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EPILEPTIC BRAIN DAMAGE IN ADOLESCENT BABOONS FOLLOWING SEIZURES INDUCED BY ALLYLGLYCINE

BY

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THE occurrence of neuronal loss and gliosis in the hippocampus of chronic epileptics was described by Sommer (1880) and subsequently by Bratz (1889). Among patients with epilepsy in institutions it is the commonest cerebral lesion, being found at post-mortem in 50 to 70 per cent of cases (Sano and Malamud, 1953; Margerison and Corsellis, 1966). Although the early German authors associated Ammon's horn sclerosis with generalized seizures, more recent studies (Stauder, 1935; Sano and Malamud, 1953; Falconer, Serafetinides and Corsellis, 1964; Margerison and Corsellis, 1966; Falconer, 1970*b*) have emphasized a correlation with temporal lobe epilepsy. The abolition of such seizures by the unilateral neurosurgical removal of tissue showing mesial temporal sclerosis (Falconer, 1970*a, b*, 1972) suggests that the lesion may be a cause of temporal lobe epilepsy.

The origin of the lesion of mesial temporal sclerosis is not clearly established. Among causes which have been proposed are injury at birth ("incisural sclerosis," Earle, Baldwin and Penfield, 1953), perinatal asphyxia (Veith, 1970), neonatal or infantile infection (bacterial or viral meningitis or encephalitis) and febrile convulsions in infancy (Ounsted, Lindsay and Norman, 1966). If seizures themselves can cause hippocampal sclerosis, it is important to identify the factors which determine whether particular seizures will produce such a lesion. If secondary physiological changes occurring during seizures are largely responsible for the cerebral lesions, they may be readily preventable. These problems are difficult to study in man. We have recently shown, however, that prolonged seizures induced in baboons by bicuculline produce ischaemic cell change with the same pattern of distribution in the neocortex, hippocampus, thalamus and cerebellum as is found in man after status epilepticus (Meldrum and Brierley, 1973). Such damage can be correlated with the severity of certain systemic changes during the seizure (Meldrum and Horton, 1973). In a preliminary report we stated that closely grouped brief seizures induced by allylglycine can lead to the appearance of lesions confined to the hippocampus, characterized by loss of neurons and glial proliferation in the Sommer sector and end folium (Meldrum and Brierley, 1972). We are now reporting the physiological

changes associated with such sequences of seizures. We also give a more detailed presentation of the histological nature and evolution of these lesions.

MATERIALS AND METHODS

Adolescent baboons (9 *Papio papio* from Senegal and 4 *Papio cynocephalus* from Kenya, weights 3.4–6.6 kg), while under pentobarbitone anaesthesia, were chronically prepared for regional EEG recording by the insertion of 14 or 15 epidural silver–silver chloride electrodes connected to a multisolet cemented to the skull. In some animals a femoral arterial cannula was also inserted chronically; in others it was inserted acutely under local anaesthesia (procaine 2 per cent).

Before inducing the seizure the animal was seated in a primate chair and the EEG and electrocardiogram recorded on a Galileo Model E18 B. Rectal temperature was monitored by means of an Ellab thermometer (Copenhagen). Arterial blood pressure was recorded via the femoral cannula using a Statham strain gauge and a Beckman Type R Polygraph. Respiratory movements were similarly recorded using a perithoracic cuff. Arterial blood gas tensions and pH were determined by means of a Radiometer pH Meter and micro-electrode units (Clark and Severinghaus types). Arterial haemoglobin concentration, saturation and oxygen content were measured with an IL Co-Oximeter. Enzymatic methods were used to determine arterial glucose concentration (Lowry, Passonneau, Hasselberger and Schulz, 1964) and arterial lactate concentration (Boehringer test combination).

To induce a sequence of seizures, allylglycine (Sigma Chemical Co.) up to 550 mg/kg body weight, dissolved in sterile saline (up to 25 ml) was injected intravenously in one to three minutes. Later, animals sometimes received atropine (0.3 mg intramuscularly), glucose (5–20 ml 50 per cent solution intravenously) or 6 per cent w/v dextran (Dextraven 110, Fisons Ltd.). Late in the seizure sequence animals were either maintained sitting up (SB 32), laid in lateral decubitus on the left (SB 40, 41, 42), or right side.

Animals were either allowed to recover in their own cage or were given an appropriate dose of pentobarbitone and the brain fixed by *in vivo* perfusion with a formalin, acetic acid and methanol mixture (as described by Meldrum and Brierley, 1973). "Recovered animals" were treated similarly after an appropriate survival period. Subsequent processing of the histological material was as described by Meldrum and Brierley (1973).

RESULTS

Temporal Pattern of Seizures

The average latent interval to the first spontaneous seizure following the intravenous injection of allylglycine (350–550 mg/kg) was one hundred and twenty-seven minutes. (One animal, SB30, had no spontaneous seizures, but photic stimulation at hourly intervals induced 6 tonic-clonic seizures.) The mean number of brief tonic-clonic seizures for the 14 experiments was 26 (see Table I). The temporal pattern of seizures in 4 baboons is illustrated in fig. 1.

A typical tonic-clonic seizure began with conjugate deviation of the eyes, associated with turning of the head and neck and horizontal nystagmus. Myoclonus beginning unilaterally in the peri-orbital muscles spread to the facial muscles and then to the ipsilateral and contralateral trunk and limb muscles. A brief tonic phase (ten to twenty seconds) was followed by a slow myoclonic phase and a short period of post-ictal depression. The electrocorticogram showed a rhythmic spike discharge originating unilaterally in the posterior parietal or occipital cortex, and progressively generalizing. The tonic phase was associated with a highly rhythmic discharge,

TABLE I.—ALLYLGLYCINE AND SEIZURES IN 13 BABOONS

Group	Baboon	Sex	Weight (kg)	Dose (mg/kg)	Recurrent seizures		Status epilep. (min)	Max. temp. (°C)	Lowest art. gluc (M.M)	Minim. art. PO ₂ (mmHg)
					Lat. (min)	Durat. (h.m.)				
A	KB 6	F	6.0	360	116	14	2.00	—	—	—
	SB 30	F	4.0	360	(180)	6	5.00	—	—	—
	SB 35	M	6.2	400	121	26	4.15	—	41.0	2.1
	SB 36	M	6.6	400	117	24	3.20	20	41.2	4.1
	SB 40	F	6.0	480	214	16	10.00	—	37.8	1.2*
B	KB 2	M	5.5	400	113	21	2.30	—	39.8	1.2
	KB 3	M	5.0	350	119	36	9.20	—	38.7	2.8*
	SB 29	F	5.5	500	100	34	8.00	—	—	—
	SB 32	F	3.4	470	157	63	11.00	—	(36.0)	—
	SB 39	M	5.0	450	158	26	6.35	—	40.0	0.7*
C	KB 1	M	4.8	500	85	8	1.20	63	42.8	1.6
	SB 40	F	6.0	550	117	42	4.42	35	41.5	3.9*
	SB 41	M	5.5	510	120	26	2.48	60	41.0	1.3*
	SB 42	F	6.0	510	125	20	3.35	14	41.8	1.3*

Group A—no brain damage. Group B—recurrent seizures and brain damage. Group C—recurrent seizures, status epilepticus and brain damage.

NOTE.—SB 40 experienced 2 seizure sequences, separated by six days; there was no pathology attributable to the first sequence
*Received parenteral glucose during the seizure sequence.

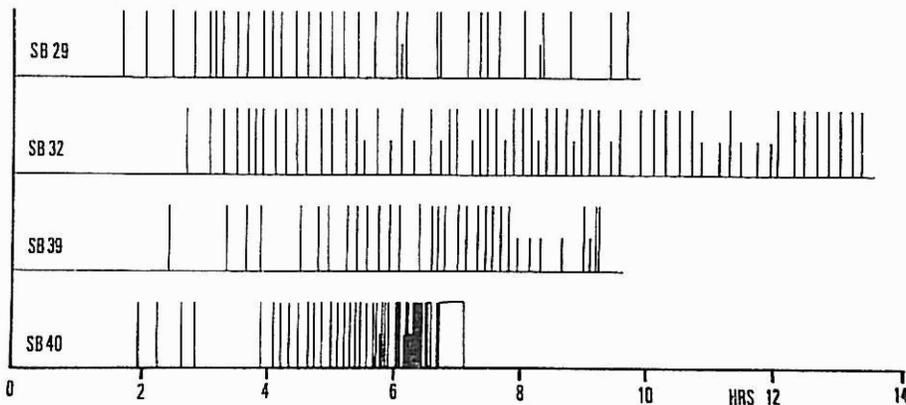


FIG. 1.—Diagram to show the timing of seizures after allyl glycine administration in four baboons (*Papio papio*). Each tall vertical line represents a tonic-clonic seizure followed by post-ictal silence on the EEG. Each short vertical line represents a partial seizure, without post-ictal silence. The rectangle terminating SB 40 represents sustained seizure activity.

augmenting in amplitude and giving way to symmetrical rhythmic bursts of polyspikes (2-3 per second) accompanying the generalized clonic jerks. A post-ictal silence was followed by slow activities with initially a return to a normal EEG appearance in two to four minutes. In the longer sequences of seizure return to a normal EEG post-ictally became progressively delayed until successive seizures originated on a background of sustained high amplitude delta activity.

In 5 animals, following a sequence of 8 or more such brief seizures a period of sustained seizure activity occurred. This usually took the form of prolonged myoclonus associated with rhythmic spikes and waves.

Pauses in this activity (with an isoelectric record) terminated with either generalized or focal onset of seizure activity. No animal which developed status epilepticus subsequently returned to a normal pattern of EEG activity.

As described below (*see Neuropathology*), 9 of the 14 seizure sequences led to neuropathological changes. In 4 cases status epilepticus had been present. Comparing seizure sequences that led to damage with sequences that did not produce damage, the latency to onset of the first spontaneous seizure was not significantly different (*see Table I*). Excluding animals developing status epilepticus, the mean number of seizures was 36 (range 2-63, $N=5$) in the sequences producing lesions and 17 (range 6-26) in the sequences not producing cerebral lesions.

Blood pressure.—Arterial blood pressure was recorded in 11 of the 14 seizure sequences. The changes were similar in all cases (*see figs. 2 and 3*). Control systolic pressures were in the range 135-160 mmHg, diastolic pressures in the range 100-135 mmHg. Each seizure was associated with a marked rise in systolic and diastolic pressures. Peak systolic pressures nearly always exceeded 200 mmHg, and occasionally pressures above 260 mmHg were recorded. These rises lasted one to three minutes. Between seizures the BP returned to control level. Falls in mean pressure followed the appearance of status epilepticus. In these animals the systolic pressure was finally in the range 80-90 mmHg, and diastolic pressure was between 55 and 60 mmHg.

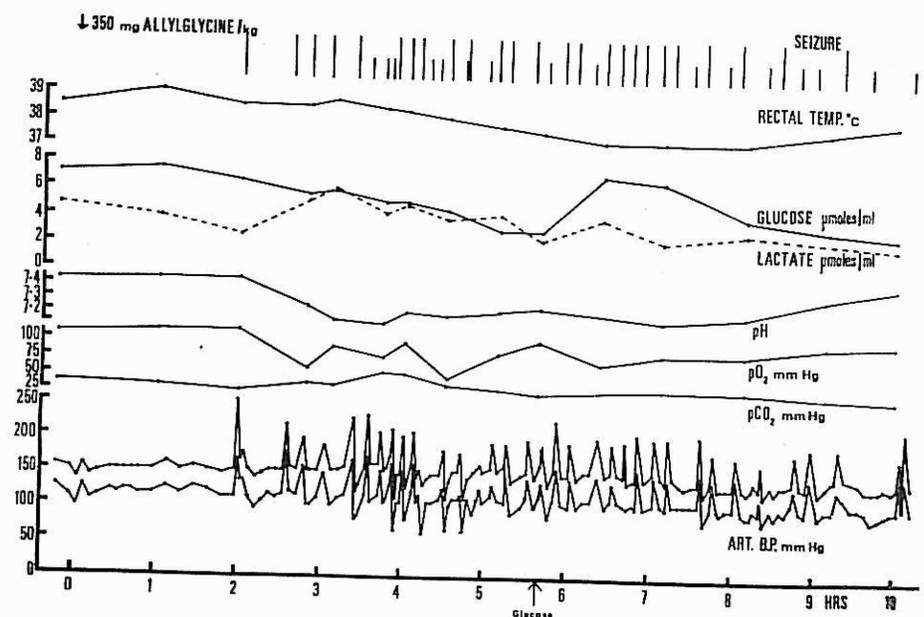


FIG. 2.—Physiological events in a seizure sequence induced by the intravenous administration of allylglycine in baboon KB 3 (*Papio cynocephalus*). Vertical lines represent tonic-clonic seizures as in fig. 1. Glucose (5 g in 10 ml) was given intravenously at the arrow. Glucose, lactate, pH, pO₂ and pCO₂ were determined in arterial blood samples.

Hæmoglobin and blood gases.—Initial hæmoglobin concentrations were in the range 7.0-12.6 g/100 ml blood (Mean 9.97, $N=9$). Seizures were followed by a rise to a mean peak of 11.14 g Hb/100 ml blood. Later while fluid replacement (saline and glucose solutions) was in progress, hæmoglobin fell to a mean of 9.16 g/100 ml.

Arterial pO₂, before seizure onset, was in the range 96.5-120 mmHg (mean 108 mmHg, $N=11$). Samples during and directly after seizures showed falls of 20-60 mmHg. Values for the lowest

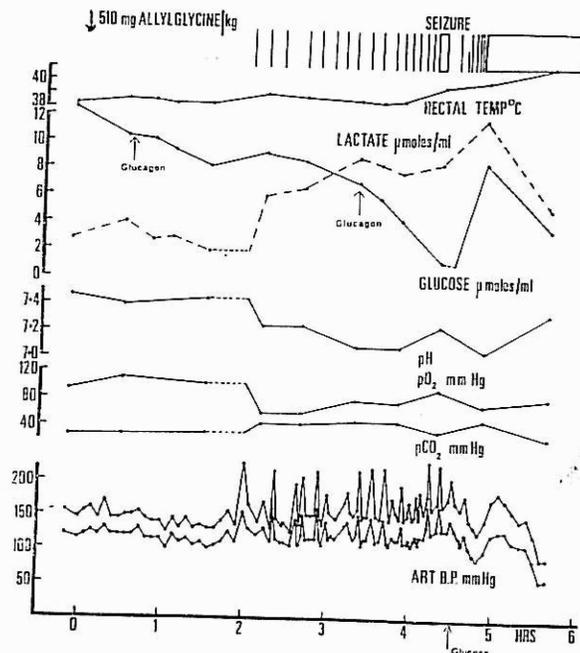


FIG. 3.—Physiological events in a seizure sequence induced by allylglycine in a baboon, *Papio papio* (SB 41). Transient and sustained seizure activity indicated as in fig. 1. Glucagon (30 $\mu\text{g}/\text{kg}$) and glucose (10 g in 20 ml) were given intravenously as indicated by arrows. Lactate, glucose, pH, pO_2 and pCO_2 were determined in arterial blood samples.

arterial pO_2 recorded in each animal were between 45 and 80 mmHg (mean 56.6 mmHg, $N=11$). In general, arterial pO_2 returned to the normal range within one to five minutes of the end of a generalized seizure.

The initial arterial pCO_2 was in the range 26.5–38.3 (mean 30.4 mmHg, $N=11$). The highest values recorded during or directly after seizures were in the range 42.6–59.5 mmHg (mean 49.6, $N=11$).

Blood lactate and pH.—Before the first seizure, blood lactate was in the range 0.8–3.9 $\mu\text{moles}/\text{ml}$ (mean 2.54, $N=11$). This rose after seizure onset, reaching a peak after 0.5–3.0 hours. The peak concentrations were in the range 4.4–13.5 $\mu\text{moles}/\text{ml}$ (mean 9.71, $N=11$).

Mean arterial blood pH was 7.41 both before allylglycine administration (range 7.32–7.49) and before the first seizure (range 7.32–7.52). During and after seizures arterial pH fell; the range of the lowest values recorded was 6.92–7.12 (mean 7.01). In general, the lowest pH values corresponded in time to the peak arterial lactate concentration. The majority of pH values in interseizure intervals were in the range pH 7.20–7.30.

Arterial glucose concentration.—Control arterial glucose measurements were sometimes elevated (mean 8.3 $\mu\text{moles}/\text{ml}$, range 5.3–12.5, $N=11$), but fell to a mean of 6.9 $\mu\text{moles}/\text{ml}$ (range 3.7–10.6, $N=11$) before the onset of the first seizure. No rise in glucose concentration was seen in 7 of the 11 animals. The 4 showing small apparent rises in arterial glucose concentration (of 0.4–1.1 $\mu\text{moles}/\text{ml}$) all showed greater percentage increases in haemoglobin concentration. During the period of recurrent seizures a progressive fall in arterial glucose concentration occurred. The mean value during the second hour after seizure onset was 4.85 $\mu\text{moles}/\text{ml}$ and the mean lowest value was 2.17 $\mu\text{moles}/\text{ml}$ (range 0.7–4.1 $\mu\text{moles}/\text{ml}$), but in 5 experiments (KB 3, SB 39, SB 40, SB 41, SB 42) intravenous or intraperitoneal glucose was given during the recurrent seizure period. (Three of these animals also received intravenous injections of glucagon.) Nevertheless, some animals

experienced long periods (three to four hours) with blood glucose levels around, or below, $2.2 \mu\text{moles/ml}$.

Temperature.—Rectal temperature was recorded in all except 2 of the seizure sequences. Initial temperatures were in the range $37.0\text{--}38.5^\circ\text{C}$. Temperature varied only slightly (up or down) with up to 6 or 7 brief seizures per hour. When the frequency of seizures was 8–10 or more per hour, or seizure activity was continuous, rectal temperature rose. The peak temperatures are given in Table I, which shows that in only one animal not having sustained seizure activity, did the temperature exceed 40°C , but that for the 5 animals with status, the mean peak temperature was 41.7°C . In one animal (SB 32, having 63 seizures) temperature was not recorded in the first half of the seizure sequence, but in the second half it fell from 36.0 to 34.2°C .

Survival and Recovery

The onset of status epilepticus was followed, after a few minutes, by a decline in mean arterial pressure. Cerebral fixation by perfusion was effected either while circulation was maintained or, when the onset of cardiac irregularities was sudden, within one to two minutes of cardiac arrest. In 4 experiments, perfusion fixation terminated a sequence of recurrent seizures. In 5 experiments the baboon was returned to his cage and observed for gross neurological abnormalities with occasional EEG recordings.

The slowest neurological recovery was shown by SB 32 (after 63 seizures in eleven hours). Eight hours after the seizure sequence, the animal on stimulation raised her head from the prone position but did not follow visually or make coordinated limb movements. The EEG showed high voltage delta activity, somewhat asymmetrical, with isolated bursts of spikes. After twelve hours she was responsive to handling and showed visual following. Spikes were absent from the EEG but she was weak and ataxic. There was complete neurological recovery two to three days later, and the EEG was not different from control. The most rapid recovery was shown by SB 40 (after 16 seizures in ten hours). Within a few minutes of the last seizure she sat partially erect, supported on forelimbs, and nine hours later was apparently normal except for occasional myoclonic twitches of the forelimbs. The other 3 animals showed an intermediate pattern of recovery.

Neuropathology

Macroscopic appearances of the brains.—The weight range of the brains was 121–160 g. Evidence of brain swelling consisting of downward herniation of the inferior cerebellar vermis and flattening of the cortical gyri was seen in three animals (moderate in baboon KB 2 and slight in baboons SB 41 and SB 42). There was a thin film of recent subarachnoid hæmorrhage over the right parietal lobe in baboon KB 2. Organizing thrombus was seen in, but did not occlude, the posterior third of the superior longitudinal sinus and the right transverse sinus in baboon SB 41. In the usual slices of the cerebrum, cerebellum and brain-stem, appearances were normal in all the brains.

Microscopic appearances of the brains.—The brains of four animals (SB 30, SB 35, SB 36 and KB 6) were considered to be normal. In 8 of the remaining 9 animals there was either some stage in the process of ischæmic cell change

neurons which showed ischaemic cell change or had disappeared was small (+) except in one animal (SB 29) in which the cell loss in h_1 twenty-one days after the seizure sequence was moderate (++) (figs. 4 and 5, Plate XXV).

It is to be noted that cell loss and gliosis in the Sommer sector were seen close to its junction with h_2 in 2 brains (SB 29 and SB 32), and corresponding alterations in the end folium occurred at its junction with h_2 (figs. 6, 7 and 8). Ischaemic cell change after status epilepticus showed a similar preponderance at the junction of h_1 and h_3 with h_2 (SB 41 and SB 42).

In the cerebral cortex, alterations attributable to the seizures were never more than slight (+). They were uniformly distributed in two brains (KB 1 and SB 41) and restricted to the occipital lobes of one (SB 40). A concentration of ischaemic neurons along the boundary zones of the cortex (SB 39 and SB 42) suggested the possibility of reduced perfusion pressure.

A proliferation of the Bergmann astrocytes in the cerebellum was observed in two brains (SB 29 and SB 32) and was associated with marginal gliosis in the cerebral cortex in one case (SB 29).

DISCUSSION

Mechanism of Action of Allylglycine

Allylglycine inhibits glutamic acid decarboxylase, the cerebral enzyme synthesizing the inhibitory transmitter substance, γ -aminobutyric acid (GABA). It is far more effective *in vivo* (1.74 mmol/kg in mice inhibits GAD activity by 40 per cent) than when tested in *in vitro* systems (0.6 M produces only a 25 per cent inhibition of GAD activity in brain homogenates) (Horton and Meldrum, 1973). The mechanism of GAD inhibition is not understood; neither substrate competition nor inhibition of the synthesis or coenzymic function of pyridoxal phosphate appear to be involved (Horton and Meldrum, 1973). The seizures, however, closely resemble those seen after pyridoxal phosphate antagonists such as isoniazid, thiosemicarbazide and 4-deoxypyridoxine (Meldrum, Balzano, Gadea and Naquet, 1970; Meldrum and Horton, 1971; Horton and Meldrum, 1973). This applies both to the long latent interval, followed by recurrent seizures with intervening recovery, and to the regional onset of seizure activity which is predominantly unilateral in the posterior parietal or occipital cortex.

Allylglycine inhibits the uptake of certain amino acids (leucine, proline) into rat brain slices (Balcar and Johnston, 1974) and reduces protein synthesis in synaptosome preparations of rat brain (Alberici de Canal and Rodriguez de Lores Arnaiz, 1972).

When directly applied to neurons by microelectrophoresis, allylglycine has a weak depressant effect (Curtis, Duggan and Johnston, 1970; Roper, 1970).

The balance of evidence is that the seizures produced by allylglycine are due to inhibition of cerebral glutamic acid decarboxylase activity (Meldrum, 1974). An action on amino-acid uptake could be a contributory factor in the subsequent onset or evolution of brain damage.

Physiological Changes during Seizure Sequence

In general, the physiological changes were much less severe than those observed during sustained seizures produced by bicuculline in similar baboons (Meldrum and Horton, 1973). In particular, hyperpyrexia was seen only when seizures were very closely spaced or clonic activity was continuous. Arterial pressure showed the expected ictal rises; mean pressure fell only when seizure activity was sustained. Falls in arterial pO_2 were transient and not severe. Respiratory and metabolic acidosis was also less severe than after bicuculline (when arterial pH usually fell below 6.8 (Meldrum and Horton, 1973)).

The lack of an initial hyperglycaemia (secondary to autonomic activity during seizures) was another difference from previous studies (Naquet, Meldrum, Balzano and Charrier, 1970; Meldrum and Horton, 1973). Secondary hypoglycaemia was sometimes severe and prolonged and presumably contributed both to delayed EEG recovery late in seizure sequences, and to the occurrence of brain damage.

Sudden cardiovascular collapse or progressive failure during status epilepticus was similar to that seen after bicuculline; hyperkalaemia, hyperpyrexia and hypoglycaemia were probably contributory factors to this.

Ischaemic Cell Change

This histological appearance can result from any disturbance of cellular energy metabolism, and shows a similar time course of evolution after arterial hypotension, hypoglycaemia or focal ischaemia (Brierley, Brown and Meldrum, 1971). In the present experiments the relative importance of the various physiological changes cannot be definitively established. None of those measured, with the possible exception of the hypoglycaemia (see Meldrum and Horton, 1971; Meldrum and Brierley, 1973), was of sufficient severity individually to have produced neuronal death (ischaemic cell change), but the effects of hypoglycaemia, hyperpyrexia, reduced arterial oxygenation and impaired cerebral perfusion (general or focal) are probably additive. The epileptic discharges augment cerebral metabolic activity and will thus exacerbate the derangement of cerebral energy metabolism.

The pattern of brain damage (hippocampal and neocortical) closely resembles that seen after prolonged bicuculline-induced seizures in paralysed, artificially ventilated baboons (Meldrum, Vigouroux and Brierley, 1973). In non-paralysed animals after bicuculline, there was a greater incidence of cerebellar damage, which could be correlated with the greater hyperpyrexia and more marked secondary arterial hypotension in this situation (Meldrum and Brierley, 1973).

Swelling of astrocytic processes can occur early in a seizure sequence (De Robertis, Alberici and de Lores Arnaiz, 1969) and may give rise to the scalloped appearance we observed in hippocampal neurons, and the finely vacuolated neuropil described by Meldrum, Vigouroux and Brierley (1973). Such changes are probably reversible, but the associated increase in tissue pressure may further impede local blood flow. These changes are particularly prominent in the h_1 sector of the hippocampus and

they may be a factor contributing to impaired focal perfusion and hence a cause of ischaemic cell change and neuronal loss.

Hippocampal Lesions after Recurrent Seizures

Hippocampal lesions, unlike those elsewhere in the brain, show a strong tendency to be asymmetrical. This is especially true of the h_1 lesion, as was emphasized in studies on chronically hospitalized patients with epilepsy (Bratz, 1889; Margerison and Corsellis, 1966). In man the left and right side are equally often affected, but there are differences according to the age at which prolonged convulsions occurred, and to the sex of the child (Taylor and Ounsted, 1971). In our animals the right side was predominantly involved. Most of the animals were laid on their right side late in the seizure sequence, raising the possibility that venous congestion was an important factor (McLardy, 1969). In one animal remaining upright (SB 32) and one laid on the left side (SB 41), lateralization to the right was also found, suggesting that an asymmetry of function might be involved, as proposed by Taylor (1969).

The hippocampal lesions we observe at one, three or six weeks after a sequence of seizures correspond in their topography and cytology to an early phase in the evolution of the lesions classically described both in patients with chronic epilepsy dying in institutions and in partial temporal lobectomy specimens removed from patients with temporal lobe epilepsy (Ammon's horn sclerosis or "mesial temporal sclerosis" (Falconer, Serafetinides and Corsellis, 1964; Margerison and Corsellis, 1966)). The loss of neurons is not so severe in the baboons, however, nor is there any macroscopically evident shrinkage of the hippocampus. This probably requires a longer time for its development.

Although there can be little doubt that the lesions we observe are a consequence of physiological events related to the seizures, it is more difficult to prove that the hippocampal lesions in epileptic patients are a consequence of their seizures.

When the pathology of mesial temporal sclerosis is found in adolescents undergoing a partial lobectomy for temporal lobe epilepsy, a history of prolonged febrile convulsions can usually be obtained (Falconer, 1970a, 1971, 1972). Our experiments strengthen the hypothesis (Falconer, Serafetinides and Corsellis, 1964; Ounsted, Lindsay and Norman, 1966) that the early seizures are commonly a cause of the pathology.

SUMMARY

Epileptic seizures have been induced in 13 adolescent baboons (*Papio papio* and *P. cynocephalus*) by the intravenous administration of allylglycine (350–630 mg/kg body weight). In 8 animals the seizures were brief, recurred 6–63 times in two to eleven hours and were followed by neurological recovery. In 5 animals a period of status epilepticus supervened.

Recurrent seizures were associated with progressive hypoglycaemia. Status epilepticus produced hyperpyrexia.

Cerebral pathology was studied after paraortic perfusion-fixation of the brain. Sequences of 6–26 seizures occurred without any pathological sequelae. Short

- MELDRUM, B. S., BALZANO, E., GADEA, M., and NAQUET, R. (1970) Photic and drug-induced epilepsy in the baboon (*Papio papio*): the effects of isoniazid, thiosemicarbazide, pyridoxine and aminoxyacetic acid. *Electroenceph. clin. Neurophysiol.*, **29**, 333-347.
- , and BRIERLEY, J. B. (1971) Circulatory factors and cerebral boundary zone lesions. *Clin. devl Med.*, **39-40**, 20-33.
- , — (1972) Neuronal loss and gliosis in the hippocampus following repetitive epileptic seizures induced in adolescent baboons by allylglycine. *Brain Res.*, **48**, 361-365.
- , — (1973) Prolonged epileptic seizures in primates: ischemic cell change and its relation to ictal physiological events. *Archs Neurol., Chicago*, **28**, 10-17.
- , and HORTON, R. W. (1971) Convulsive effects of 4-deoxypyridoxine and of bicuculline in photosensitive baboons (*Papio papio*) and in rhesus monkeys (*Macaca mulatta*). *Brain Res.*, **35**, 419-436.
- , — (1973) Physiology of status epilepticus in primates. *Archs Neurol., Chicago*, **28**, 1-9.
- , VIGOUROUX, R. A., and BRIERLEY, J. B. (1973) Systemic factors and epileptic brain damage. *Archs Neurol., Chicago*, **29**, 82-87.
- NAQUET, R., MELDRUM, B. S., BALZANO, E., and CHARRIER, J. P. (1970) Photically-induced epilepsy and glucose metabolism in the adolescent baboon (*Papio papio*). *Brain Res.*, **18**, 503-512.
- OUNSTED, C., LINDSAY, J., and NORMAN, R. (1966) Biological factors in temporal lobe epilepsy. *Clin. devl Med.*, **22**, 1-135.
- ROPER, S. (1970) Inhibition of Mauthner cells by allylglycine. *Nature, Lond.*, **226**, 373-374.
- SANO, K., and MALAMUD, N. (1953) Clinical significance of sclerosis of the cornu ammonis. *Archs Neurol. Psychiat., Chicago*, **70**, 40-53.
- SOMMER, W. (1880) Erkrankung des Ammonshorns als ätiologisches Moment der Epilepsie. *Arch. Psychiat. NervKrankh.*, **10**, 631-675.
- SPIELMEYER, W. (1922) "Histopathologie des Nervensystems." Berlin: Springer, pp. 74-79.
- STAUDER, K. H. (1935) epilepsie und Schlafennappen. *Arch. Psychiat. NervKrankh.*, **104**, 181-212.
- TAYLOR, D. C. (1969) Differential rates of cerebral maturation between sexes and between hemispheres. Evidence from epilepsy. *Lancet*, **ii**, 140-142.
- , and OUNSTED, C. (1971) Age, sex, and hemispheric vulnerability in the outcome of seizures in response to fever. *Clin. devl Med.*, **39-40**, 266-273.
- VEITH, G. (1970) Anatomische Studie über die Ammonshornsklerose im Epileptikergehirn. *Dt. Z. NervHeilk.*, **197**, 293-314.

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LEGENDS FOR PLATES

PLATE XXV

FIG. 4.—SB 29. Right hippocampus (h_1) showing loss of neurons with proliferation of fibrous astrocytes and rod cells. Paraffin. Phosphotungstic acid hæmatoxylin. $\times 170$.

FIG. 5.—SB 29. Right hippocampus (h_1) showing neuronal loss with proliferation of astrocytes and rod cells. Paraffin. Cresyl fast violet. $\times 155$.

PLATE XXVI

FIG. 6.—SB 32. Right hippocampus (h_2-h_3) showing marked loss of neurons, also proliferation of astrocytes and rod cells. Celloidin, Cresyl fast violet and Luxol fast blue. $\times 325$.

FIG. 7.—SB 32. Left hippocampus (h_2-h_3) showing focus of neuronal loss with proliferation of astrocytes and rod cells. Celloidin. Cresyl fast violet and Luxol fast blue. $\times 325$.

FIG. 8.—SB 29. Hippocampus (h_3-s) showing fibrous gliosis. Celloidin. Phosphotungstic acid hæmatoxylin. $\times 325$.

PLATE XXV

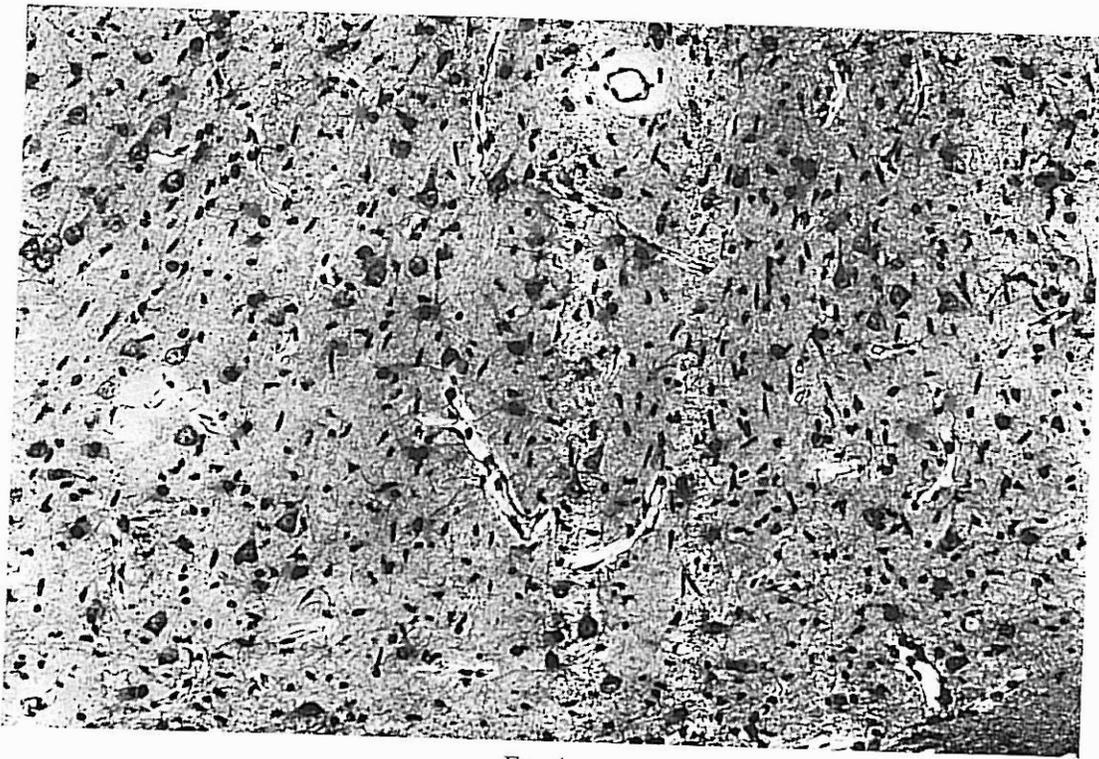


FIG. 4.

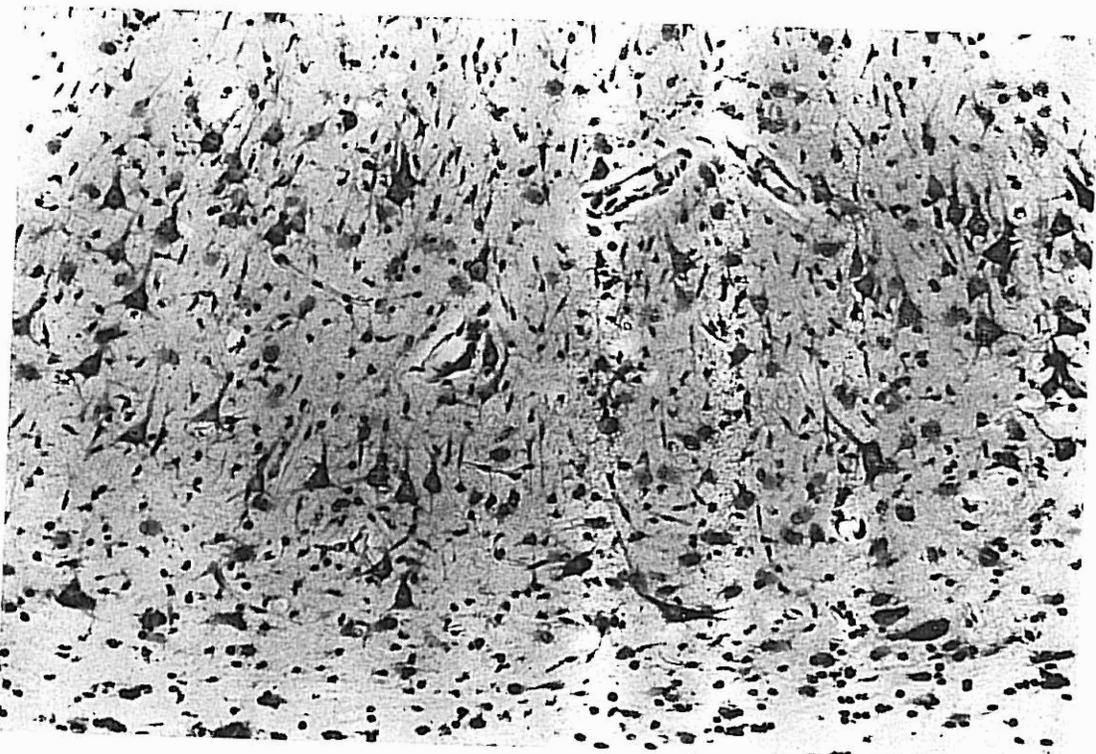


FIG. 5.

To illustrate article by B. S. Meldrum, R. W. Horton and J. B. Brierley.

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PLATE XXVI

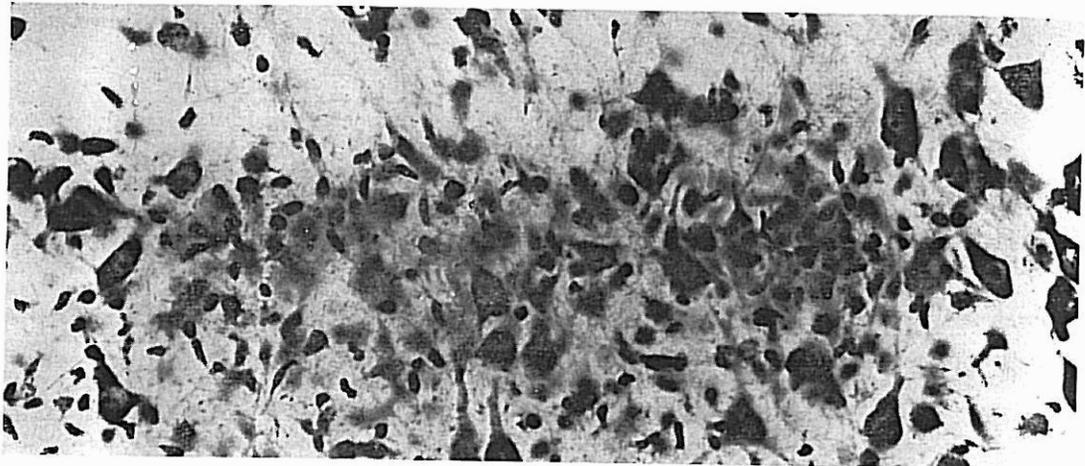


FIG. 6.

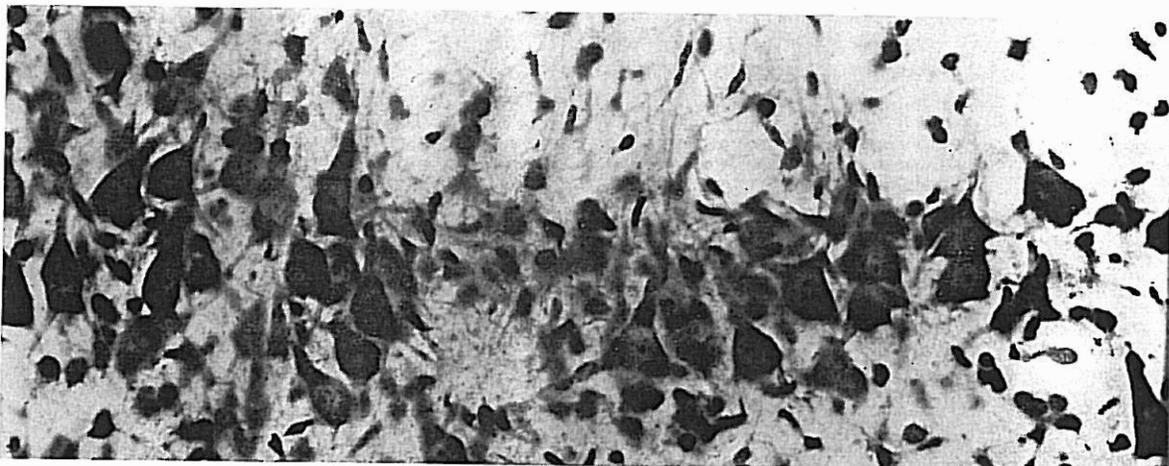


FIG. 7.

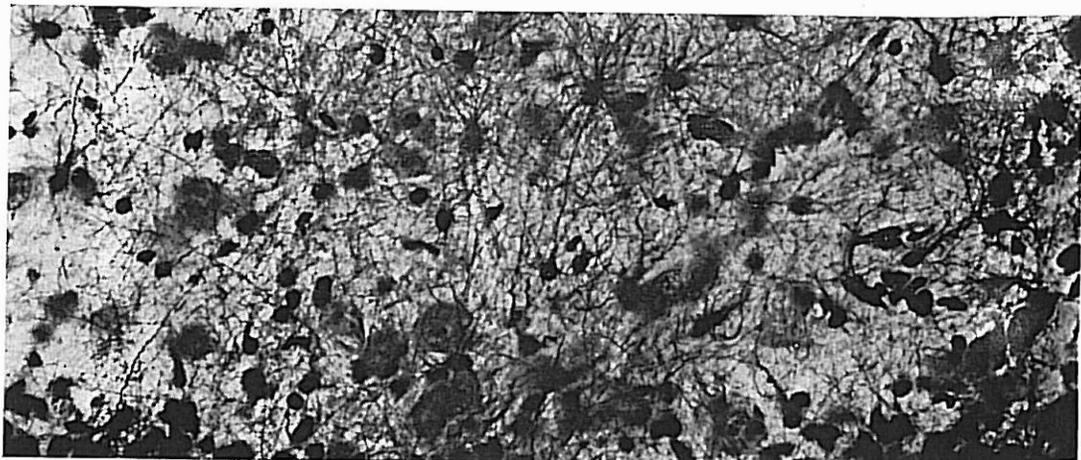


FIG. 8.

To illustrate article by B. S. Meldrum, R. W. Horton and J. B. Brierley.

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Intracerebral hemorrhage following electroconvulsive therapy

Leon A. Weisberg, MD; Debra Elliott, MD; and David Mielke, MD

Muscle relaxants and anesthetic agents are given with electroconvulsive therapy (ECT) to prevent traumatic injuries during convulsion. Cardiovascular or cerebrovascular complications may develop in high-risk patients who are hypertensive or have other cardiac disorders and undergo ECT. We now report a patient who developed an intracerebral hemorrhage (ICH) during ECT.

Case report. A 69-year-old woman was admitted for ECT. She had several recent episodes of depression that had responded to antidepressant medication; however, recent depression had lasted 4 months without improvement despite treatment with amitriptyline, imipramine, lithium, fluoxetine, and alprazolam. She was nonfunctional and required hospitalization.

The patient had no family history of dementia or psychiatric illness, had no recent head trauma, was not hypertensive, and had no prior cerebrovascular symptoms. She did not drink alcohol. When initially admitted to the hospital, her mental state was consistent with severe depression. She had no memory impairment or clinical dementia. Chest radiograph and ECG were normal. Laboratory studies, including complete blood count, platelet count, prothrombin time, partial thromboplastin time, and erythrocyte sedimentation rate, were normal.

ECT was performed on four occasions. The patient was induced with etomidate, and succinylcholine was used for muscle relaxation. Following the first three treatments, the patient had confusion for 15 minutes. After the fourth ECT, confusion lasted 4 hours. She also reported that her vision became blurred and she bumped into objects on her right side. She reported no headache or nausea. Neurologic examination showed right homonymous hemianopia, right pronator drift, right-sided Babinski's sign, and recent memory impairment. During ECT, her blood pressure was recorded at 120 to 135 mm Hg systolic and 60 to 80 mm Hg diastolic. She had no signs of head injury. Laboratory studies, including complete blood count, coagulation profile, collagen vascular studies, ECG, and echocardiogram, were normal. CT showed a left parieto-occipital hemorrhage with no abnormal enhancement (figure, A).

Four days later, she awakened from sleep feeling "strange," and she had bitten her tongue. EEG showed left posterior hemisphere slow-wave activity without spike discharges. Anticonvulsant therapy was initiated with phenytoin for a presumed seizure, and no further seizures occurred. One week later, CT showed that the hemorrhage was resolving. MRI showed the hemorrhage with surrounding edema, but there was no evidence of neoplasm or arteriovenous malformation (figure, B). Four months later, she had no more seizures and visual field examination showed improvement. Depression was markedly improved, and she had no cognitive or memory impairment. No further ECT had been performed. She now lives independently.

Discussion. The well-described adverse effects of ECT are acute confusion and memory impairment.¹ It is controversial whether ECT causes structural brain damage.²⁻⁴ There have been reports of localized edema, gliosis, and petechial hemorrhages located directly underneath the electrode site.⁴ The most common systemic complications of ECT are cardiovascular. When the electrical stimulus is applied without atropine pretreatment, there is vagal activation which causes bradycardia and hypotension. When the electrical seizure occurs, there is increased sympathomimetic activity, causing increased arterial blood pressure and tachycardia.¹

This patient was not hypertensive and had no other cardiovascular disease; however, during the course of ECT she developed a lobar hemorrhage. The CT and MRI findings showed no characteristics to indicate traumatic hemorrhagic contusion or hemorrhagic infarction from a potential cardiac embolism. Without angiography, we cannot rule out an "occult" vascular malformation.⁵ The blood coagulation profile showed no evidence of coagulopathy. The etiology of the ICH could not be determined. When an elderly normotensive patient develops a non-traumatic lobar ICH, the possibility of cerebral amyloid angiopathy (CAA) should be considered.^{6,7} There was no documented evidence of acute hypertensive episodes during ECT; however, it is probable that CAA patients have fragile vessels that are particularly sensitive to even mild blood pressure elevations that may have occurred during ECT.

In summary, we describe an elderly normotensive woman who developed medically refractory depression and suffered nontraumatic parieto-occipital hemorrhage following ECT. Since CAA is an increasingly recognized cause of behavioral change in elderly patients, it is important to consider this condition as a cause of ICH in elderly patients, especially if ECT is being considered.

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References

1. Sachs GS, Gelenberg AJ. Adverse effects of electroconvulsive therapy. In: Review of psychiatry, vol 7. Washington, DC: American Psychiatric Press, 1988:498-512.
2. Calloway SP, Dolan RJ, Jacoby RJ. ECT and cerebral atrophy: a computed tomographic study. *Acta Psychiatr Scand* 1981;64:442-445.
3. Kolbeinson H, Arnaldsson OS, Peturason H. Computed tomographic scans in ECT patients. *Acta Psychiatr Scand* 1986;73:28-32.
4. Friedberg J. Shock treatment, brain damage and memory loss: a neurologic perspective. *Am J Psychiatry* 1977;134:1010-1014.
5. Weisberg LA, Stazio A, Shamsia M, Elliott D. Nontraumatic parenchymal brain hemorrhages. *Medicine* 1990;69:277-295.
6. Vinters HV. Cerebral amyloid angiopathy. *Stroke* 1987;18:311-324.
7. Greene GM, Godersky JC, Biller J, Hart MN, Adams HP. Surgical experience with cerebral amyloid angiopathy. *Stroke* 1990;21:1545-1549.

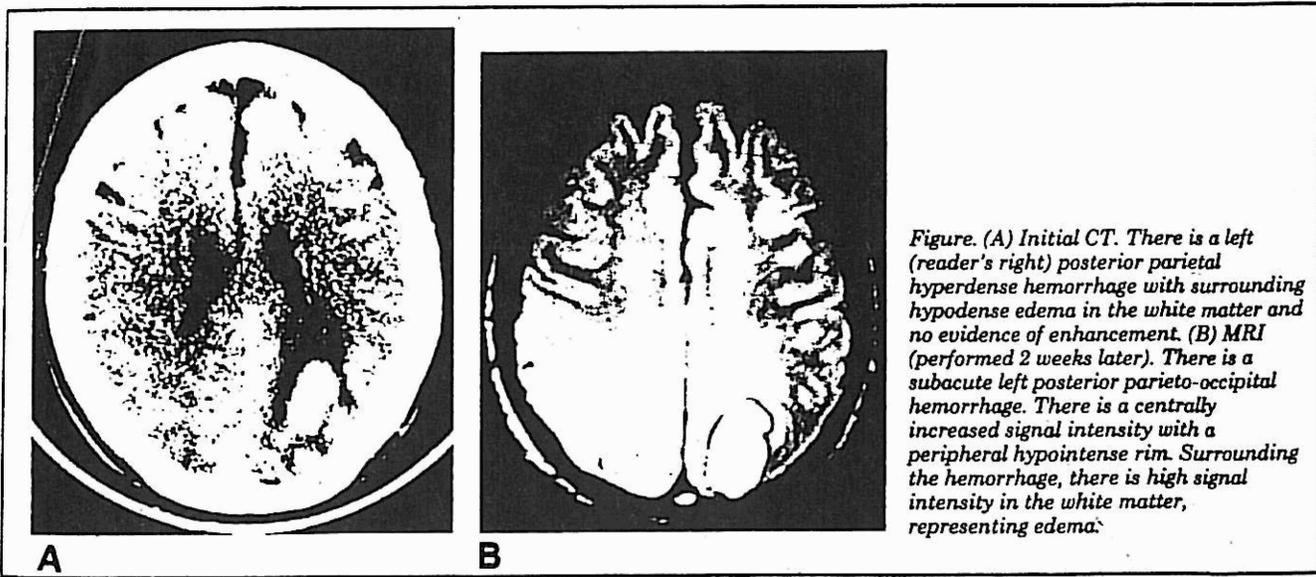


Figure. (A) Initial CT. There is a left (reader's right) posterior parietal hyperdense hemorrhage with surrounding hypodense edema in the white matter and no evidence of enhancement. (B) MRI (performed 2 weeks later). There is a subacute left posterior parieto-occipital hemorrhage. There is a centrally increased signal intensity with a peripheral hypointense rim. Surrounding the hemorrhage, there is high signal intensity in the white matter, representing edema.