight cases were supplied from private practice. Family history of epilepsy was present in 42.6 per cent, and ten per cent had brain damage of recognized etiology. The overall incidence of brain damage and mental retardation was 24 per cent. Fifty-four children (61%) had additional seizures other than petit mal, 37 per cent had them prior to, 16 per cent during, and 46 per cent after, the onset of the petit mal. Eight children were

completely controlled on phenobarbital. This point is emphasized here because there is a tendency in the neurological literature to regard phenobarbital and/or Dilantin as useless in this condition, and the drugs of choice are usually the succinimides and diones. Of seventy-two patients who had kept follow-up appointments, forty-five (62.5%) were completely controlled for at least one year. Twelve children (16.6%) were improved, and eleven (15.2%) unimproved. In four children, attacks disappeared after treatment efforts had essentially been abandoned. Anticonvulsants were discontinued in sixteen children following four years of treatment after the last seizure; this constituted 22.2 per cent of the total group. It was concluded by the authors: "The review suggests that petit mal is not entirely benign and unaccompanied by cerebral pathologic changes with effect on mentality or personality, nor spontaneously cured at puberty. The high incidence of grand mal and other seizures in these children is emphasized and prophylactic therapy suggested."

Lees and Liversedge (1962) also discussed the prognosis of petit mal. It was found that of twenty-three patients with classical petit mal and three cycles per second spike wave activity in the EEG only three were known to have ceased having attacks (one was taking anticonvulsant medication). Of nineteen patients with classical petit mal who did not show three cycles per second spike and wave activity at the time of the EEG only four had ceased to have attacks. Of thirty-two patients with classical petit mal who had, in addition, grand mal seizures, only three had ceased to have attacks. Freedom from seizures had lasted for at least one year. The authors felt also that the older the patient at the time of onset of petit mal, the greater the likelihood for the appearance of an additional seizure type. It was noted that a few patients with petit mal do cease to have attacks, some before puberty and some after, but the number in whom the disease can be considered arrested is small. The authors commented further: "If children under the care of pediatricians ceased to have attacks, then they would not attend adult clinic. This would overload the adult group with those not in remission, and would produce a falsely low arrest-rate. On the

other hand, pediatricians may have the impression of a favorable outcome if a child is relatively free from attacks at puberty; but even if he is completely free from them, a few years' follow-up into adult life may be long enough for further attacks of petit mal, or for other forms of epilepsy to appear. Very long follow-up studies from childhood to adult life are required to produce more data on prognosis." Lees and Liversedge continued: "Another point which emerged in our study was that many patients gradually learn to live with petit mal and to disregard their attacks very largely. This disregard and eventual cessation of visits to doctors or hospital may add to the general impression of a high natural arrest-rate in the disease. This impression may also be created when petit mal becomes mixed epilepsy, often in late childhood or adult life, and the 'category' of the epilepsy changes. These patients are often thought of not as cases of petit mal (with a bad prognosis) but as grand mal, despite the onset as petit mal. The exclusion of such cases from studies of petit mal weighs in favour of a good prognosis for the disease. One is scarcely justified in regarding a change from petit mal to grand mal as a good prognostic factor." If one calculates the total remission rate of Lees and Liversedge's patients, one finds forty-two patients with pure petit mal; ten of these could not be traced by the authors; seven (21%) had shown terminal remissions of seizures.

Doose and Scheffner's report on the therapy and prognosis of petit mal absences appeared also in 1962. Ninety-nine children were included, half of whom had been seen for one to five years and the other half for six to fourteen years. Fifty-nine children became free from seizures and forty continued to have attacks (no statement was made in regard to the duration of time for which the patients had been seizure-free). It was found that in 80 per cent of the children who had become seizure-free, therapy was started relatively early in the course of the illness. In the forty children who had not become seizure-free, only 30 per cent were treated regularly, another 30 per cent were treated for a short period of time only, and medication was regarded as having been inadequate in 40 per cent. As far as grand mal was concerned, fifty-one patients had had grand mal seizures at some

time during the illness. Petit mal preceded the major seizures, at times by several years, in twenty-nine cases. In eighteen cases, grand mal preceded petit mal, and in four instances the two seizure types occurred nearly simultaneously. Of thirty-four who had pure petit mal at the beginning of treatment, only one developed subsequent grand mal. The authors attributed this to the effect of adequate anticonvulsant medication. The risk for subsequent grand mal also seemed to be somewhat higher for boys than for girls. This is similar to Paal's conclusion. The authors also stated it had been claimed by Christian that absences, with some features of automatisms like chewing, smacking and picking movements, were more difficult to influence therapeutically than absences without these symptoms. In their own material forty-seven children had such symptoms, but they were no different as far as therapeutic results were concerned from those which did not have this symptomatology. A family history of epilepsy had no influence on the therapeutic results. It was concluded that under optimal therapy 95 per cent of patients with pure absences can achieve freedom from seizures. The reasons for this conclusion are not immediately apparent from the statistics that were presented in this particular paper.

In 1963, Currier *et al.* reported on the prognosis of pure petit mal. Thirty-nine patients were studied and strict criteria were employed for the definition of petit mal. Furthermore, the patients had visited the hospital with the primary difficulty of petit mal rather than grand mal seizures. It was found on follow-up examination that three of the patients had had infantile convulsions. Thirty-two cases could be followed, but follow-up EEGs were obtained only in eleven. The average length of time of follow-up was eighteen years. Thirteen patients continued to have petit mal (40%); two had grand mal only (6%); five had grand mal and petit mal (15%); and twelve had no seizures for two years or more (37%). A total of twelve patients had experienced grand mal seizures after the onset of petit mal, and in five of these it had ceased spontaneously or was under complete control with medications. Psychomotor seizures did not develop in any of the patients. It was noted that if the patient reached the age of twenty-one and still had petit mal seizures, the sei-

zures would continue indefinitely within the limits of the follow-up. It was also stated that in all but one in whom petit mal persisted the frequency of attacks had greatly decreased to an average of one or less a day. When petit mal attacks continued they were in general not bothersome to the patient and did not interfere with his activities to any extent. If the patient had not experienced grand mal by the age of eighteen, it did not develop later. It was difficult to predict whether a patient would continue to have petit mal or would experience grand mal seizures, but favorable prognostic signs were listed as follows: early onset (between three and ten years), more than ten petit mal spells a day when at the most frequent, positive family history, normal mentality, and a normal neurological examination. Favorable electroencephalographic findings relative to nonoccurrence of grand mal appeared to be the posterior emphasis of the spike wave discharges and single rather than multiple spike discharges. Unfavorable electroencephalographic findings in regard to future grand mal appeared to be a slow basic pattern, and slow two or three per second spike wave bursts. There was no evidence of progressive physical or mental deterioration in any of the patients except one who developed multiple sclerosis. The authors concluded that ". . . 'Pure' petit mal appears to be a relatively benign disorder which occurs twice as often in girls as in boys, is associated with a family history of grand mal seizures in half the cases, occurs usually between the ages of three and thirteen, more often than not continues into adult life, usually does not bring on grand mal seizures, is not transformed into psychomotor seizures, and is not associated with mental or neurologic deficits or degeneration."

Hertoft reviewed the literature in 1963 and also reported on fifty patients who had been followed for an average of just under thirteen years after the first attack. EEG criteria were used for diagnosis; however, the EEG was not necessarily taken at the onset of the illness but at some time during its course. Twenty-four patients (48%) had no seizures at follow-up; fifteen still had petit mal; eleven had petit mal and/or grand mal. Only six patients (12%) had a completely normal EEG; 54 per cent still had spike wave formations in the record at the time of

follow-up, and of these, four continued to have regular generalized spike wave paroxysms. The oldest of these patients was thirty-six years of age. Twenty-three patients (46%) received no antiepileptic drugs at time of follow-up; of these, nineteen were seizure-free. Ten patients (20%) were below average in regard to intelligence (IQ below 90), but only nineteen of these patients were actually tested by a psychologist; thirty-one were estimated clinically. Ten patients were unable to manage for themselves socially; seven received public allowances. The prognosis was identical for females and males and was found to be independent of the age of patient at the first seizure and independent of possible etiologic factors.

In 1965, Bergamini *et al.* studied the late development of grand mal epilepsy in patients with "pure" petit mal. Seventy-eight cases were followed from five to fourteen years. Forty-two did not develop grand mal; thirty-six did. Of the forty-six patients who were treated early and adequately, 30 per cent developed late grand mal; and of thirty-two treated later and/or inadequately, 68 per cent developed late grand mal. The majority of patients without late grand mal had an age of onset between four and six years, while the late grand mal group had an age of onset mostly between eight and ten years. There was no difference in regard to family history of epilepsy. A clinical cure (an interval of more than one year without petit mal and an additional two years without grand mal) occurred in 70 per cent of patients with petit mal treated early and adequately, and only in 18 per cent treated late and/or inadequately. Of the clinically cured patients, 57.8 per cent had EEGs that were free of abnormalities.

One of the most recent reports on the prognosis of patients with petit mal comes from Livingston *et al.* (1965). The authors also felt that it is a relatively rare type of epileptic seizure, and out of 15,102 epileptic patients only 364 (2.3%) had "true" petit mal. One hundred and seventeen patients had been followed regularly for at least five years, and the duration of follow-up ranged between five and twenty-eight years. At the time of first visit 94.9 per cent were found to have been neurologically and intellectually normal; 5.1 per cent had evidence of

mental retardation and brain damage. The cerebral pathology was present in these patients before the onset of their petit mal seizure disorder. Seventeen (14.5%) of the 117 patients had other types of seizures prior to the onset of petit mal. Four had simple febrile convulsions, and thirteen had major epileptic seizures. Patients were regarded as controlled when there was no recurrence of petit mal during the entire observation period, after freedom from seizures had been obtained and the EEG showed absence of typical diffuse bilaterally synchronous spike and wave forms. Ninety-two (78.6%) of the 117 patients were controlled of their petit mal spells. Twenty-five (21.4%) were uncontrolled. One hundred of the 117 began with petit mal; of these one hundred, fifty-nine were treated with a major motor anticonvulsant regime such as phenobarbital or Dilantin in addition to a specific petit mal anticonvulsant. Twenty-one of the fifty-nine (35.6%) who were treated with the combined therapy developed grand mal seizures; whereas thirty-three (80.5%) of the forty-one patients who were treated with a specific petit mal anticonvulsant alone subsequently developed grand mal seizures. It was also felt that the later petit mal seizures started, the more likely they were to be followed by other seizure types. Of eighty-one patients in whom seizures started between two and one-half and ten years of age, thirty-six subsequently developed major seizures, but this was the case in eighteen out of nineteen patients who started with petit mal between the ages of eleven and fifteen years. No statement was made in the paper about the controllability of the grand mal seizures in these fifty-four patients. Of the 117 patients, eleven suffered with attacks of petit mal status, and six of these manifested evidence of brain damage at the termination of the investigation. It was felt this indicated that petit mal status should be considered as a serious disorder and one which is commonly associated with the development of brain damage.

Kuhlo's (1965) report represents an extension of the material published by Paal. Seventy-six patients with typical petit mal absences and three cycles per second spike wave activity in the EEG, but without associated grand mal seizures, had been followed for at least six years. Twenty-seven (35%) had changed

to grand mal; eighteen (24%) continued to have petit mal; thirty-one (40%) had had a terminal remission of at least two years. Transition to grand mal occurred somewhat more often in male patients. Persistence of petit mal or cessation of petit mal seizures tended to occur more frequently in females. Persistent focal EEG abnormalities and appearance of petit mal status showed a tendency to be associated with future grand mal. If absences had been present for two years, hydantoins or phenobarbital were found to have been ineffective in preventing grand mal seizures.

Gibberd (1966) concluded on the basis of 139 cases that had been seen since 1949 at The London Hospital that a tendency for petit mal to cease existed at any age and not just at puberty. Sex, family history, psychological state, and electroencephalographic findings did not influence the prognosis for petit mal in his sample. Prognosis was better if grand mal did not occur in addition to petit mal. The presence of frequent myoclonus was regarded as being possibly a poor prognostic sign. The tendency to develop grand mal was associated with a poorer prognosis for petit mal, an abnormal psychological state, a poor response of petit mal to treatment, and an abnormal background activity in the EEG.

Eighty-two of the 139 patients (59%) had associated grand mal. Grand mal developed after the onset of petit mal in seventy patients (50%). The total number of patients who had shown complete remissions could not be extracted from the material presented in the paper. If one limits oneself to the fifty-nine cases on whom two EEGs were available, one finds thirty-four patients (57%) in whom petit mal was regarded to have ceased clinically (no episode of petit mal for five years). Of these thirty-four patients, fourteen (41%) still had spike wave activity in their EEGs. Gibberd's paper did not distinguish between classical three per second spike waves and brief bursts of atypical spike wave activity, but this distinction is essential when one talks about cessation of petit mal. It is not clear, therefore, even from this subgroup, how many patients had actually ceased to have petit mal seizures. It is also remarkable that a paper dealing with the prognosis of petit mal written in 1966 bases its

case material on clinical description of the attacks rather than on EEG criteria. While the EEG leaves much to be desired in its relationships to other forms of epilepsy, the three cycles per second spike wave pattern lasting several seconds is so pathognomonic that its presence in the EEG should be required before accepting a final diagnosis of petit mal. It happens rather frequently that the clinical description suggests petit mal, but the electroencephalogram demonstrates the presence of a temporal lobe focus. Incorrect classifications therefore are bound to occur when one has to rely only on clinical histories.

Having listed various authors and opinions, what is one to conclude about the prognosis of "pure" petit mal? To facilitate a comparison of the various findings, two tables have been constructed listing the observations of several authors. Table 9 gives remission rates for petit mal, and Table 10 the incidence of occurrence of grand mal after the onset of petit mal. The material of Livingston *et al.* is not included in Table 9 because remission rates are given for petit mal only and not for associated grand mal. Therefore, we do not know how many patients enjoyed freedom from all types of seizures. It should also be pointed out that Table 9 shows only minimum length of follow-up which is

TABLE 9

COMPLETE REMISSION OF PETIT MAL

	Minimum Duration of Follow-up (in years)	*Percentages of Patients Remitted*	*Number of Patients Examined*
Doose and Scheffner, 1962	1	59	99
Holowach *et al.* 1962	1	62	72
Lees and Liversedge, 1962	1	21	32**
Pohlisch, 1923	2	46	26
Rosenthal, 1935	2	27	36
Paal, 1957	6	36	38
Kuhlo, 1965	6	40	76
Hertoft, 1963	8	48	50
Janz, 1955*	10	16	163
Currier *et al.* 1963	15	37	32

* No seizures of any type and seizure free without medication for at least two years.

** Untraced cases omitted.

Note: No seizures of any type; arranged by minimum duration of follow-up.

TABLE 10

DEVELOPMENT OF GRAND MAL AFTER ONSET OF ILLNESS AS PETIT MAL

	Percentages of Patients Developing Grand Mal	*Number of Patients Examined with Petit Mal*
Janz, 1955	53	163
Paal, 1957	31	38
Lennox, 1960	54	404
Holowach *et al.* 1962	46	88
Currier *et al.* 1963	37	32
Bergamini *et al.* 1965*	46	78
Kuhlo, 1965	38	76
Livingston *et al.* 1965**	54	100
Gibberd, 1966	50	139

* 30% of patients who were treated early and adequately.
68% of patients treated later and/or inadequately.
** 36% of patients having combined therapy.
80% of patients who had received petit mal therapy only.

not necessarily identical with duration of remission. The length of time of freedom from seizures prior to follow-up was not specified in the majority of cases reported. The figures might also differ if EEGs had been obtained on all patients at time of follow-up, because they might have shown classical three cycles per second spike wave activity in a number of cases that were regarded from the clinical point of view as seizure-free.

In general, it would seem that the weight of the evidence shows the following:

1. The condition is relatively rare and the stricter the criteria employed the more infrequently it is found.
2. Although numerous seizures tend to occur per day for several years in childhood, they tend to decrease in number and intensity during adolescence and adulthood so that they do not form a major handicap for the patient later on.
3. Approximately one-third to one-half of all patients who start with petit mal will develop grand mal seizures later in life. There is suggestive evidence that this might be prevented to some extent by giving phenobarbital or

Dilantin in addition to specific petit mal drugs at the beginning of treatment.

4. Petit mal starting after the age of eight to ten years seems to carry a higher risk for the development of future grand mal than its occurrence prior to that age.

5. Mental deterioration is unlikely.

As far as petit mal status and its relation to subsequent brain damage is concerned, this condition is so rare that more work has to be done before a definitive conclusion can be reached.

Chapter 5

INFANTILE SPASMS—HYPSARHYTHMIA; AKINETIC AND MYOCLONIC SEIZURES

Lennox (1960) had tried to include "pure" petit mal absences, as defined in the previous chapter, with akinetic and myoclonic seizures into a petit mal triad, but this suggestion generally was not well received by other authors. This probably resulted from the fact that the prognosis and etiologies differ markedly between these conditions. Akinetic or astatic attacks are usually regarded as being associated with brain damage and are, for practical purposes, resistant to treatment at the present time. The electroencephalographic expression has been reported as consisting of a slow spike wave discharge repeating at one and one-half to two cycles per second instead of three cycles per second (Petit Mal Variant—Gibbs and Gibbs, 1952), but hypsarhythmia or other EEG abnormalities can also be observed.

Myoclonic jerks and myoclonic seizures—characterized electroencephalographically by multiple spikes followed by a wave —are not limited to childhood and can be the expression of a variety of different conditions. If they occur in infancy or early childhood, they tend to carry an exceedingly serious prognosis. In contrast to "pyknolepsy," this condition has been regarded as a form of epilepsy for more than one hundred years. The names that have been applied have varied considerably, as did the presumed etiologies, but its relative refractoriness to treatment has stayed essentially constant. The most widely used term to describe the condition at the present time is "infantile spasms" and/or "hypsarhythmia." Neither of these terms is completely satisfactory because "infantile spasms" do not occur only in in-

fancy but also in early childhood, and the word "spasm" does not emphasize the epileptic nature of the attacks strongly enough. Furthermore, the term does not convey the severity of the clinical condition. Hypsarhythmia, on the other hand, a term used by Gibbs and Gibbs to describe the EEG picture that is frequently found in these children, pertains to the EEG only, and is not necessarily present in all patients with "infantile spasms." Other names that have been applied include the terms: massive myoclonic jerks of infancy, lightning seizures, minor motor seizures, salaam seizures, drop seizures, epilepsia nutans, secousses, flexion spasms, BNS (Blitz-Nick-Salaam seizures), propulsive petit mal and the West syndrome. The latter term is used as tribute to Doctor West, who had described the condition in a letter to the editor of *The Lancet*, dated January, 1841, in order to obtain help for his son who had developed this illness. His description is so vivid and concise, covering all the essential clinical features, that the main portions of his letter will be reproduced here.

"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 the day; they come on whether sitting or lying; just before they come on he is all alive and in 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."

West goes on saying that he had tried all known remedies, without success, and had subsequently taken the child to ". . . Sir Charles Clarke and Dr. Locock, both of whom recognized the complaint; the former, in all of his extensive practice, had only seen four cases, and, from the peculiar bowing of the head, called it the 'salaam convulsion'; . . . . Sir C. Clarke knows the result of only two of his cases: one perfectly recovered; the other became paralytic and idiotic; lived several years in that state, and died at the age of seventeen years. I have heard of two other cases, which lived one to the age of seventeen, the other nineteen years, idiotic, and then died. . . . Although this may be a very rare and singular affection, and only noticed by two of our most eminent physicians, I am, from all I have learnt, convinced that it is a disease (*sui generis*) which, from its infrequency, has escaped the attention of the profession. I therefore hope you will give it the fullest publicity, as this paper might rather be extended than curtailed."

In a postscript Dr. West gave a brief progress note: "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."

For further historical review of the condition the reader is referred to the paper by Bower and Jeavons (1959), and the

chapter on astatic epilepsy in Lennox's book. There is still some controversy in the literature whether these attacks are predominantly due to an inhibitory mechanism or whether the falls result from massive myoclonic jerks. The myoclonic jerks are readily observable in a number of children, but others merely seem to lose posture and crumple to the floor, while still others may have both seizure types on different occasions. Inasmuch as it has not been demonstrated that the prognosis differs substantially between these various forms and there is so much overlap even in a given patient, no attempt will be made to enter into this controversy here.

Chao *et al.* (1957) noted that the prognosis was good in regard to eventual cessation of massive spasms. "However, over 15 per cent of patients have other types of seizures (focal, generalized, or akinetic) or develop them after the massive spasms cease. The severe mental deterioration represents a most serious aspect with respect to prognosis. Intellectual ability may improve after spasms cease entirely but it seldom returns completely to normal. . . . A more favorable prognosis with respect to mental development exists when seizures continue only for short periods. . . . Patients whose massive spasms occur singly rather than in series also tend to carry a better prognosis."

Livingston *et al.* reported in 1958 on 698 children with what he called "minor motor epilepsy"; the earliest age of onset was found to have been eight days, and the latest five and one-half years. These constituted approximately 9 per cent of all children studied at the Epilepsy Clinic of Johns Hopkins Hospital out of a total of 7,832 children. The condition is, therefore, somewhat more common than pure petit mal absences. IQ at one year of age was estimated to have been normal in fourteen children; twenty-one were slightly retarded; 248 moderately retarded, and 388 severely retarded. Hypsarhythmia was found to have been present in the electroencephalogram in 511 out of 594 EEGs (86%). The etiological conditions were quite diverse. The authors noted that these spells are exceedingly difficult to control with anticonvulsant drugs and felt that the ketogenic diet was the most effective therapy. Seizures rarely recurred after five or six years of age. With the ketogenic diet, complete control of

spells was obtained in 91 of 186 patients who had been on this form of therapy (49%). The most serious aspect of minor motor epilepsy was, however, the associated mental retardation. Bower and Jeavon's writing in 1959 on infantile spasms and hypsarhythmia stated: "All workers agree that most patients remain mentally defective although the spasms diminish in frequency or disappear. A few die within a few years of the onset of spasms." They went on to say that of their twenty-two patients, two had died, nineteen remained mentally retarded, and one child recovered completely in all respects.

Being confronted with such a hopeless outlook, Stamps *et al.* (1959) were impressed by the exhibit of Sorel and Dusaucy-Bauloye in 1958 on the results of treatment of these patients with ACTH and they tried this compound subsequently in sixty of their patients. Their report presents an example of how the investigator's hopes can at times exceed factual data. The summary and conclusions state: "Before the introduction by Sorel of ACTH for the treatment of hypsarhythmia, the prognosis for patients with this condition was extremely poor; 85 per cent became mentally retarded and 10 per cent died. Electroencephalographic and clinical studies on sixty consecutive patients with infantile spasms with hypsarhythmia, some of whom have been followed up for over a year, indicate that ACTH therapy results in a dramatic improvement in at least 30 per cent of such cases. When a good response to ACTH is obtained, the electroencephalogram normalizes, a great clinical improvement occurs, the spasms cease, and further retardation is prevented." The attentive reader will note that "some" of the patients were followed "for over a year." The body of the paper gives no indication about the length of follow-up of any of the children and it is therefore difficult to see how the conclusion that "further retardation is prevented" can be justified. A further point of interest emerges from the study of the paper, namely, a statement: "Although the seizures tend to subside by the fourth year of life even without treatment, retardation is permanent." This points out the fact that the stopping of seizures is not necessarily equivalent to significant improvement in mentality. If one examines the table that accompanies the paper, one finds that seizures were

eliminated (time unspecified) in eighteen (30 per cent), decreased in thirteen (22 per cent), and unchanged in twenty-nine (48%). As far as "motor performance and alertness" was concerned, six (10%) became normal, eighteen (30%) were improved, and thirty-six (60%) were unimproved, while nine (15%)patients showed a relapse after improvement. If we subtract the nine patients who had shown a relapse, we find that fifteen out of sixty patients (25%) had shown normalization or improvement in "motor performance and alertness." To turn this figure around, 75 per cent remained mentally retarded, which is not too strikingly different from the 85 per cent quoted in the introductory paragraph of the paper.

Fukuyama *et al.* (1960) reported "excellent results" from ACTH injections, in the summary of their paper, but in the paragraph on results, one finds: "Among forty-eight cases, twelve cases (25%) became entirely free from seizures, and in seventeen cases (35.4%) seizures diminished remarkably." In the discussion one reads: "Our global result was inferior to that of above-mentioned authors because complete control of both clinical seizures and electroencephalographic abnormalities was attained in only eight among thirty-four cases (23.5%), while other authors reported the effectiveness in 70 to 100 per cent of patients."

Trojaborg and Plum (1960) found that 25 per cent of all children between birth to two years admitted for the first time because of convulsions to the Paediatric Clinic of Copenhagen University Hospital had infantile spasms. Hypsarhythmia was found in 80 per cent. Definite clinical effects were found in regard to reduction or cessation of the attacks in seven of twenty-two children treated with ACTH (32%). No definite effect upon the mental state was found. Pauli *et al.* (1960) reported poor success with ACTH treatment in fourteen children; only four showed improvement in regard to seizures, and in no instance was there significant improvement in the mental state.

A decreasing incidence of treatment effect in relation to length of follow-up was noted by Dumermuth in 1961. Thirty-eight patients were treated with ACTH or hydrocortisone. Initially, 68 per cent of this group showed a good result. Twenty-six patients were followed for more than one year; of these twenty-six pa-

tients, sixteen had had a good result initially (61%), but after one year only six of them (37%) still had a good outcome. If the percentage of patients with good outcome is calculated for the total group of twenty-six patients who were followed, regardless of initial success, one finds definite improvement in only 23 per cent. The clinical findings gave no indication why some patients had a good result while others did not.

Noting these varying statements about the effectiveness of steroid treatment, Jeavons and Bower (1961) subsequently decided to study the natural history of infantile spasms in order to have definitive figures against which the effects of the treatment could be measured. Their summary is quoted in its entirety because of its obvious importance: "Thirty infants with the syndrome of infantile spasms and mental retardation occurring before the age of one year have been followed by clinical and EEG examination for periods of two to six years. None were treated with corticotrophin or steroids. There was a steady reduction in the number still having spasms, and at three years over half the patients were free of them. Focal or major fits occurred in one-third of the total and did not show the same tendency to disappear with age. The EEGs became more organized and at three to three and one-half years more than one-third were normal. Hypsarhythmia was rare by this age but was found even at six years. Mental improvement was much rarer and only two patients became mentally normal. The mortality rate was 13 per cent by three and one-half years. There was little difference between the symptomatic and cryptogenic groups with regard to the rate of disappearance of spasms and EEG improvement. Mental retardation, however, was less severe in the cryptogenic group even at one year and this group showed a slight but definite general improvement later; whereas none occurred in the symptomatic group."

Bower and Jeavons (1961) compared these results with the outcome in twenty-three children who had been treated with corticotrophin and/or prednisolone. It was found: "Spasms ceased during treatment in eighteen patients but recurred in thirteen after treatment. Some EEG improvement occurred in all patients except one, and a non-epileptic record was achieved

in nine, though relapse occurred in five of those whose spasms recurred. Eight were given a second course of treatment but seven again relapsed. At the end of an average follow-up period of eight months, eleven patients had no spasms" (48%). "The effect of corticotrophin was similar to that of prednisolone; although, with the doses employed, corticotrophin appears preferable. No immediate mental improvement occurred, and only two cases eventually achieved a development quotient of eighty or more. Although the drugs had a temporary beneficial effect in both the symptomatic and cryptogenic groups, better results were achieved in the latter group. A comparison is made with a group of patients not treated with hormones and it is concluded that on the whole these drugs have a long-term beneficial effect on the spasms; whereas their effect on mentality is doubtful. It is possible that under hormonal treatment there is an acceleration of the natural changes which occur with age."

The observation that "idiopathic" cases of infantile spasms have a better prognosis, regardless of type of treatment, was also made by Matthes (1954). The symptomatic group contained 30 per cent of ninety patients, half of these had died by the time of follow-up which ranged up to thirty-three years; the other half, with exception of one case, was profoundly retarded mentally. As far as the idiopathic group was concerned 80 per cent were alive at time of follow-up and one-quarter had shown normal physical and mental development.

Stolecke and Pache (1962) made the point that children who were treated prior to age nine months had a better outcome than those who received their first treatment after that age. Of eleven children who were treated with ACTH prior to nine months of age, four had a complete remission with subsequent normal physical and mental development. This was the case in three out of seventeen children only, who were treated after the ninth month. The length of follow-up was not stated in their paper.

Bray reported in 1963 a four-year follow-up study of the ten patients who had been originally reported by Low in 1958. Although the number of patients is small, it is the only report dealing with long-term results of corticotrophin and cortisone therapy. Bray concluded from his study: "No correlation was

found between the infants' initial clinical and electroencephalographic response to therapy and their follow-up intelligence quotients. The similar initial electroencephalographic findings, contrasted with the marked follow-up differences in levels of intellectual functioning, illustrate the limited prognostic value of the electroencephalogram in this syndrome. Similarly, no correlation was noted in the patients' initial response to therapy, and the presence or absence of microcephaly or focal neurological deficit. In the absence of any other rational treatment, and despite the dismal prospect suggested by this report and those of others, renewed efforts to treat patients earlier and more intensively with cortisone and corticotropin could be undertaken. However, in the light of four years' experience, such an approach might be a reflection more of therapeutic desperation than of rational expectation of good results."

Schmidt (1964) reported on the effects of ACTH and prednisone in a group of thirty-two children with infantile myoclonic seizures. Four children were regarded as cured after treatment (12%); sixteen improved, and twelve had not changed. Seizures and EEG were more easily influenced than psychomotor development. It was felt that success can be expected only with high dosages and long-term administration of the compounds. It was also felt that the shorter the period of time between onset of the condition and treatment, the better the ultimate success. The follow-up duration ranged from three months to three years.

Another study appearing in 1963 was by Doose who reported on eighty-one children with this condition. He pointed to the discrepancies in the literature regarding treatment results but felt that these were due to different dosages used, different compounds, and different length of treatment. As far as his own series was concerned, out of thirty-six adequately treated children thirty became initially seizure-free (83%); three improved, and three remained unchanged. In regard to final result of follow-up ranging between three months and two and one-half years, twenty-four children were seizure-free (77%); three improved; four were unchanged, and five patients had died. He listed the following factors as being important for the success of treatment:

1. Children who are severely damaged frequently respond quite slowly, temporarily, or not at all, but strict correlations between type and extent of preexisting damage and response to treatment were not present, because occasionally, even severely damaged patients showed a good response.
2. Seizures were more easily influenced in infancy than in older children and treatment results were better with a shorter duration of illness.

He found, as have others, that the influence of hormonal treatment on mental development was more difficult to assess. The majority of children had marked mental retardation prior to treatment. A positive effect of therapy on mental development was seen rarely in such cases. In less damaged children improvement in development could be seen more frequently. In some children a marked discrepancy between physical and mental development could be observed. Some children regained their motor functions soon after cessation of seizures without at the same time showing definite progress in their mental development. He concluded that treatment with ACTH or corticosteroids can bring about a rapid cessation of seizure activity in the majority of cases (70%). Children who have not been already damaged can be saved from mental and physical deterioration. In children who are retarded a progression of this damage can be prevented, and the physical and mental development can be beneficially influenced on occasion. In general, he felt that there are quite narrow limits to the success of hormonal therapy, because in the majority of patients the condition is due to marked cerebral damage. Nevertheless, the treatment results can be improved if the children are treated immediately after the onset of seizures. Start of treatment within the first weeks was regarded as even more important in infantile myoclonic seizures than in other forms of epilepsy. We will return to this point in more detail later.

In 1964 Harris reported on seventy-five children suffering from infantile spasms and treated with ACTH. She found: "Only six have apparently recovered at a follow-up of one or two years, though temporary favourable clinical and EEG response had been seen in many more cases. None of the patients who did not

show EEG improvement in relation to the first course of ACTH eventually recovered." One of the most recent reports at the time of this writing was by Danielsen in 1965, who treated twenty-three children with corticosteroids. The attacks ceased during treatment in fourteen (60%) and improved in one. Seventeen patients had hypsarhythmia, which disappeared in twelve during treatment but recurred afterwards in one. Seizure freedom had dropped to eight cases (34%) by the time of follow-up, which ranged between six months and four and one-half years. Mental retardation was found to be unaffected by steroid treatment. Danielsen concluded: "Although the effect on the mental development is doubtful, the effect on the incidence of attacks and on the EEG pattern is considerable. Steroid treatment of patients with infantile spasms and hypsarhythmia must therefore be regarded as the best treatment available at present, and treatment should be instituted as soon after the commencement of the attacks as possible."

This brings us to the crux of the problem. Although Sorel and Dusaucy-Bauloye's paper is widely quoted in references, its main message does not seem to have reached subsequent investigators. Their report was based on twenty-one children with hypsarhythmia, seventeen of whom were followed for one month to six and one-half years. Seven of these seventeen received ACTH treatment. In five of the seven cases the EEG normalized completely within several days, and in one the tracing improved markedly but a left temporal focus remained. The EEG was not influenced in the last case. From a clinical point of view the epileptic attacks disappeared immediately in six cases. The patient whose EEG did not respond also showed no clinical improvement. The main point of the paper is contained in the sentences: In two of these cases treatment could be instituted during the first week. Motor and mental status returned to normal, and physical and intellectual development subsequently proceeded in a normal manner, with a follow-up of two years in one case and nine months in the other. In the other two cases where treatment was instituted after three to four months, the seizures had disappeared but the intellectual state had not normalized completely. In the two cases where treatment could not

be instituted until quite late the dementia was total. This treatment, therefore, completely modifies the prognosis of this serious condition of infancy, but it should be instituted with the greatest possible speed.

If we were to summarize the relevant points of the paper, one would say that out of seven patients treated with ACTH, six had complete freedom from seizures during the limited follow-up period, but only two subsequently continued with normal mental and physical development. These two patients had been treated within the *first week* of the onset of the illness. Gastaut *et al.*, reporting on four cases in 1959, also emphasized this point. They stated that if the illness has been present only for several days or weeks before treatment is started and before signs of mental regression are noted, recovery is rapid and total. If, on the other hand, treatment is started only after several months or several years, the intellectual deficit cannot be overcome and the status quo remains.

The conditions under which one could expect an improvement in mentality were, therefore, quite clearly spelled out in these two papers. With the literature having reached considerable proportion in the subsequent years, one might have expected that this point would have been considered and that we would by now have definitive figures that would allow us to compare the effects of treatment instituted within the first one or two weeks after the onset of the illness, against the results achieved if treatment is started after one to two months, or even later. If one reviews the literature from this specific point of view, one finds a remarkable paucity of material. The majority of authors either do not give definite data as to the time of initiation of treatment in relation to the first appearance of symptoms, or they create larger groups with treatment starting within the first three months or first six months after onset of illness. It is impossible from their tables or figures to select those cases that were treated within the first month or weeks. Gastaut *et al.* had only one case out of the four that was treated within one month after the onset of the illness, and this child recovered completely. Bower and Jeavons had one case of cryptogenic infantile spasms that was treated within three weeks after onset of the illness. The developmental

quotient before and after treatment was low but ". . . this child subsequently reached eighty-three." There was also one case in their symptomatic group that was treated within four days, but no effect on mentality occurred. Dummermuth's Case 1 was treated within a few days, and immediate cessation of seizures was noted with subsequent normal psychomotor development. The developmental quotient two years later was 117. Harris' Case 2 was treated ". . . very soon after the onset of infantile spasms. The EEG improvement occurred very rapidly and no further spasms occurred, but he was moderately retarded at follow-up." Koch and Gruetzner's (1960) Case 1 was treated six weeks after onset. The EEG normalized; seizures stopped, and normal physical and mental development occurred. Their Case 2, also treated six weeks after onset, showed initial improvement but subsequent relapse. At follow-up, three months later, there were occasional infrequent seizures. Mental development had progressed but was retarded in contrast to his unaffected twin brother. Pauli *et al.* (1960): Cases 8 and 11 were treated one month after the onset of the illness, but both children were already definitely retarded; there was no effect on the condition. Schmidt noted among the patients who could be treated "immediately" that there were three of the four patients who showed subsequent normal development. What is meant by the term "immediately" cannot be reconstructed from his figures, because the table combines patients treated within one to three months. Stolecke and Pache's Cases 7 and 26 were treated after two weeks of illness. One showed completely normal physical and mental development; the other improved in regard to seizures but remained retarded mentally.

We are therefore confronted with the fact that on this apparently most important variable we still have quite inadequate information. I am especially emphasizing this point because we are dealing with a condition which represents a human catastrophe. If there is any hope that permanent mental retardation is avoidable, even in a segment of the various conditions that can cause the clinical and EEG picture of infantile spasms, it should certainly be pursued most energetically. It would be most interesting to see whether the long-term results in regard to the

mentality of a large number of children, treated within the first two to three weeks after onset of the condition, do in fact differ from those who are treated later or not at all. This answer is not available at the present time. It could only become available if pediatricians and general practitioners were informed that the symptom of infantile spasms and/or hypsarhythmia represents a medical emergency, as acute as ileus for instance, and immediate vigorous steroid treatment is indicated. EEGs obtained at weekly intervals would give an indication about the effectiveness of treatment. Dosages could be adjusted in an upward or downward direction depending upon the EEG picture rather than relying on clinical observation only. A program like this would, within a few years, tell to what extent the steroids are effective, and one could then define the subgroups in which success can be anticipated. It is obvious that if a severe congenital malformation of the brain exists, steroids are not likely to be of much help, but at the beginning of the illness one may not be absolutely certain about the presence or absence of congenital malformations. It would seem better at this point in time to treat the total group of patients regardless of presumed etiologies and to evaluate later who is responding and why. The results of such a program might prove a complete failure in the long run, but this should certainly not deter us from the attempt.*

* Since this chapter was written, some evidence has appeared that high doses of Valium® can be beneficial in this condition. The Valium analogue Mogadon® appears to be even more effective. It is not yet approved by the Food and Drug Administration in this country, but reports from Europe and selected investigators in the United States are encouraging. While these drugs may be as effective as the steroids—or even more so—they will probably not change in the least the relationship between time of onset of treatment and long-term mental state. The studies suggested above will have to be carried out regardless of the type of treatment that is "most modern" at any given point in time.

Chapter 6

POSTTRAUMATIC EPILEPSY

As far as the evaluation of prognostic factors in posttraumatic epilepsy is concerned, we are not only confronted by the problem as to what constitutes epilepsy (i.e. single seizure versus recurrent attacks), but also by the difficulties in deciding when a head injury is serious enough to be regarded as a cause of seizures. An additional difficulty lies in the technique of follow-up. Results based merely on correspondence are likely to be different from those obtained through personal interviews. The combination of these factors, as well as the variability in the length of follow-up of patients, is bound to reflect itself in diversified opinions not only in regard to the incidence of epilepsy after a blow to the head, but also in regard to control of seizures once they have become established. The majority of statistics regard the occurrence of even a single seizure at any time after trauma as posttraumatic epilepsy. This will obviously bias medication results in a favorable direction because one will never know whether the patient would have had further spontaneous attacks or not. On the other hand, it is equally possible that a number of patients may develop seizures after a relatively minor insult to the cranium, and the etiology of the disorder is not at all related to the injury, but resides in the large pool of "cryptogenic" epilepsy, and seizures would have made their appearance regardless of the intervening trauma. These are difficult diagnostic problems which can only be solved by careful study of the individual patient and his family. These investigations are quite time-consuming and may even necessitate in certain instances electroencephalographic recordings from the parents and siblings of the

patient in order to avoid improper classifications. These points are emphasized here because it has been claimed that true posttraumatic epilepsy tends to have a good prognosis. However, before we address ourselves to this aspect we should return to more basic questions. They could be formulated as follows:

1. What is the incidence of epilepsy after head trauma?
2. What are the characteristics of the injury or of the individual that will favor the subsequent development of epilepsy?
3. Once epilepsy has developed, what are its chances for remission?
4. What are the characteristics of the patient with established posttraumatic epilepsy who will enjoy a complete remission?

As far as incidence is concerned, Table 11 provides some findings of investigators spanning nearly fifty years. Reviewing the table we can see that the figures range from a low of 4 per cent to a high of 43 per cent. It is clear that these figures are quite meaningless as far as any prediction is concerned because they are bound to be contaminated by the problems mentioned in the first paragraph of this chapter. However, the picture changes considerably if we limit our survey to statistics dealing only with penetrating head injuries. As shown in Table 12 the spread is considerably narrower, with the majority of studies showing incidence figures around 40 to 50 per cent. Dural penetration per se is, of course, not the most severe injury that can be survived, and the various series that are listed in the table still contain different degrees of cerebral injuries.

We may now ask ourselves how long after injury the patient is liable to experience the first seizure. Table 13 provides some figures from the literature and shows, in essence, that the vast majority of patients who develop posttraumatic epilepsy have their first seizure within one to two years after injury. The literature points out that most patients actually have the first attack within a few months, but there is no absolute end point in time at which the patient can be definitely reassured that epilepsy will not occur. Baumm (1930) reported an onset as late

as twelve years, and Ascroft (1941) even between sixteen and twenty years after injury.

This brings us to the second question, What characteristics of the wound or of the patient favor the appearance of seizures after an injury? It has been shown rather conclusively by sev-

TABLE 11

INCIDENCE OF POSTTRAUMATIC EPILEPSY

	Type of Sample	*Percentages of Patients with Posttraumatic Epilepsy*	*Number of Head Injured Patients Involved in Study*
Sargent, 1921	WW I	4.5	18,000
Rawling, 1923	WW I gunshot wounds	25	452
Alajouanine *et al.* 1948	WW I	23	602
Wagstaffe, 1928	WW I gunshot wounds	10	377
Baumm, 1930	WW I	24	1,040
Credner, 1930	WW I	38	1,990
Ascroft, 1941	WW I gunshot wounds	34	317
Denny-Brown, 1942	WW II	8	630
Gliddon, 1943	WW I gunshot wounds	10	500
Watson, 1952	WW II penetrating head injuries only	42	286
Russell and Whitty, 1952	WW II penetrating head injuries only	43	820
Phillips, 1954	WW II closed head injuries	6	500
Brun, 1955	Civilian	8	1,648
Walker and Jablon, 1961	WW II	28	739
Caveness and Liss, 1961	Korean Campaign	24	407
Evans, 1962*	Korean Campaign	20	422
Jennett, 1965	Civilian, blunt head injuries	10	1,000

* Selected sample, onset of illness no sooner than one month after injury.

eral authors on large series of cases that the degree of cerebral damage resulting from an injury stands in direct relationship to the incidence of future epilepsy (Ascroft; Baumm; Caveness and Liss (1961); Credner (1930); Evans (1962); Gliddon (1943); Rawling (1922); Wagstaffe (1928); Walker and Jablon

TABLE 12

INCIDENCE OF POSTTRAUMATIC EPILEPSY WHEN ONLY PENETRATING HEAD INJURIES ARE CONSIDERED

	Percentages of Patients with Posttraumatic Epilepsy	*Number of Head Injured Patients Involved in Study*
Rawling, 1923	35	206
Wagstaffe, 1928	19	176
Baumm, 1930	44	562
Credner, 1930	49	1,234
Ascroft, 1941	45	129
Gliddon, 1943	19	137
Watson, 1952	42	286
Russell and Whitty, 1952	43	820
Caveness and Liss, 1961*	51	73
Walker and Jablon, 1961**	51	133
Evans, 1962	42	137

* Dura and brain penetration of profound degree.

** Recalculated by Caveness and Liss according to their criteria.

(1961). Representative figures contrasting the incidence of epilepsy after simple closed head injuries and penetrating head injury are shown in Table 14. Although percentages vary among different investigators, all series demonstrate the substantially higher risk of epilepsy with increasing severity of the injury. Linear skull fractures do not seem to increase the risk for future epilepsy over that for simple closed head injuries with scalp lacerations. Comparing the figures given by Evans, both of these groups yielded 8 per cent of epileptic patients. Depressed frac-

TABLE 13

TIME BETWEEN INJURY AND ONSET OF POSTTRAUMATIC EPILEPSY

Denny-Brown, 1942	Within 1 year	86%
Russell and Whitty, 1952	Within 1 year	73%
Caveness and Liss, 1961	Within 1 year	75%
Baumm, 1930	Within 2 years	66%
Credner, 1930	Within 2 years	72%
Ascroft, 1941	Within 2 years	78%
Phillips, 1954	Within 2 years	86%
Walker and Jablon, 1961	Within 2 years	75%

TABLE 14

COMPARISON OF INCIDENCE OF EPILEPSY AFTER SIMPLE CLOSED HEAD INJURIES AND PENETRATING INJURIES

	Simple Closed Head Injuries		*Penetrating Injuries*	
	%	N	%	N
Rawling, 1923	11	47	35	206
Wagstaffe, 1928	3	60	19	176
Credner, 1930	20	244	49	1,234
Ascroft, 1941	24	66	45	129
Gliddon, 1943	4	130	19	137
Walker and Jablon, 1961	18	50	36	472
Caveness and Liss, 1961	12	117	51	73
Evans, 1962	8	136	42	138

tures are, of course, more epileptogenic, and the figures reported merge with those given for dural penetration.

Another method of estimating the degree of cerebral injury as a result of a blow to the head is provided by the length of unconsciousness and the length of posttraumatic amnesia. The duration of unconsciousness has been shown to stand in direct relationship to the frequency of occurrence of posttraumatic epilepsy by Walker and Jablon as well as by Evans. Some figures demonstrating the relationship between length of posttraumatic amnesia and occurrence of seizures are shown in Table 15. It is

TABLE 15

RELATIONSHIP OF DURATION OF POSTTRAUMATIC AMNESIA TO INCIDENCE OF POSTTRAUMATIC EPILEPSY

Denny-Brown, 1944	Posttraumatic amnesia	Less than 24 hours	10.9%
		1 to 7 days	4.6%
		More than 7 days	3.4%
Phillips, 1954		Less than 24 hours	4.6%
		More than 24 hours	11.5%
Jennett and Lewin, 1960	Early epilepsy	Less than 24 hours	3.0%
		More than 24 hours	12.0%
	Late epilepsy	Less than 24 hours	6.7%
		More than 24 hours	14.2%
Evans, 1962		Less than 24 hours	13.8%
		More than 24 hours	36.2%

again apparent that the longer the period of posttraumatic amnesia, the more likely the occurrence of seizures. Only Denny-Brown's report (1944) differed from these trends. He felt that local rather than generalized brain damage was the most important factor in the production of epilepsy.

Apart from intensity of injury, what are some of the other potential etiological factors that have been investigated? Walker and Jablon examined the following variables and found them unrelated to the development of seizures: age at time of injury, difficulties during delivery of the patient, birth order, previous systemic illness, alcohol consumption, previous head injury, postinjury EEG, and frequency of nervous disorders in the immediate family. As far as family history of epilepsy is concerned, it was felt that this might have played some role in a subgroup of patients whose seizures were not of the focal type. A constitutional factor on which epileptics with focal seizure types differed significantly from the nonepileptic sample was peculiarly enough a more frequent history of constipation in the epileptic patient. Other features that did play a role in the production of epilepsy were increase in dimensions of the wound in all planes (both diameter of defect and depth of wound), duration of unconsciousness after the injury, amount of neurological impairment (but no evidence that any one type of impairment was a more potent determinant than another), presence of intracranial foreign bodies, and all factors tending to delay healing of the wound. Location of the wound was not of major importance in their series.

Although Walker and Jablon's findings are, in general, quite representative of the literature, a few points should be elaborated upon. As far as wound healing is concerned, Ascroft found that if healing took place within fifteen days the incidence of seizures was 22 per cent; but if healing was delayed beyond sixty days it rose to 45 per cent.

Location of the wound in relation to posttraumatic seizures has been extensively investigated and some representative figures are shown in Table 16. Baumm's figures did not lend themselves to this type of tabulation, but they point out likewise that lesions in the Rolandic area are most epileptogenic while occipi-

tal lesions show this propensity the least. Russell and Whitty (1952) noted also that wounds situated within five centimeters of the sagittal line resulted in a significantly lower incidence of seizures than those that were farther down on the convexity. This observation stands by itself, since I have not found it mentioned in other reports.

Reviewing the figures in Table 16, one should remember that the locations mentioned are mostly approximations. What one author may call frontal or parietal might be included under Rolandic by another. It would seem that the general trend of the

TABLE 16

RELATIONSHIP OF SITE OF LESION TO INCIDENCE OF POSTTRAUMATIC EPILEPSY

	Frontal (%)	*Rolandic* (%)	*Parietal* (%)	*Temporal* (%)	*Occipital* (%)
Credner, 1930	45		47.3	36.7	32.3
Ascroft, 1941					
Total group	26.5	46	38.5	42.5	27.5
Subgroup with dural penetration	31	54	52	59	41
Gliddon, 1943	6.1	22.9	11.4	12.9	5.7
Watson, 1947	26.7	50.7		35	33.3
Russell and Whitty, 1952	39	55	65	38	38
Walker and Jablon, 1961	33.7		36	32.5	23.9
Evans, 1962					
Missile injuries only	24	39	42	35	17

figures is more valuable than their absolute level. The tendency appears to be for wounds in the general vicinity of the Rolandic region to have the highest incidence of seizure disorders. The figures in Table 16 are also of some theoretical interest in regard to the primary cause of epilepsy. A widely held assumption is that the most important cause of epilepsy resides in injury to the central nervous system. This could occur *in utero*, at birth, or postnatally, and manifest itself in a seizure disorder at some later stage of life. If cerebral trauma were indeed the necessary *and sufficient* cause then we should obtain in the overwhelming majority of patients a positive history of such trauma and—even more importantly—the incidence of posttraumatic epilepsy

after penetrating head injuries should not be only approximately 45 per cent, if all studies are combined, but should be around 90 per cent. Even if we take into account the location of the lesion, the highest percentage that has been reported is that by Russell and Whitty, namely, 65 per cent for penetrating injuries in the parietal area. If we combine Russell and Whitty's figures with those of Credner, in regard to penetrating parietal injuries, we still arrive at only 56 per cent. We are therefore confronted with the problem why only approximately one out of two severely brain injured individuals, with approximately the same amount of injury in approximately the same area, will develop seizures while the other will be spared this additional complication. These observations are merely mentioned in order to point out that, although cerebral trauma is a potent epileptogenic factor, it does seem to need an additional, as yet unknown, process in order to trigger a seizure disorder.

As far as foreign bodies remaining in the brain are concerned, Redlich (1919) observed that in 34 per cent of patients with epilepsy, foreign bodies were present in the brain, but this was the case in only 22 per cent of nonepileptics. He felt, however, that this difference was too small to be of major importance. He found no differences between bone and metal fragments in regard to their epileptogenicity. Baumm also found only a 3 per cent difference (12% versus 9%) in the epileptic versus nonepileptic sample in regard to foreign bodies and felt that this was clearly too small to be significant. This finding agrees with the observations of Watson (1947). Ascroft felt that foreign bodies were not important in the production of future epilepsy if they consisted of metal. Evans agreed with this observation but thought that remaining bone fragments were epileptogenic. Gliddon concluded that retained foreign bodies were epileptogenic, and bone fragments more so than metal.

The problem of heredity is also somewhat controversial. No evidence for hereditary predisposition was found by Watson, and by Phillips (1954), but Evans found a somewhat greater incidence of positive family history of epilepsy in the sample of Korean War veterans who developed seizures than those who did not.

These observations dealt with the problem of whether or not seizures will develop at all. We can now address ourselves to the third question, What can be expected in regard to the course of the illness once a seizure has made its appearance? Several authors feel that it is prognostically important to distinguish between "early" and "late" epilepsy. Unfortunately, different workers apply different criteria to what constitutes early epilepsy and the results are therefore not directly comparable. Ascroft felt that ". . . in about one-third of the patients having fits after gunshot wound of the head, epilepsy may be of a more or less transient character. The earlier the fits begin the less likely are they to become persistent. In the first week after injury, . . . the risk of a man having fits is about 5 per cent (15 of 317 cases), but the risk of the fits becoming persistent is only one in five. Fits starting in the second week stand an equal chance of being temporary or of becoming persistent. As the weeks pass the odds against the fits being of a temporary character rapidly increase. From the sixth month to the end of the second year the risk of developing epilepsy is about 10 per cent, but the odds favor the epilepsy becoming persistent as five to one. If the onset of fits is delayed beyond two years, the epilepsy will be persistent." He commented further that seizures soon after injury are of little prognostic significance for the occurrence of late epilepsy.

Jennett (1965) defined early epilepsy as occurring within one week of the injury, and felt the real significance of early epilepsy is that it increases by about four times the chance of epilepsy developing later. This applies even if there has been only a single seizure in the first week, no matter how severe or trivial the injury. He pointed out that there is one exception in "immediate" epilepsy when a generalized convulsion occurs within a minute of an injury, usually a trivial one. Such an episode, according to him, does not seem to predispose to later epilepsy. He found the highest risk for late epilepsy in patients who have had a combination of prolonged posttraumatic amnesia and a depressed skull fracture; 47 per cent of these patients developed late epilepsy.

Credner defined early epilepsy as occurring during treatment of the wound and late epilepsy as occurring after wound

healing was accomplished and the scar had been formed. With this definition in mind, she examined 330 patients with open head injuries and found that forty-one patients (12%) fell into the group of early epilepsy. Of these forty-one patients, sixteen (39%) had seizures only during the time of wound treatment, while the seizure disorder persisted in the remaining cases.

Denny-Brown (1942), although giving no figures of his own, stated that epilepsy occurring within the first four weeks after injury has an excellent prognosis. Evans who defined early epilepsy as seizures occurring within the first month after injury, noted that patients with early seizures were likely to develop late epilepsy, except for those having seizures within twenty-four hours after injury. The type of seizure was found to be of no value in forecasting the appearance of late epilepsy. Of 105 patients with epilepsy, thirty-seven had their first seizure within eighteen days of the injury, and this period stood out because it was followed by a gap of two weeks in which no initial seizure occurred; therefore, this figure expressed the number of initial seizures in the first month after injury. Ascroft noted that all patients who experienced seizures within the first month after injury had their first attack within the first fourteen days. Maki (1964) observed that 58 per cent of early epileptics were also late epileptics, and this was based on a sample of 125 cases. Masquin and Courjon (1963) found seven cases of early posttraumatic epilepsy (occurring within three weeks after injury) in a series of sixty-two patients. All except one had subsequent seizures within one year. It is important to point out here that some of these studies (Jennett; Masquin and Courjon; Maki) dealt with civilian head injuries only. There may well be a difference whether one deals with a sample of war head injuries or those that occur in everyday life. It would seem that a war injury sample is more likely to contain a much larger selection of true posttraumatic epilepsy cases; while a civilian sample with mostly mild head injuries will tend to contain a larger representation of the "cryptogenic" cases which are not necessarily related to the trauma. These possible differences will have to be kept in mind when one compares results of different authors.

Walker and Jablon felt that their data supported the concept

of a more favorable prognosis for the early epilepsies. When they plotted the course of epilepsies occurring within the first week, and compared it with similar plots containing patients whose seizures started between the first week and three months, as well as patients whose seizures started after three months, it was found that the early epilepsies had a definitely lower incidence each year than the later developing cases. They concluded that an onset less than one week after the injury carries the best prognosis, and an onset more than three months after injury the poorest. A decreasing incidence of future attacks, depending on the time of occurrence of the first siezure, was also noted by Baumm, and his figures are shown in Table 17. These

TABLE 17

RELATIONSHIP OF TERMINAL REMISSIONS TO TIME OF ONSET AT FIRST SEIZURE AFTER INJURY ACCORDING TO BAUMM, 1930

(N = 562)

First Seizure Occurring	*Terminal Remission* (%)
Up to 1 week after injury	55
Up to 1 month after injury	41
Up to 3 months after injury	31
Up to 6 months after injury	24
Up to 1 year after injury	25
Two to 3 years after injury	8.7
More than 3 years after injury	2.9

figures are of importance because they come from the bromide-phenobarbital treatment era. They are also similar to those of Ascroft which also date from that period. In Russell and Whitty's series, 35 per cent of patients with convulsions during the first month had no further seizures.

Symonds (1935) and Wagstaffe have been quoted in the literature as saying that early posttraumatic epilepsy has an excellent prognosis, but this is not borne out by a review of their original papers. Symonds wrote: "Although it is probably true that the early fits frequently do not recur, their occurrence indicates an increased risk of future epilepsy." Wagstaffe actually stated that the number of early fits observed in his cases that

could be traced was too small for definite conclusions to be drawn.

While these are examples of positive relationship between early onset and good outcome, Caveness (1963) in his series of Korean War veterans found no relationship between time of first seizure and subsequent cessation of attacks.

Walker and Jablon's findings that patients with early onset of seizures had a better prognosis was not borne out by Evans' study, when only those cases were considered that had their first seizure at least one month after onset of injury. No relationship between time of onset and subsequent course of epilepsy was noted, either in regard to duration of the subsequent seizure disorder or change in frequency of attacks. Ascroft had mentioned that seizures starting two years after the injury were always persistent, but this was not confirmed by Evans. Nevertheless, there seems to be a group of patients who start with seizures more than two years after injury and who carry a poor prognosis. Phillips pointed out that 15 per cent of 190 cases fell into this category. He felt that this group contained severe posttraumatic epilepsies; the seizures were mainly generalized and started, in several instances, with status epilepticus. He thought that these formed a most interesting group and would require a more detailed survey than was possible in his study.

It seems, therefore, that the majority of reports point out that seizures occurring within the first week or two may be followed by a chronic seizure disorder, but this is not nearly as common as it is when seizures start later. The tendency seems to be that the later the seizure disorder starts after injury, the more likely it is to become chronic.

If we disregard time of onset for the moment, what tends to be the usual course after seizures have made their appearance? Symonds felt that "All observers agree that the liability to the attacks once established tends to persist, that the fits become more frequent and more severe, and their repetition is often accompanied by slight progressive dementia of the kind observed in idiopathic epilepsy. Therefore, as a late complication of head injury, traumatic epilepsy is likely to be a cause of total disability for both the manual and the mental worker." He also

stated that the prognosis of traumatic epilepsy is much the same as that of the idiopathic variety as far as major seizures are concerned, but patients with minor seizures might have a better prognosis. This rather pessimistic statement can be contrasted with the opinion by Walker (1957) that ". . . posttraumatic seizures . . . do not have the same prognosis or implications as so-called idiopathic epilepsy." Walker (1962) commented further: "The fact that permanent disability is not a result of posttraumatic epilepsy is emphasized in addition to the need to reassure patients of this favorable prognosis." Table 18 gives some results of remission rates cited in the literature. Again we are handicapped by the fact that a number of authors give terms like "cure" without mentioning for what period of time seizures have been absent prior to the last follow-up examination. The table shows considerable spread: 4 per cent as the lowest rate for remissions having lasted at least six years, and 53 per cent as the

TABLE 18

PERCENTAGES OF TERMINAL REMISSIONS GIVEN IN THE LITERATURE FOR POSTTRAUMATIC EPILEPSY

	Duration of Seizure Freedom	*Percentages of Patients Remitted*	*Number of Patients Involved in Study*
Alajouanine *et al.*, 1938*	At least 6 years	4.1	143
Baumm, 1930	"observed for at least 7 years"	15	247
Credner, 1930	No time given	6	339
Ascroft, 1941	"for some years prior to last examination"	31	96
Watson, 1952	At least 1 year	17	126
Brun, 1955	No time given "cured"	53	92
Walker and Jablon, 1961	At least 2 years At least 5 years	34 21	207
Evans, 1962	2 years or more	39	81
Caveness, 1963	2 years or more	53	109

* Selected series, all patients had cranial surgery after injury.

highest for a period lasting at least two years. When we remember that a number of these series contain patients who have had only one or two seizures altogether, the figures shown are not markedly different from those seen in "idiopathic" epilepsy. Although there is probably not much difference in this particular respect, there may be some in the frequency of occurrence of seizures in the patients who continue to have posttraumatic epilepsy. Redlich pointed out in 1919 that patients with gunshot wounds tend to have infrequent seizures. This observation agrees with Walker and Jablon's findings reported in 1961. They mentioned that, as far as major seizures are concerned, ". . . only 30 per cent of the men who ever had major fits have had such attacks more than twice a year, and 45 per cent had none for two years." Evans found that only eighteen out of seventy-five patients had more than one seizure a year in the two years prior to follow-up carried out seven to eleven years after injury. This agreement between authors is of importance because in Redlich's time only phenobarbital and bromides were available as anticonvulsant medications, and the infrequent occurrence of major seizures can therefore not be credited to modern anticonvulsant medications.

Masquin and Courjon emphasized also the good prognosis of posttraumatic epilepsy, and stated that well and regularly applied medication in patients not suffering from alcoholism leads to recovery within one to five years in 75 per cent of cases. They noted also that the majority of patients showed relatively few seizures (one to two convulsive attacks). This is, of course, an obvious problem in regard to definition of epilepsy. If we insist on a definition that epilepsy means recurrent seizures, the majority of Masquin and Courjon's patients might not have qualified for inclusion in the series, and the final opinion of the authors regarding the good prognosis of posttraumatic epilepsy might have been considerably different.

Watson's series (1952) is of interest because he deliberately excluded patients in whom epilepsy developed within the first four weeks unless seizures persisted subsequently; fifty-three patients were followed for a three-year period, all had penetrating head injuries. He found that only nine (17%) of the patients were

free from seizures for one year or longer, while forty-four (83%) continued to have seizures. Of these forty-four patients, twenty (37.8%) had shown some improvement in their seizure disorder, nine (17%) were unchanged, while fifteen (28.2%) had become worse.

In regard to seizure types that can result from trauma, it is generally agreed that nearly all the forms of epilepsy occurring spontaneously can also be seen after injury, but it is important to point out that Walker and Jablon have not found classical three cycles per second spike wave activity and associated petit mal in any of their patients. Although the older literature frequently gives accounts of "petit mal" in some posttraumatic cases, a review of the actual case reports indicates that one is dealing with temporal lobe type seizures and other abortive seizure manifestations rather than true petit mal.

In regard to mental deterioration, Stevenson (1931) felt that it is more rapid in traumatic than in idiopathic epilepsy and is related mainly to the frequency of the seizures. When seizures are infrequent, however, deterioration is more rapid and marked in severe wounds of the head than in idiopathic epilepsy with a similar frequency of seizures.

One might assume that the electroencephalogram could be a useful tool in the prognosis of patients with posttraumatic epilepsy, but this does not appear to be the case. Marshall and Walker (1961) compared EEGs that were obtained within six months after injury with those taken five or more years later, and correlated these with cessation of attacks for at least two years versus continuance of seizures. No statistically significant correlation could be found between these factors and normalcy or abnormalcy of the electroencephalograms. It was concluded that the EEG is not a sufficiently sensitive indicator to foretell the course of posttraumatic epilepsy. Masquin and Courjon agreed that it is remarkably difficult to predict posttraumatic epilepsy from the electroencephalogram. Their study was based on sixty-two seizure patients who had been followed since their initial injury. Unfortunately, their study suffers from a serious handicap, inasmuch as the authors did not report on control patients who had received head injuries without developing

epilepsy. This limitation has to be kept in mind when one evaluates their conclusions. They stated that while ". . . normalization of the EEG is not a definitely favourable prognostic sign, the finding of a focus of slow spikes and waves, spikes, or subclinical seizures is of unmistakable unfavourable prognostic significance . . . the gradual disappearance of localized changes as a rule carries a good prognosis; whereas persistence, exacerbation, and bilateralization of the changes spell a protracted epileptic aftermath, particularly when focal irritative changes are concerned."

Phillips stated that he had only insufficient electroencephalographic information on his patients, but found that in nearly 30 per cent of cases the EEG was quite normal. Walker commented further in 1962: "Serial recordings do not enable an accurate prognosis, for although episodic discharges may precede the convulsion, they may also resolve without overt seizures. Perhaps the only valid conclusions to be drawn from the electroencephalogram is that a normal record after a head injury indicates little brain damage and hence a slight chance of epilepsy developing, whereas an abnormal tracing is usually associated with more severe cerebral injury and hence a greater chance of seizures. However, even the most disorganized electroencephalogram does not mean that seizures will invariably occur in the future. . . . Once epilepsy has been established, the EEG does not distinguish the cases that have a good versus a bad prognosis."

In the early days of electroencephalography, Williams (1944) had thought that "When changes that have been described as larval attacks are seen at an interval after injury, epilepsy is virtually certain to supervene." He regarded as "larval attacks" EEG changes that consisted of "characteristic epileptic outbursts." It is fair to assume that these changes are similar to what Walker called "episodic discharges," which can resolve without overt seizures. The disappearance of electroencephalographic seizure discharges without the development of overt clinical epileptic manifestations has also been seen by ourselves in a sample of severe head injured patients who had a fatal outcome (Rodin *et al.*, 1965).

The question still remains why some patients stop having seizures after a period of time, but others continue with the disorder indefinitely. Walker and Jablon made a detailed study and found that location of the wound, depth of wound, time of debridement, wound complications, neurological deficit, handedness, and type of attacks showed no difference in regard to whether seizures persisted or ceased. There were only two differences found: the seizure-free group had a lower incidence of posttraumatic syndrome and a higher intelligence quotient than the group where seizures persisted. It was pointed out, however, that both of these phenomena may have been the *result* of seizures, rather than being related to their *cause*.

Caveness (1963) reported on the material of Korean War veterans and defined cessation of attacks as a terminal remission of at least two years prior to last follow-up. Fifty-eight out of 109 patients fell into this group. Comparing these fifty-eight patients against the others, no statistically significant differences were found in regard to missile versus nonmissile injury, time of onset of seizures in relation to injury, attack pattern, site of injury, severity of injury and whether or not the patient had ever been placed on medication. The only finding that showed statistically significant differences between Caveness's two groups was in regard to frequency of seizures. Eighty-five per cent of patients who had suffered one to three seizures had a terminal remission, but this was the case only in 53.1 per cent of patients with four to thirty seizures, and 21 per cent of "multiple" seizures which "defied accurate count." Seizures ceased in 42 per cent of the patients who had been placed on continued anticonvulsant medication and in 56 per cent of men who had never received such treatment. This is obviously an important piece of information because it points out that in a number of cases the natural course of the illness is apparently self-limiting. Another important point that emerges from Walker's, as well as Caveness's studies, seems to be that although a more severe injury tends to favor the initial appearance of epilepsy, it subsequently plays no role in its persistence. This should again provide considerable food for thought about the real causes of chronic seizure disorders.

Finally, we come to the question of mortality in patients with posttraumatic epilepsy. This is a difficult problem and not too much information is available. Credner noted that out of fifty patients who died, forty-one (82%) had suffered from seizures. Limiting herself only to patients with penetrating head injuries, it was noted that forty-seven of the fifty patients who died had had penetrating head injuries; 81 per cent of this group had epilepsy. The overall incidence of epilepsy in patients with penetrating head injuries was, however, only 49 per cent; there was, therefore, an excess of mortality for patients with epilepsy in this group. Walker referred to the problem in 1957 and stated that over a period of ten years the risk to life is increased at least two to three times by posttraumatic epilepsy, but: "How much of this increased risk is due to the cerebral wound, the neurological deficit, or the epilepsy is not easy to determine." Wagstaffe gave somewhat contradictory statements. He said in the paragraph dealing with mortality that the onset of seizures has no marked effect on the mortality. He went on to say that epileptic patients had a mortality of 16 per cent; whereas the mortality rate of all head injury cases was 10 per cent. This, he felt, was not a sufficient difference to justify any conclusions, but in the summary of his paper he stated that "the mortality in cases which have developed traumatic epilepsy is rather higher than in other cases of gunshot wounds of the head."

Reviewing these opinions, it is probably fair to assume that patients who suffer from chronic posttraumatic epilepsy carry a slightly higher mortality risk than those head injured patients in whom this complication is absent.

In summary, one could conclude in regard to the four questions that were initially posed:

1. The incidence of epilepsy after head trauma stands in direct relationship to the severity of the injury, ranging from approximately 12 per cent in simple closed head injuries to approximately 37 per cent for penetrating head injuries. These figures are approximations only, and represent the averages of the studies listed in Tables 11 and 12.

2. In regard to the characteristics of the injury or of the individual that would favor the subsequent development of epilepsy, it is apparent that factors which increase the severity of the injury or interfere with wound healing are most important. Also, central-parietal wounds seem to be most epileptogenic. The role of hereditary predisposition is controversial at the present time.

3. In regard to frequency of terminal remissions, there does not seem to be too much difference between posttraumatic and "cryptogenic" epileptic patients. A two-year terminal remission appears to occur in about one-third of the posttraumatic group. There is, however, a suggestion that patients with posttraumatic epilepsy tend to have relatively infrequent seizures.

4. In regard to characteristics of the patient with established posttraumatic epilepsy who will enjoy a complete remission, the literature fails to provide convincing criteria that would allow accurate prognostication. The only exception might be that patients who have very frequent seizures tend to have a poorer chance for remission than patients whose seizures are spaced by long intervals.