

Cerebellar atrophy in epilepsy

Pneumographic and histological documentation of a case with psychosis

ADEL K. AFIFI¹ AND MAURICE W. VAN ALLEN²

From the Neurosensory Center³ and the Department of Neurology, College of Medicine, University of Iowa, U.S.A.

Anoxia and the toxic effects of diphenylhydantoin (Dilantin) are the two most commonly cited causes for the cerebellar atrophy which occasionally occurs in epileptics. While the histopathology of this condition has been well documented (Spielmeyer, 1930; Zimmerman, 1938; Meyer, Beck, and Shepherd, 1955), few reports (Meurice, 1956; Minoque and Latham, 1965) have attempted a clinicopathological correlation. The case to be presented is that of a young woman, subject to convulsions since the age of 5. Ataxia appeared and progressed at a time when the patient was free from seizures and not taking diphenylhydantoin (Dilantin). Psychotic symptoms appeared before the onset of ataxia. There was no family history of cerebellar disease.

Three pneumoencephalograms gave graphic evidence of the temporal course of cerebellar atrophy and a biopsy of the cerebellum done at exploratory surgery yielded tissue for microscopic studies.

CASE HISTORY

A 19-year-old white female, the eleventh of 14 living siblings was apparently normal at birth following an uneventful gestation. Two siblings had febrile convulsions. Both died, one during an attack of scarlet fever, the other with bronchopneumonia. A maternal first cousin is said to have had convulsions for 47 years.

The patient's neonatal history and subsequent development were normal until the age of 5 years when she had a grand mal convulsion. She was first seen in the Neurology Department at the University Hospital in October 1951, at the age of 7 years. She had had by then a total of eight grand mal seizures. The results of physical and neurological examinations were within normal limits. An electroencephalogram was abnormal with frequent spikes predominantly seen over the left temporal, frontal,

and motor areas. Spinal fluid examination was normal. Pneumoencephalogram was normal. She manifested difficulty in articulation with lateral emission of sibilants including 's', 'sh', and 'ch'. The diagnosis of cryptogenic epilepsy was made and the patient was started on 90 mg phenobarbital daily.

She was seen again in June 1952 and reported occasional right-sided facial twitches but no major convulsions. The E.E.G. was unchanged. Phenobarbital dosage was increased to 120 mg daily. In November 1952, because of an increase in frequency and severity of focal seizures, methyl phenylhydantoin (Mesantoin), 120 mg/day, was added to her regimen. This drug was ineffective and was discontinued. Diphenylhydantoin (Dilantin), 200 mg/day, was started in February 1953. The facial twitching ceased.

A Stanford-Binet test in November 1953 revealed an I.Q. of 77. She performed best on verbal testing and did poorly on motor coordination.

In May 1954 after 15 months of diphenylhydantoin (Dilantin), 200 mg/day, she was admitted because of diplopia, ataxia, incoordination, and nystagmus. She had been seizure free since August 1953. All of these symptoms subsided 48 hr after discontinuing diphenylhydantoin (Dilantin). During this admission the haemoglobin level, white blood cell count, lumbar puncture, and radiographs of the skull were normal; an E.E.G. revealed diffuse slow and fast activity. This acute episode was attributed to drug toxicity, but because the seizures were well controlled by diphenylhydantoin (Dilantin) it was prescribed again in doses of 200 mg/day with phenobarbital, 100 mg/day. Ataxia soon recurred and diphenylhydantoin (Dilantin) was stopped. In August 1954 she was seizure free and had some residual ataxia.

She was admitted to the mental health facility at Independence, Iowa, in August 1960 in an uncommunicative state and received 10 electroconvulsive treatments (E.C.T.). She had taken no medication since 1958 but diphenylhydantoin (Dilantin), 200 mg/day, and phenobarbital, 120 mg/day, were given during this hospitalization.

She was readmitted to the mental health facility at Independence a year later (August 1961). She was negativistic and mute. After a few days, she became responsive and communicative but remained emotionally flat. During her stay in that hospital (August 1961 to

¹Present address: Department of Medicine (Neurology), American University of Beirut Hospitals, Beirut, Lebanon.

²Reprint requests to Dr. M. W. Van Allen, Department of Neurology, University of Iowa Hospital, Iowa City, Iowa, U.S.A.

³The Neurosensory Center is supported by Program-Project Grant No. NB03354 of the National Institute of Neurological Diseases and Blindness, Bethesda, Maryland, U.S.A.

October 1961) she had two grand mal seizures and recurrent episodes of agitation necessitating restraint. There were no other abnormal physical or neurological findings. In particular, there was no evidence of ataxia or incoordination. She was treated with 300 mg diphenylhydantoin (Dilantin), 750 mg primidone (Mysoline), and 800 mg chlorpromazine hydrochloride (Thorazine) daily.

She was readmitted to the Neurology Department in October 1961. There were no specific physical findings; in particular there was no ataxia; laboratory examination revealed normal haemogram, spinal fluid, blood serology, fasting blood sugar, and serum calcium and phosphorus levels. Roentgenograms of skull and chest were normal. Pneumoencephalogram was normal (Fig. 1a and b) and an E.E.G. revealed recurrent spike discharges with occasional focal discharges from the left anterior temporal region. During her stay, she was seizure free but manifested episodes of agitated and combative behaviour and at times was withdrawn and catatonic. She was discharged on diphenylhydantoin (Dilantin) 200 mg/day. This was discontinued in December 1961 and for the rest of her course.

In April 1962, four months after all medication except chlorpromazine hydrochloride (Thorazine) had been stopped, she began to have difficulty in her gait. Ataxia was progressive early but stabilized later. She was admitted to the Neurology Department a year later (April 1963) for evaluation of this new difficulty. She was uncommunicative and resistive to examination. Her gait was unsteady and she needed support while walking. She was able to stand alone but swayed irregularly and tended to fall backward. Tendon stretch reflexes were normal. There was no Babinski sign. Further evaluation of her neurological status was not possible because of lack of cooperation. The electroencephalogram was unchanged except for absence of diffuse spiking. Laboratory examination revealed normal haemogram, calcium and phosphorus levels, and fasting blood sugar.

She was readmitted in December 1963 at the age of 19 years for re-evaluation of her gait. She was more cooperative and permitted a more thorough examination. Positive findings on this admission included ataxia of gait and extremities, mild temporal pallor of optic discs, decrease in alternate motion rate of tongue and all four extremities, bilateral Babinski signs, and hyperactive reflexes in the lower limbs. Speech was mildly dysarthric. She was dull, moderately disoriented, and had difficulty in simple subtraction. The E.E.G. was abnormal with bilateral spike activity. Pupillography was normal. The finding of concentric constriction of visual fields was believed to be due to the patient's mental state. A third pneumoencephalogram revealed evidence of advanced cerebellar atrophy (Fig. 2a and b), a striking change from the findings two years before.

Surgical exploration was undertaken on March 10 1964 because of the possibility of cerebellar compression from a cyst. At exploration, the dura was found to be slack and not bulging. On incising the dura a very large cisterna magna and a small atrophic cerebellum were encountered. The arachnoid appeared thickened and more opaque than normal and was adherent to the pia. Numerous fibrous strands were seen between the arach-

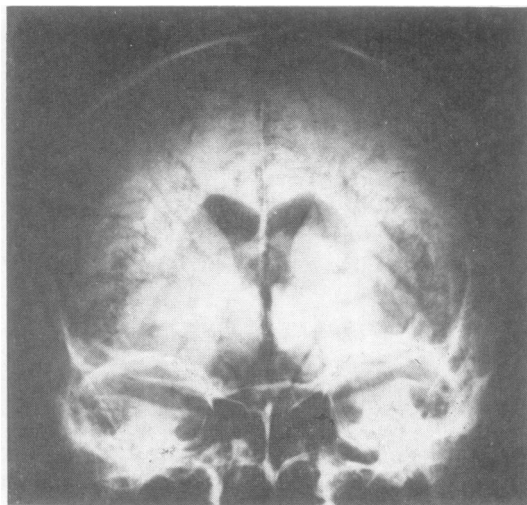


FIG. 1a

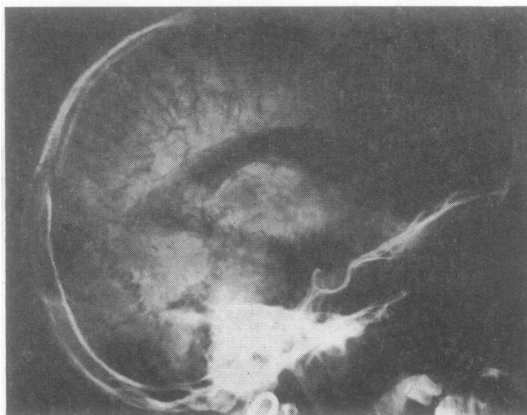


FIG. 1b

FIG. 1a and b. *Normal pneumoencephalogram (October 1961). There was no ataxia at this time. Psychotic symptoms were present.*

noid and pia. A portion of the arachnoid and underlying cortex was taken for microscopic study. The patient recovered well and was discharged with no change in her gait. She continues to be ataxic, hypotonic, and unable to walk alone. Sporadic seizures for which she has been receiving primidone (Mysoline) occur about twice yearly. Chlorpromazine hydrochloride (Thorazine), and thioridazine (Mellaril) have been given for her schizophrenic state. Figure 3 shows her clinical course and medication.

PATHOLOGY The tissue from the cerebellum was fixed in 10% formol saline and embedded in paraffin. Ten micra thick sections were stained with haematoxylin and eosin and by Nissl, Weil, Bodian, and Heidenhain

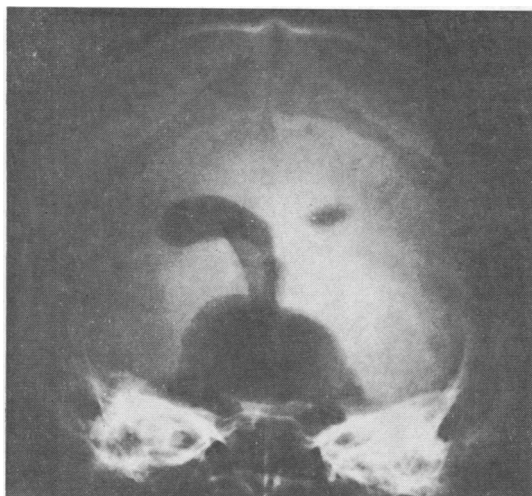


FIG. 2a

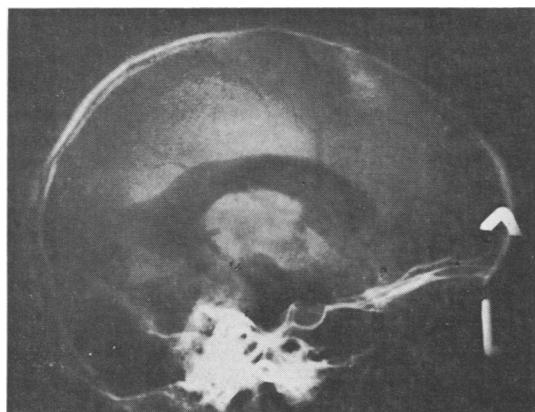


FIG. 2b

FIG. 2a and b. *Pneumoencephalogram (December 1963) showing massive accumulation of air in the posterior fossa. Other views showed evidence of cortical atrophy of moderate degree.*

methods. Light microscopy revealed almost complete absence of Purkinje cells (Fig. 4a-c) with some degree of rarefaction of the granule cell layer. No aetiological features—for example, vascular changes, cellular infiltrations, or cystic gliosis—were present. The arachnoid was fibrotic.

DISCUSSION

The findings are consistent with those of 'parenchymatous cortical cerebellar atrophy'. This is a syndrome of varied causal association. The commonly cited aetiologies are heredofamilial, metabolic, toxic,

infectious, traumatic, and ischaemic. The family history of our patient is negative with regard to cerebellar disease. The convulsions in the siblings were febrile, and deaths were attributable to non-neurological disease. The seizures in the first maternal cousin occurred over a period of 47 years and probably were cryptogenic. The onset of ataxia at the age of 18 would appear to exclude the diagnosis of the late cortical atrophy of Marie, Foix, and Alajouanine.

The association of convulsions, diphenylhydantoin (Dilantin) administration, electroconvulsive therapy, and cerebellar degeneration bring to mind the patients described by Thorpe (1935), Haberland (1962), Minoque and Latham (1965), and Meurice (1956). Their patients were also epileptic. The patients of Thorpe (1935), Haberland (1962), and Minoque and Latham (1965), like our patient, had in addition prominent mental problems necessitating E.C.T. in some (Haberland, 1962). Evidence of cerebellar degeneration appeared in the course of administration of diphenylhydantoin (Dilantin) except in the case of Thorpe (1935). Cerebellar degeneration in their cases was progressive in nature and ended in incapacitation. Our patient can feed herself and take care of her own daily needs. She walks with support. Serial electroencephalograms and cerebrospinal fluid examinations have not changed substantially throughout the course of her illness.

The aetiology of the cerebellar atrophy in our case is speculative. Several possibilities should be considered.

CONVULSIONS The association of cerebellar degeneration and epilepsy has been well documented. It is believed that anoxia is responsible. The pathophysiological changes in anoxia are not well understood. Alexander and Löwenbach (1944), and Scholz (1959) demonstrated evidence of anaemic and hypaemic areas in brains of animals submitted to convulsions induced by electroshock. These areas increased in size during a series of seizures and persisted 40 min after the convulsions. Scholz (1959) considered these areas a manifestation of a circulatory disturbance associated with the seizure. Cerebellar changes similar to those occurring in epileptics were described by Lindenberg (1955) in cases of increased intracranial pressure and were attributed to compression of arteries which might occur during an epileptic attack.

In a study of alteration of cerebral dynamics associated with seizures, White, Grant, Mosier, and Craig (1961) found evidence of increase in cerebral blood flow and rise in cerebrospinal fluid pressure. Whether any of the above factors were operative in

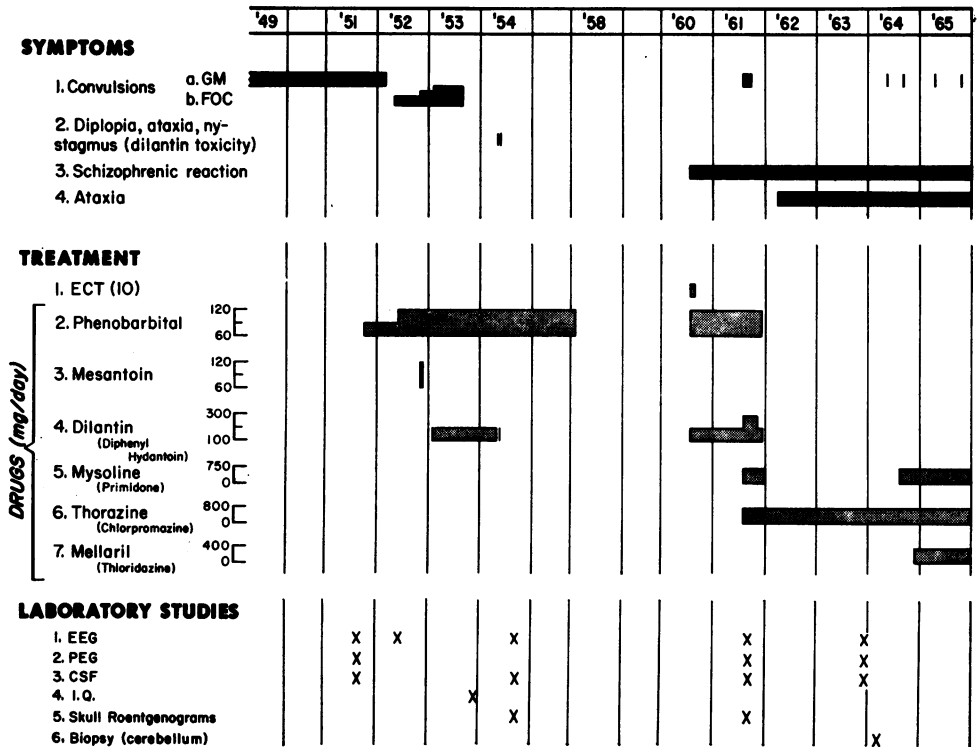


FIG. 3. Scheme of symptoms, treatment, and laboratory studies.

our case is difficult to say. The clinicopathological correlations of seizures and cerebellar degeneration in the literature are too few to permit a comparison. In contrast to the cases of Meurice (1966) and Minoque and Latham (1965), the seizures in our patient were at no time very severe, and at no time did the patient go into status epilepticus. The total number known of grand mal seizures did not exceed 20. Ten convulsions were induced by E.C.T. Symptoms in our patient began several months after she was seizure free.

ELECTROCONVULSIVE THERAPY Our patient as well as the two patients described by Haberland (1962) had E.C.T. sometime in their clinical course before the onset of cerebellar symptoms and signs. The same argument would hold here as discussed above under convulsions for the role of E.C.T. in the genesis of this state. If the E.C.T. is a factor in this atrophy, it is strange that more cases of ataxia are not encountered among the many patients receiving shock therapy.

DIPHENYLHYDANTOIN (DILANTIN) The association of ataxia with diphenylhydantoin (Dilantin) has

been recognized since Merritt and Putnam (1939) noted ataxia, tremor, diplopia, drowsiness, and headache during diphenylhydantoin (Dilantin) administration. These symptoms usually develop with large doses and generally subside after a decrease in the dosage or discontinuance of the drug. Utterback, Ojeman, and Malek (1958) and Roger and Soulayrol (1959), however, described patients who, having developed ataxia while taking diphenylhydantoin (Dilantin), experienced only incomplete recovery after the drug was discontinued. Utterback *et al.* (1958) and Hofmann (1958) demonstrated selective Purkinje cell degeneration in patients receiving large doses of diphenylhydantoin (Dilantin), and Utterback *et al.* (1958) showed similar findings in normal cats given diphenylhydantoin (Dilantin). In Hofmann's (1958) patients, the granule cell layer was spared and in the cats of Utterback *et al.* (1958) granule cells were diminished after large doses of diphenylhydantoin (Dilantin).

The contribution of diphenylhydantoin (Dilantin) toxicity to the ataxia and cerebellar degeneration in our case is difficult to assess. Although our patient had manifestations of diphenylhydantoin (Dilantin) toxicity, these were transitory and subsided on

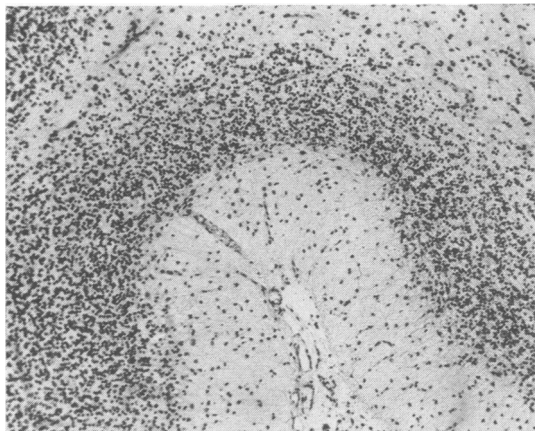


FIG. 4a

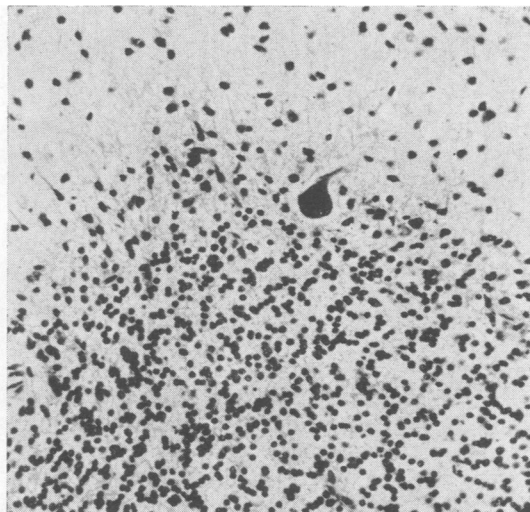


FIG. 4b

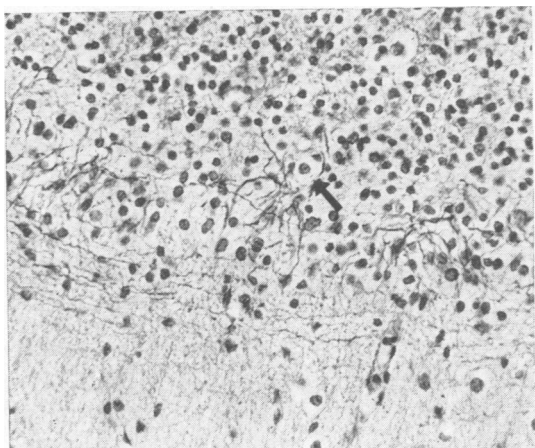


FIG. 4c

FIG. 4a. Nissl stain showing the striking absence of Purkinje cells and rarefaction in the granule cell layer. $\times 77$.

b. Nissl stain showing a solitary densely staining Purkinje cell. $\times 165$.

c. Bodian stain showing an empty basket (arrow) the former site of a Purkinje cell. $\times 286$.

discontinuing the drug. The persisting ataxia first appeared at a time when the patient had not been taking diphenylhydantoin (Dilantin) for several months and was taking only chlorpromazine hydrochloride (Thorazine). The evidence for the absence of atrophy earlier in her course is seen in comparing the air studies of 1951, 1961, and 1963. The rarefaction of the granule cell layer in our patients is at variance with the observations in Hofmann's (1958) case who did not show this and the cats of Utterback *et al.* (1958) which showed it only with relatively high doses of diphenylhydantoin (Dilantin).

The prominence of mental symptoms in our case and in those of Thorpe (1935), Haberland (1962), and Minoque and Latham (1965) is of interest. One wonders whether the psychiatric manifestations are not part of a symptom complex of epilepsy, cerebellar degeneration, and organic psychosis reflecting

an unusual vulnerability of the cerebrum and cerebellum in such patients to the effects of seizure-induced anoxia. The role of diphenylhydantoin (Dilantin) in the development of such a symptom complex can be debated since Thorpe's (1935) cases never received diphenylhydantoin (Dilantin).

Our report confirms observations in the literature on the existence of a syndrome of cerebellar degeneration and ataxia in patients suffering from epilepsy. Our case differs from others in the occurrence of ataxia and cerebellar degeneration when the patient was not taking anticonvulsive medication and when she was seizure free. The availability of serial pneumoencephalograms serves to confirm the time of onset of cerebellar atrophy and helps to place the different chronological events in perspective. Our case does not throw light on the pathophysiology of this syndrome. No vascular changes were seen. The

unavailability of tissues from other areas known to be vulnerable to anoxia (Ammon's horn, motor cortex) makes it difficult to be dogmatic about selective cerebellar damage versus diffuse damage involving other areas of the brain. Judging from the appearance of the pneumoencephalogram, the cerebellar atrophy is much more extensive than is atrophy elsewhere.

SUMMARY

The case of a young female epileptic who developed persistent and disabling ataxia at the age of 18 is presented. She had been treated by moderate doses of phenobarbital diphenylhydantoin (Dilantin), primidone (Mysoline), and methyl phenylhydantoin (Mesantoin) at various times.

Symptoms suggesting schizophrenia appeared when she was 16 and were treated by 10 E.C.T. and chlorpromazine hydrochloride (Thorazine).

Three pneumoencephalograms documented the development of cerebellar atrophy. Tissue studies showed changes typical of 'parenchymatous cerebellar degeneration'.

A syndrome of cerebellar degeneration, psychosis, and epilepsy is discussed.

The senior author (A.K.A.) is indebted to the Lebanese Research Council for a travel grant which made collaboration on this paper possible.

REFERENCES

- Alexander, L., and Löwenbach, H. (1944). Experimental studies on electro-shock treatment: the intracerebral vascular reaction as an indicator of the path of the current and the threshold of early changes within the brain tissue. *J. Neuropath. exp. Neurol.*, 3, 139-171.
- Haberland, C. (1962). Cerebellar degeneration with clinical manifestation in chronic epileptic patients. *Psychiat. et Neurol. (Basel)*, 143, 29-44.
- Hofmann, W. W. (1958). Cerebellar lesions after parenteral Dilantin administration. *Neurology (Minneapolis)*, 8, 210-214.
- Lindenberg, R. (1955). Compression of brain arteries as pathogenetic factor for tissue necroses and their areas of predilection. *J. Neuropath. exp. Neurol.*, 14, 223-243.
- Merritt, H. H., and Putnam, T. J. (1939). Sodium diphenyl hydantoinate in treatment of convulsive seizures. *Arch. Neurol. Psychiat. (Chic.)*, 42, 1053-1058.
- Meurice, E. (1956). D'un syndrome cérébello-spasmodique progressif de longue durée dans l'épilepsie d'allure temporale. *Acta neurol. Belg.*, 56, 396-401.
- Meyer, A., Beck, E., and Shepherd, M. (1955). Unusually severe lesions in the brain following status epilepticus. *J. Neurol. Neurosurg. Psychiat.*, 18, 24-33.
- Minoque, S. J., and Latham, O. (1965). Cerebellar degeneration with epilepsy. *Med. J. Aust.*, 1, 430-433.
- Roger, J., and Soulayrol, R. (1959). A propos des accidents neurologiques du traitement de l'épilepsie par les hydantoïnes. *Rev. Neurol.*, 100, 783-785.
- Scolz, W. (1959). The contribution of patho-anatomical research to the problem of epilepsy. *Epilepsia (Amst.)*, 4th ser., 1, 36-55.
- Spielmeier, W. (1930). The anatomic substratum of the convulsive state. *Arch. Neurol. Psychiat. (Chic.)*, 23, 869-875.
- Thorpe, F. T. (1935). Familial degeneration of the cerebellum in association with epilepsy. *Brain*, 58, 97-114.
- Utterback, R. A., Ojeman, R., and Malek, J. (1958). Parenchymatous cerebellar degeneration with Dilantin intoxication. *J. Neuropath. exp. Neurol.*, 17, 516-519.
- White, P. T., Grant, P., Mosier, J., and Craig, A. (1961). Changes in cerebral dynamics associated with seizures. *Neurology (Minneapolis)*, 11, 354-361.
- Zimmerman, H. M. (1938). The histopathology of convulsive disorders in children. *J. Pediat.*, 13, 859-890.