# Prolonged Epileptic Seizures in Primates

## Ischemic Cell Change and Its Relation to Ictal Physiological Events

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**Neuronal alterations typical of ischemic cell change were seen in the brains of ten adolescent baboons after generalized seizures, lasting 82 to 299 minutes, induced by bicuculline. These changes involved the neocortex (diffusely, in all ten cases, with some accentuation occipitally), the cerebellum (Purkinje and basket cells, predominantly in the arterial boundary zone) and the hippocampus ($h_1$ and $h_{3\text{-}5}$ sometimes asymmetrically). The brain damage apparently originated during the second phase of the seizure when hyperpyrexia, mild arterial hypotension, mild systemic hypoxia, and acidosis were characteristically, and severe hypoglycemia occasionally, seen. Cerebellar damage was related to hyperpyrexia and arterial hypotension. Numerous factors (including the cerebral epileptic activity) interacted to produce the cortical damage.**
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Status epilepticus in children can give rise to neuronal loss which may later be manifest as cerebellar or cerebral cortical atrophy.[1-6] In its nature and distribution, the neocortical and cerebellar damage following status epilepticus is more or less similar to that seen after systemic circulatory arrest,[7] systemic hypotension,[8] or hypoglycemia.[7,9,10] However, the relationship between brain damage in epileptics and the physiological events during and after prolonged seizures has not yet been documented. Previous experimental studies[11-13] have described physiological changes associated with brief seizures induced in cats, dogs, and primates. Corresponding physiological information during seizures sufficiently long and severe to produce brain damage has not been available.

The preceding paper[14] describes the sequence of physiological events in 18 adolescent baboons in which prolonged seizures were induced by injecting the alkaloid bicuculline. Some of these animals developed brain damage, and the present paper describes the nature and distribution of the altered neurons and correlates this with physiological events during and after the seizure activity.

### Materials and Methods

Fifteen adolescent *Papio papio*, weighing 2.9 to 6.4 kg, were used. The procedures for their chronic preparation and the physiological monitoring systems employed during the bicuculline-induced seizures have been described by Meldrum and Horton.[14]

At the end of the chosen survival peri-

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Table 1.—Factors Possibly Related to the Occurrence, Distribution, and Evolution of Ischemic Cell Change

| Group* | Baboon | Duration of Seizure, min: Generalized | Duration of Seizure, min: Focal: Central | Duration of Seizure, min: Focal: Occipital | Minutes After Onset: On Right Side | Minutes After Onset: Change | Minutes From End of Generalized Seizure to Perfusion | Mean Temperature Last 90 Minutes Before Perfusion | Ischemic Cell Change† |
|---|---|---|---|---|---|---|---|---|---|
| A | 11 | 120 | ... | 190 | 16 | 244V¶ | 240 | 36.3 | 0 |
| | 12 | 78 | ... | 110 | 21 | | 64 | 36.6 | 0 |
| | 17 | 49(+1) | ... | 60(L)¶ | 76 | | 36 | 39.7 | 0 |
| | 20 | 70 | ... | ... | 71 | | 2 | (40.0) | 0 |
| | 24‡ | 27+29 | 85+90 | ... | ... | | 275+188 | 39.0 | 0 |
| B | 7 | 165 | ... | ... | 1 | 118L | 12 | 41.5 | MV ICC >ICC |
| | 9 | 150 | ... | ... | 1 | 78L | 72 | 38.8 | ICC< ICC' |
| | 15 | 134 | 208 | ... | 71 | | 107 | 37.6 | ICC> ICC' |
| | 16§ | 29+28+25 | ... | (29)+60+(25) | 12 | | 134+73+14 | 40.5 | MV, ICC |
| | 19 | 106 | 157 | ... | 25 | | 154 | 38.3 | ICC< ICC' |
| | 23‖ | 49+66+65 | 121+66+65 | ... | ... | | 277+125+10 | 40.3 | ICC |
| | 25 | 168 | ... | ... | 52 | | 148 | 39.4 | ICC< ICC' |
| C | 10 | 299 | ... | ... | 13 | 233L | 11 | 40.8 | ICC> ICC' |
| | 18 | 148 | ... | ... | 66 | | 125 | 39.8 | ICC> ICC' |
| | 27 | 90 | ... | 165 | 34 | | 226 | 38.0 | ICC= ICC' |

* Group A, no damage; group B, mild or moderate damage; and group C, severe damage.
† MV signifies microvacuolation; ICC, ischemic cell change; ICC', ischemic cell change with incrustations.
‡ Received two injections of bicuculline. § Received three injections of bicuculline. ‖ Received glucose twice.
¶ V signifies vertical, L on left side.

Table 2.—Ischemic Cell Change in Brains of Ten Baboons: Regional Distribution and Gradation*

| Baboon | Cerebral Cortex: Occipital | Parietal | Frontal | Temporal | Hippocampus: $h_1$ | $h_{3-5}$ | Laterality | Thalamus: Anterior | Dorsomedial | Striatum | Amygdala: Central-Medial | Basolateral | Cerebellum |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 7 | ++ | + | + | + | 0 | + | L=R | + | + | 0 | 0 | 0 | +(BZ) |
| 9 | + | + | + | + | 0 | + | L=R | + | 0 | 0 | 0 | 0 | +(BZ) |
| 10 | +++ | ++ | ++ | ++ | +++ | ++ | R>L | 0 | 0 | ++R>L | + | ++ | +(BZ) |
| 15 | + | 0 | 0 | 0 | ++ | 0 | L=R | + | 0 | 0 | ++ | + | 0 |
| 16 | + | + | + | + | 0 | + | R | 0 | 0 | 0 | 0 | +R<L | + |
| 18 | ++ | ++ | ++ | ++ | ++ | + | L=R | + | + | + | + | + | +(BZ) |
| 19 | + | + | + | ++ | ++ | ++ | L=R | 0 | 0 | 0 | 0 | + | +++(BZ) |
| 23 | + | + | + | + | + | + | L=R | 0 | + | 0 | 0 | ++ | + |
| 25 | + | + | + | + | 0 | 0 | R>L | 0 | | 0 | 0 | 0 | 0 |
| 27 | +++ | ++ | ++ | ++ | +++ | + | L=R | 0 | 0 | 0 | + | ++ | +(BZ) |

* Ischemic cell change is graded as + signifying involvement of a few scattered cells; ++, involving a moderate number of cells; +++, involving a large proportion of neurons. BZ indicates ischemic cell change affecting Purkinje cells at the boundary zone between the superior cerebellar artery and the posterior inferior cerebellar artery. Two baboons showed slight damage in other thalamic nuclei: 9 in the ventrolateral nucleus (+R>L) and 18 in the pulvinar (+). In baboon 16, the entorhinal cortex was symmetrically involved (++).

od, the heparinized animals, if not already unconscious, were given pentobarbitonal sodium intravenously.

Perfusion-fixation via an intra-aortic cannula began with a brief saline washout at a pressure of 120 to 150 mm Hg, followed by perfusion with 1½ to 2 liters of 40% formaldehyde, glacial acetic acid, and absolute methanol in ratios, 1:1:8, during a period of at least 20 minutes. The head was then removed and stored at 4C for 1½ to 2 hours, In a stereotaxic apparatus, the calvarium and dura were removed, and a pair (right and left) of stainless steel needles was inserted in the stereotaxic plane A 10, each at 15 to 18 mm from the midline. The hindbrain was removed by transection of the midbrain. The cerebral hemispheres were cut along the guide needles and then into slices 8 mm thick. The brain stem was sliced at right angles to its long axis. A slice was taken from each cerebellar hemisphere perpendicular to the folia of the dorsal surface.

Small blocks from the cerebrum and one cerebellar hemisphere were embedded in paraffin wax, and the remaining blocks were embedded in low viscosity nitrocellulose. Paraffin and celloidin sections were stained with cresyl fast violet, cresyl fast violet and Luxol fast blue, and with hematoxylin-eosin.

## Results

**Macroscopic Appearances of the Brains.**—The weight range of the brains was 114 to 166 gm. Evidence of brain swelling consisting only of downward herniation of the inferior cerebellar vermis was seen in four animals (moderate in baboon 7 and slight in baboons 9, 10, and 12). In the usual slices of the cerebrum,

Table 3.—Physiological Changes Early in the Seizure, Grouped According to Brain Damage

| | | Peak Arterial Pressure, (mm Hg) | | $Po_2$(1 to 3 min), (mm Hg) | | Highest Arterial Lactate, (mM) | Lowest Arterial pH | Duration pH Below 6.80, (min) | Highest Arterial Glucose, (mM) |
|---|---|---|---|---|---|---|---|---|---|
| | Baboon | Systolic | Diastolic | Arterial | Cerebral Venous | | | | |
| A | 11 | 195 | 165 | 61 | ... | 11.09 | <6.80 | 25 | 14.22 |
| | 17 | 220 | 170 | 101 | ... | 5.73 | 6.57 | 67 | 6.56 |
| | 24 | 260 | 200 | 66 | 44 | 15.89 | 6.745 | 13 | 14.39 |
| | Mean | **225** | **178** | 120 | 64 | | | | |
| | | | | **85** | **54** | **10.90** | **6.66** | **35** | **11.73** |
| B | 7 | 208 | 180 | 74 | ... | ... | <6.80 | 10 | ... |
| | 15 | 175 | 135 | 118 | 40 | 3.82 | 6.85 | 0 | 20.78 |
| | 16 | 225 | 170 | 107 | 69 | 9.89 | 6.485 | 77 | 18.94 |
| | 19 | 225 | 175 | 57 | 40 | 15.44 | 6.515 | 56 | 9.67 |
| | 23 | 200 | 165 | 104 | 39 | 12.67 | 6.86 | 0 | 7.28 |
| | 25 | 265 | 190 | 62 | 38 | 14.22 | 6.47 | 87 | 19.28 |
| | Mean | **216** | **169** | **87** | **45** | **11.21** | **6.64** | **38** | **15.19** |
| C | 10 | 248 | 198 | 94 | ... | ... | <6.80 | 17 | |
| | 18 | 255 | 175 | 68 | 54 | 12.78 | 6.705 | 18 | 13.11 |
| | 27 | 265 | 215 | 96 | 65 | 15.44 | 6.545 | 46 | 14.17 |
| | Mean | **256** | **196** | **86** | **60** | **14.11** | **6.625** | **27** | **13.65** |

Table 4.—Physiological Changes Late in the Seizure, Grouped According to Brain Damage

| | | Minutes During Which | | Blood Gases (Excluding First 30 min) | | | Last Seizure (30 min) | |
|---|---|---|---|---|---|---|---|---|
| | Baboon | Temperature Above 40 C | Arterial Glucose Below 1.6 mM | Lowest Arterial $Po_2$, (mm Hg) | Lowest Cerebral Venous $Po_2$, (mm Hg) | Highest Arterial $Pco_2$, (mm Hg) | Mean Arterial Pressure, (mm Hg) | Mean Arterial pH |
| A | 11 | 0 | 0 | 44 | ... | 57 | 110 | 7.09 |
| | 12 | 0 | ... | ... | ... | ... | ... | ... |
| | 17 | 30 | 0 | 61 | ... | 30 | 76 | 6.62 |
| | 20 | 40 | ... | ... | ... | ... | ... | ... |
| | 24 | 62 | 0 | 70 | 23 | 54 | 69 | 7.04 |
| | Mean | **26** | **0** | **58** | | **47** | **85** | **6.92** |
| B | 7 | 159 | ... | 49 | ... | 57 | 49 | 7.20 |
| | 9 | 13 | ... | ... | ... | ... | ... | ... |
| | 15 | 0 | ... | 73 | 31 | 40 | 77 | 6.97 |
| | 16 | 148 | 0 | 86 | 23 | 52 | 86 | 7.00 |
| | 19 | 105 | 106 | 67 | 31 | 46 | 63 | 7.00 |
| | 23 | 265 | 0 | 53 | 19 | 60 | 95 | 7.19 |
| | 25 | 0 | 0 | 81 | 18 | 59 | 80 | 7.10 |
| | Mean | **99** | **21** | **68** | **24** | **52** | **75** | **7.08** |
| C | 10 | 182 | ... | 53 | ... | 53 | 73 | 7.19 |
| | 18 | 183 | 131 | 78 | 31 | 53 | 56 | 7.21 |
| | 27 | 180 | 0 | 74 | 25 | 45 | 67 | 6.89 |
| | Mean | **182** | **66** | **68** | **28** | **50** | **65** | **7.10** |

cerebellum, and brain stem, appearances were normal in all the brains.

**Microscopic Appearances of the Brains.**—The observed neuronal alterations consisted solely of "ischemic cell change"[15] and occurred in ten of the brains; the other five were considered normal.

The earliest identifiable stage in the development of ischemic cell change was "microvacuolation."[16,17] The contour of the cell and its nucleus was normal. The cytoplasm that showed a normal or somewhat increased staining with cresyl fast violet contained numerous circular or oval apparently empty spaces. Electron microscope studies[16,18,19] have shown that these microvacuoles are swollen mitochondria within which there is variable disorganization of the cristae. This alteration was frequent in two animals (7 and 16), in which there was only a short interval between the end of seizure activity and perfusion-fixation (Table 1). Classical ischemic cell change (Fig 1) was seen in all ten animals. In baboons 7 and 16, the presence of some vacuoles in such cells represented the transitional stage from microvacuolation. Ischemic cell change with incrustations (Fig 2) was seen in seven animals (Table 1) and was the commonest alteration in three animals (9, 19, and 25) in which the interval between seizure termination and perfusion was 1 to 2½ hours.

In the neocortex, ischemic alterations were most frequent in the smaller pyramidal neurons of the third, fifth, and sixth layers (Fig 1, right) and around sulci rather than over the crests of gyri. While all areas of the cortex showed a diffuse involvement, there was an accentuation of damage in the occipital lobes of three animals (7, 10, and 27) and in the temporal lobes of one (19). Involvement of the two hemispheres was symmetrical except in baboon

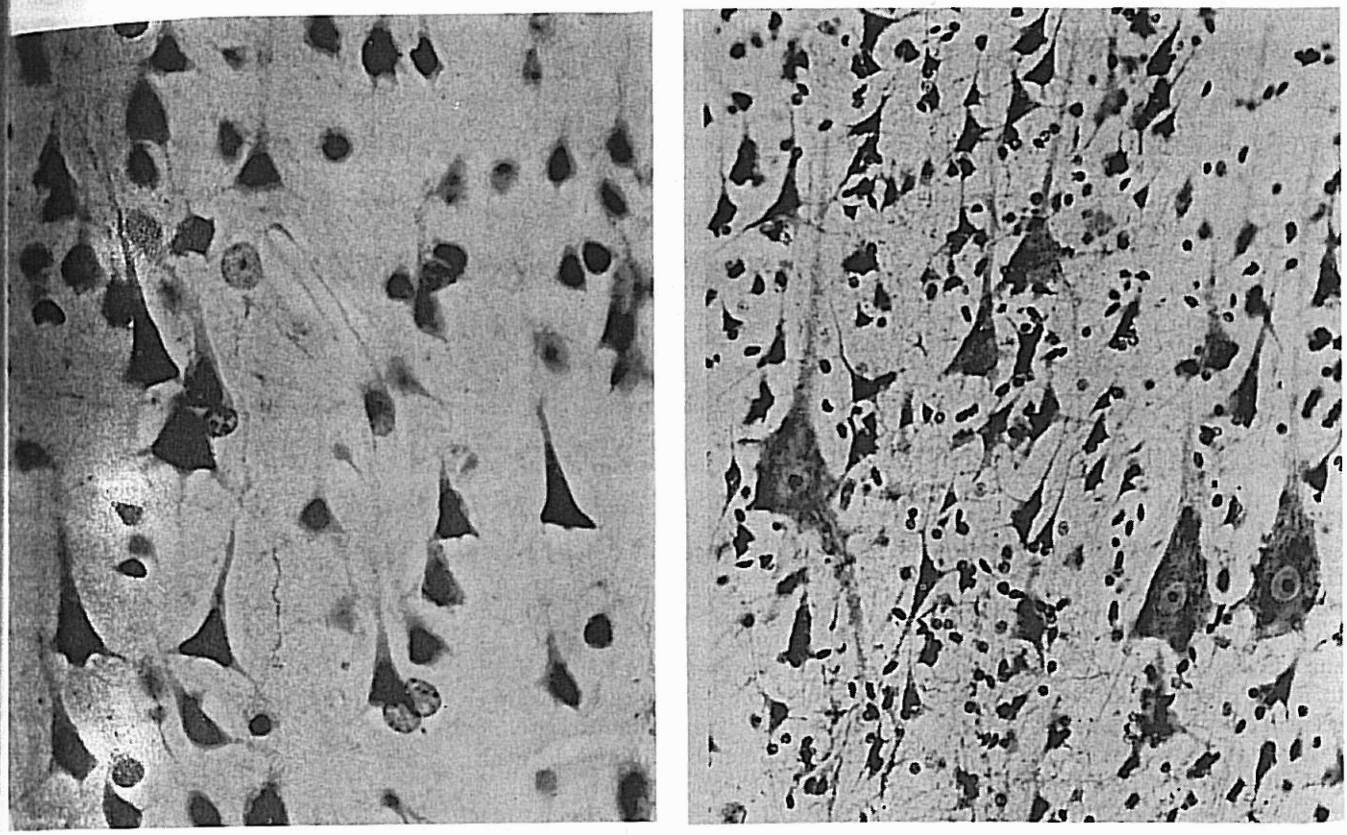


Fig 1.—Left, Occipital cortex showing ischemic cell change in neurons of third layer. Shrunken cells contain triangular hyperchromatic nucleus, fixed in celloidin (baboon 7) (cresyl fast violet and Luxol fast blue, original magnification ×800). Right, Precentral cortex showing ischemic cell change in smaller pyramidal neurons, fixed in celloidin (baboon 10) (cresyl fast violet and Luxol fast blue, original magnification ×310).

10 where alterations were more severe on the right. In the hippocampus, ischemic alterations were seen in the Sommer sector (Fig 3 and 4) in six animals (Table 2). The endfolium ($h_{3-5}$) was involved in eight animals, but damage was never more than moderate. The hippocampi were symmetrically involved except in three animals (10, 16, and 25) where the emphasis was on the right side.

Thalamic damage, seen in five animals, took the form of scattered ischemic neurons usually in the anterior and dorsomedial nuclei. In two severely damaged animals (10 and 18), the small neurons of the striatum were involved. In seven animals, there was mild or moderate involvement of the amygdaloid nuclei, particularly in their basolateral portions. The Purkinje (Fig 5) and basket cells of the cerebellum showed ischemic alterations in eight animals, and in six of these damage was restricted to, or concentrated along, the boundary zone between the territories of the superior and the posterior inferior cerebellar arteries.

In nine animals, the above changes were the only form of cerebral abnormality observed histologically, but one baboon (27) also showed foci of status spongiosus disseminated in the outer layers of the neocortex.

**Relationship of Brain Damage to Ictal Events (Tables 1 Through 4).**—All animals developing brain damage had experienced generalized seizure activity lasting 82 minutes or more. In the only nonbrain-damaged animal with generalized seizure activity lasting longer than this (baboon 11), the rectal temperature did not rise above 40 C. The significance of more focal seizure activity is less clear. Comparison of Tables 1 and 2 shows that two out of the three brains showing a relative excess of neocortical damage in the occipital region did not show persistence of seizure activity in this region. Only in baboon 27 was sustained occipital seizure activity followed by enhanced occipital neuronal alterations.

The preponderance of right-sided hippocampal damage may have been a result of the right lateral position that was maintained for more than two hours in each of the three animals with asymmetric damage. Nevertheless, six animals placed on the right side did not show such asymmetry.

In four animals, the interval between the end of generalized seizure activity and perfusion-fixation was only 10 to 15 minutes. Microvacuolation was prominent in two of these. Ischemic cell change with incrustations was prominent when one to three hours elapsed between the end of the seizure and perfusion-fixation. Our earlier study[17] on arterial hypotension and hypoglycemia in monkeys at 37 C indicates that microvacuolation is most prominent 15 to 60 minutes after the critical stress initiating ischemic cell change. Ischemic cell change with incrustations is

most prominent 90 to 240 minutes after the critical stress. Although the precise influence of body temperature on the rate of evolution of ischemic cell change is not known, the stages of ischemic cell change and the time relationships given in Table 1 are consistent with the stress initiating the ischemic cell change occurring in each case sometime between 30 minutes after seizure onset and the termination of generalized seizure activity.

Table 3 presents data related to the severity of the seizure in its initial phase. The motor activity and the autonomic discharge contribute to the immediate rise in blood pressure and the subsequent rise in arterial lactate and glucose concentration. There is no evidence that the severity of the early part of the seizure as assessed by any of these criteria correlates with the ultimate occurrence of brain damage.

Table 4 shows that the rectal temperature did not rise above 40C in two of the baboons that developed brain damage (both these animals, 15 and 25, failed to show cerebellar damage). Hyperpyrexia of this severity lasted for more than three hours in all three severely brain-damaged animals. A rectal temperature of 43C was recorded in baboons 18 and 23.

Prolonged severe hypoglycemia (arterial glucose concentration less than 1.6 millimolar = 26 mg/100 ml blood) was seen in two of the brain-damaged animals.

Late in the seizure, as in the initial phase, there was no evidence for a relation between ultimate brain damage and minimal recorded oxygen tensions in arterial and cerebral venous blood. Also hypercapnia and persistent acidosis occurred to a similar extent in nondamaged, mildly damaged, and severely damaged groups.

Mild arterial hypotension (mean arterial pressure below 75 mm Hg) was seen in five of the six animals developing boundary-zone lesions in the cerebellum (in the sixth animal, arterial pressure was not recorded). The time course of this arterial hypotension and its relationship to some other physiological variables in one of the most severely damaged animals (10) is illustrated in Fig 6; hypotension was only mild late in the seizure, but a transient, more severe hypotensive episode occurred earlier.

## Comment

This study has demonstrated in experimental primates that epileptic seizures lasting 82 to 299 minutes can lead to ischemic cell change in neurons of the cerebral cortex, hippocampus, cerebellum, and basal ganglia. Classically, ischemic cell change has been regarded as the consequence of a severe anoxic-ischemic stress.[15] However, it is not proof of an antecedent tissue hypoxia because it is also seen after prolonged and severe hypoglycemia with normal arterial oxygen tension.[10] It represents the histologically demonstrable sequence of changes between an irreversible disturbance of cellular metabolism and the death and disappearance of the neuron.

The distribution of ischemic neurons within the layers of the neocortex, the zones of the hippocampus, certain portions of the basal ganglia, and among certain cell types in the cerebellum corresponds to the pattern of selective vulnerability in the human brain found after status epilepticus.[2,5,7] Had the baboons been allowed to survive, the dead nerve cells would have been removed by phagocytes, and there would have been proliferation of glial and mesodermal elements. The end result where the three severely damaged animals of group C are concerned would have been moderate atrophy of the cortex of cerebrum and cerebellum, and sclerosis of the hippocampus.[3] The brain damage in the

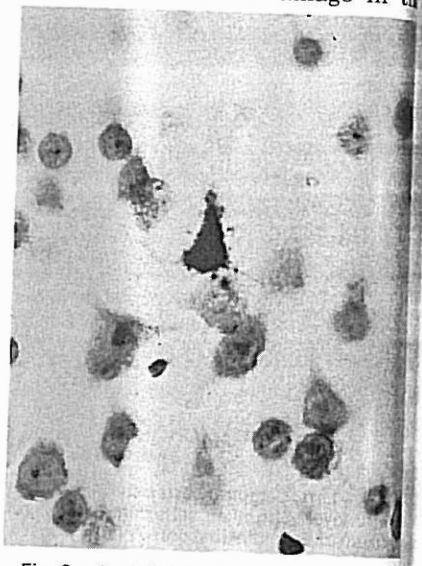


Fig 2.—Occipital cortex showing ischemic cell change with pericellular incrustation fixed in paraffin (baboon 9) (cresyl fast violet and Luxol fast blue, original magnification ×1130).

Fig 3.—Right hippocampus showing circumscribed ischemic damage in Sommer sector ($h_1$) fixed in paraffin (baboon 10) (cresyl fast violet and Luxol fast blue, original magnification ×30).

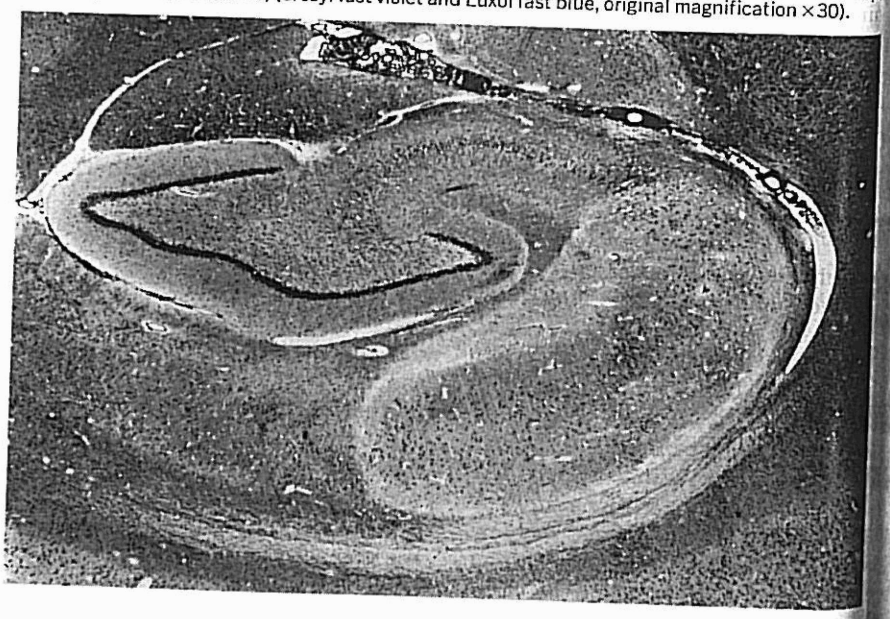


Fig 4.—Left hippocampus showing ischemic cell change in most neurons of Sommer sector ($h_1$), fixed in paraffin (baboon 18) (cresyl fast violet and Luxol fast blue, original magnification ×225).

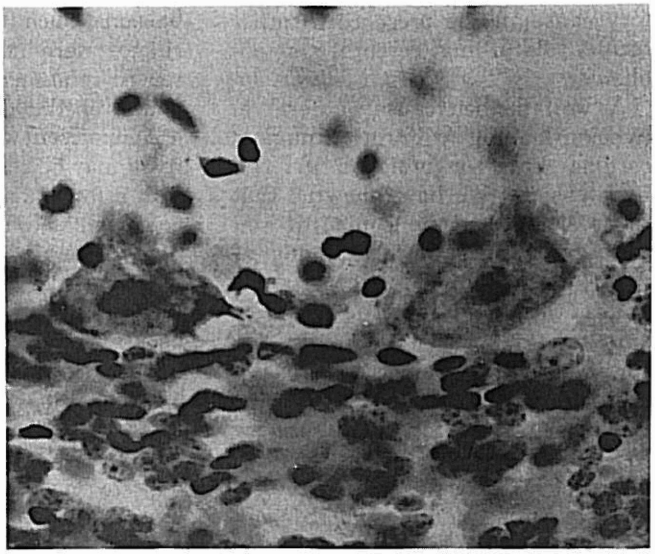
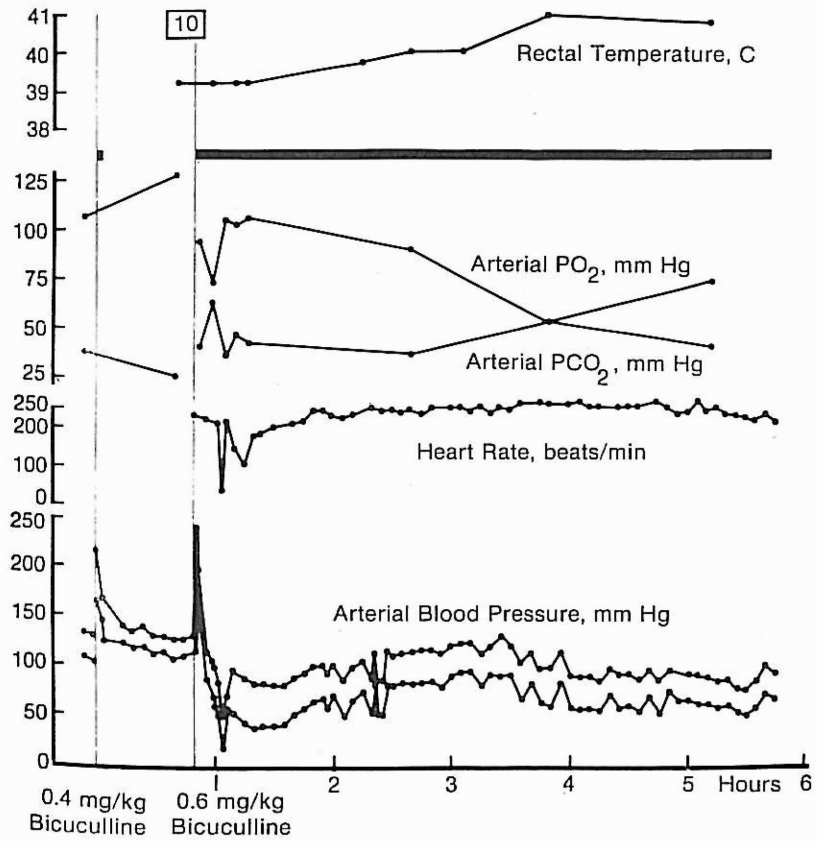


Fig 5.—Cerebellum showing ischemic (homogenizing) cell change in Purkinje cell at left, fixed in celloidin (baboon 10) (cresyl fast violet and Luxol fast blue, original magnification ×930).

Fig 6.—Physiological changes in baboon 10. The second injection of bicuculline (0.6 mg/kg) provoked a generalized seizure lasting 299 minutes. Transient hypotension and bradycardia was seen minutes after seizure onset.




animals of group B was generally less severe than that reported in patients dying after status epilepticus.[1-5] The possibility remains that damage of the grade seen in these seven animals may exist in the brains of patients who recover from status epilepticus but show more or less transient neurological signs.

Because some degree of systemic hypoxia is clinically evident in most patients in status epilepticus, and because the lesions, in their histological nature and regional distribution, are commonly indistinguishable from those seen after all forms of cerebral hypoxia,[7] it is commonly stated that such epileptic brain damage results from systemic or local hypoxia occurring during the seizure.[20-22] However, in our baboons, measurements during the seizures failed to show more than a mild reduction in arterial oxygen tension. Cerebral venous oxygen tensions were normal early in the seizure. Later they were normal or slightly reduced, but in only two cases did they ever fall into the range that has been shown in previous experimental studies of anoxia[23] to be critical for cerebral function (ie, < 19 mm Hg). It appears that the degree of cerebral hypoxia was not such as to be capable of causing brain damage on its own, but it might be a contribu-

tory cause in the presence of other factors disturbing cerebral metabolism.

A well defined cause of cerebral hypoxia leading to brain damage is cardiac arrest or profound arterial hypotension.[8] We have shown[24] that in order for uncomplicated arterial hypotension to produce ischemic cerebral lesions in experimental primates, the cerebral perfusion pressure has to fall below 25 mm Hg. Characteristically, neocortical and cerebellar damage after such a stress is concentrated in the boundary zones between the major arterial territories.[24] The localization of the lesions in the boundary zones in six of the eight animals with cerebellar damage suggests that a reduction of vascular perfusion pressure was a significant factor in the causation of cerebellar damage. Meldrum et al[25] observed that the combination of (1) hypoglycemia not severe enough to cause cerebral damage with (2) arterial hypotension, also not critical for producing cerebral damage, could lead to the appearance of neocortical boundary zone lesions. However, in the ten baboons, the neocortical damage was diffuse and not concentrated in the boundary zones suggesting that the mild arterial hypotension frequently observed was not an important factor in producing the neocortical lesions.

The rise in body temperature throughout the period of motor convulsive activity may contribute to the occurrence of brain damage in two ways. First, raising body temperature increases the cerebral metabolic rate so that any impairment of metabolism produced by hypoxia, oligemia, hypoglycemia, etc will be exacerbated. Second, hyperpyrexia with a temperature of 42C or above may itself cause an abnormal pattern of cerebral metabolism[26] or possibly lead to brain damage.[27-29] Neurological sequelae, particularly involving the cerebellum, have been reported after severe febrile illnesses or heat stroke.[30-32] Post mortem, neuronal loss in the cortex and cerebellum is commonly seen,[1,32] sometimes with hemorrhagic lesions involving the gray and white matter. In the baboons, such intracerebral hemorrhages were not seen, but the observed relationship between pyrexia and cerebellar damage suggests that a comparison with human hyperpyrexia may be relevant.

In a few baboons, a secondary hypoglycemia occurred after the initial hyperglycemia. In one case this approached and in another exceeded, the duration and severity that has been shown to be capable of producing cerebral lesions in the Rhesus monkey.[10,25]

It is evident that various factors so far considered (hypoxia, hypotension, hyperpyrexia, and hypoglycemia) all operate late in the seizure (arterial hypoxia may be most marked in the first few minutes, but at that time it is associated with a rise in cerebral venous oxygen tension). The analysis of the data of Table 1 in the light of our previous experimental determination of the time course of ischemic cell change in the primate[17] indicates that the critical metabolic stresses initiating the sequence of "ischemic" cellular changes occur predominantly before the end of the seizure but later than its initial phase. This is consistent with the finding that measurements indicative of the severity of the initial part of the seizure showed no relation to the occurrence or severity of brain damage, whereas those relating to the period beginning 30 minutes after seizure onset did.

Correlations observed between the severity of hyperpyrexia, hypotension, and hypoglycemia, with the occurrence and severity of regional brain damage, do not constitute proof of a causal connection, because the experimental design did not allow isolation of the factors, and each one is secondary to the severity and duration of the cerebral epileptic discharges. Previous experimental studies of arterial hypotension,[24] hypoglycemia,[10,25] and hyperpyrexia[28] allow us to estimate the probable contribution of these factors, had they been occurring with a normally functioning brain, but there are no studies that permit us to assess the cerebral effects of the intrinsic seizure activity, or how this will interact with the systemic stresses. Experimental studies of seizures in curarized, artificially ventilated animals can provide some indication of the effects of those systemic changes that are secondary to the motor activity. Biochemical studies on brief seizures in rodents[33] show that after very transient changes in cerebral energy balance, a steady state in energy metabolism is rapidly reached while the seizure continues. Biochemical changes in prolonged seizures have not been reported. After prolonged seizures induced in cats by pentylenetetrazole (Metrazol), penicillin or electroshock,[34] all Betz cells removed from the cortex failed to show respiratory activity. The relationship of this observation to metabolic changes during the seizure or to the selective pattern of vulnerability in epilepsy is not known. A more or less total destruction of the neocortex is not reported in the human neuropathological literature, nor was it seen here, although its occurrence after cardiac arrest or related anoxic-ischemic stresses (giving rise to the so-called "apallic syndrome"[35,36]) is well known. This is presumably because, as soon as systemic metabolic factors are severe enough to reduce the energy metabolism of the brain to a critical level, the cerebral seizure activity is thereby stopped, permitting some recovery of the systemic state.

Many authors[37-39] have suggested that local vascular factors, arterial spasms or obstruction, or venous congestion, are important in the genesis of the hippocampal lesions seen in epileptics, and some experimental studies[40] have supported this concept. Asymmetric lesions in our baboons, like those in McLardy's hyperpyrexial guinea pigs,[40] tended to occur on the side the animal was lying on, suggesting that some element of vascular congestion or obstruction may play a contributory role.

The prevention of neurological sequelae must be a primary concern in the treatment of patients in prolonged seizures. Such sequelae may arise from the cause of the seizures (eg, viral encephalitis or cerebral

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injury) but, insofar as they are a consequence of the seizure activity, they may be largely preventable. Our baboons were young and healthy with a very efficient respiratory system, which perhaps explains the lack of significant systemic hypoxia. In other physiological respects, there is probably a close parallel between them and patients in status epilepticus. Prevention or arrest of the seizure itself must be the first therapeutic objective, but our experiments suggest that prompt recognition and treatment of hyperpyrexia, arterial hypotension, and secondary hypoglycemia will be of value in preventing brain damage.

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