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Later Changes in Brain Death. Signs of Partial Recirculation*

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Summary. The varying cell picture of the brain in brain death is impressive. Some authors have interpreted this cell picture as a result of intravital autolysis and others as necrosis, at which the maturation time obviously plays an important part.

The following time-dependent cerebral changes were established on the basis of an evaluation of 190 brain death cases: (1) neuronal necroses that arise at different rates within the cerebral cortex and the lower brain stem; (2) a hemorrhagic-meningoencephalitic reaction that occurs exclusively at least 4 days after brain death or hemorrhages alone after intervals of at least 48 h; and (3) a washed-out tissue picture. The alterations in the spinal border zone of the total infarction, like in the brain itself, increase rapidly after 48 h.

The regular onset of inflammatory alterations after long brain death intervals can only be explained by partial recirculation due to a decline of the high intracranial pressure. The hemorrhages and increasing necroses in some cases with longer intervals therefore are likewise evidence of a not entirely complete cerebral ischemia in spite of an angiographically demonstrable circulatory arrest.

Key words: Brain death – Ischemic neuronal alterations – Brain stem – Meningoencephalitic reaction – Reperfusion

Introduction

An aseptic-autolytic state of the brain with predominantly nonspecific cell alterations exists in brain death caused by intracranial circulatory arrest resulting from maximally increased intracranial pressure (Dolman and Forstner 1963; Girard et al. 1963; Kramer 1963, 1966; Mantz et al. 1965; Schneider et al. 1967, 1969). However, in some cases alterations resembling diffuse cerebral necrosis appear that cannot be caused by primary brain damage prior to the onset of complete cerebral ischemia. Recently, these alterations have often been considered the true neuropathologic characteristic feature; a longer maturation period, however, is required for their development (Ingvar 1971; Nedey et al. 1974; Walker et al. 1975; Korein 1978; Lyudkovskaya and Popova 1978; Pearson et al. 1977, 1978). Likewise, in our cases ischemic neuronal alterations proved to be time-dependent. However, the same could be found, among others, relative to hemorrhagic-meningoencephalitic reactions, which indicate a certain degree of reperfusion.

Material and Methods

The evaluated autopsy material consisted of 190 cases (age range: 8 months to 75 years) with a clinically established diagnosis of brain death (confirmed by additional examinations, such as EEG and/or angiography) or with a tentative clinical diagnosis confirmed by postmortal demonstration of demarcation in the border zones of the ischemic cerebral total infarction (i.e., optic nerve, anterior pituitary lobe, upper cervical region of the spinal cord). The typical spinal dislocation of cerebellar particles was present in 45% of our 117 cases with spinal cord section.

The basic initial cerebral lesions leading to brain death were hemorrhage in 60% (by ruptured aneurysm, traumatic, hypertonic and other), diffuse ischemic or hypoxic damage in 10%, hemisphere malacia in 9%, tumor in 10%, encephalitis or meningitis in 7%, and various others in 4%. The signs of brain death used correspond to the internationally fixed criteria, recently reformulated by an author team from the Deutsche Bundesärztekammer (Kuhlendahl et al. 1982).

Neither the time at which artificial respiration was begun nor the time at which brain death was conclusively established can be correlated with the duration of the total cerebral ischemia, since the establishment of brain death depends on organizational and technical factors as well as safety periods and, more or less, marks the terminal point of intensive care. In the retrospective evaluation, the *probable* time of the total and irreversible loss of the cerebral functions was

* Dedicated to Professor Dr. R. A. Frowein on the occasion of his 60th birthday

determined as exactly as possible on the basis of medical records[1] and discussion with the clinicians, considering all possible limiting factors. At this, the probable time point means the time at which the clinical syndrome was complete, but EEG or angiography were still lacking. The duration of brain death until systemic circulatory arrest varied accordingly from 1 h to 13 days.

Specimens taken from several areas of the brain, and not just from the initial lesions, were examined histologically. To see the general state of the neuronal cells within the remaining brain, sections taken from the parietal region contralateral to the primary process and the medulla oblongata at the level of the inferior olive were evaluated. In 75% of the cases, at least one of the demarcation zones was examined. Standard stains used were HE and luxol fast blue/nuclear fast red. The naphthol-AS-D-chloroacetate esterase reaction was used in some cases for better granulocyte demonstration.

Results

Neuronal Ischemic Changes

Neuronal ischemic changes were only evaluated when the neuronal cytoplasm showed a marked reddish change in color on HE staining. Absence of the Nissl substance alone, often with granular cytoplasmic structure as well as cell and nucleus shrinkage, occurs independently and was interpreted as nonspecific alteration.

Since neuronal ischemic alterations can be influenced decisively by the initial brain lesion, cases with clinically established, primarily severe hypoxidotic brain damage were excluded from this evaluation, particularly since an association with longer brain death intervals was established. Cases with necrotizing encephalitis were also eliminated. A temporal grouping of the remaining 169 cases was chosen which ensured groups of roughly the same size and with easy-to-survey time markers.

Cerebral Cortex. The findings differed considerably from case to case. Ischemic alterations of the nerve cells were found at all time intervals examined. In most cases, however, less than nearly 5% of the total neuronal population was involved. Even the rare cases with almost total neuronal loss appeared at very different intervals. In addition, it was striking that, as compared to the usual picture of necrotic cells in local infarction, ganglion cells with the characteristic color change often did not show considerable cell and nucleus shrinkage. On the other hand, only nonspecific alterations of the nerve cell population were present in most cases which, however, also included high-grade chromatolysis. This absence of necrotic nerve cell alterations was ascerteinable with a certain degree of regularity for as long as 53 h after the onset of brain death and, in one case, even after an interval of 3.5 days. A nearly unaltered cell picture with preserved Nissl substance and normal nuclear and nucleolar structure was observed in isolated neurons for intervals of up to 6 days.

Due to the widely varied alterations, correlation with the duration of total cerebral ischemia can only be obtained by quantification of the findings. In this way, the incidence of the cases with at least isolated ischemically altered nerve cells (approximately 1%) and the incidence of the cases with almost total loss (appoximately 90%) were determined (Table 1, Fig. 1). The curve for the cases with almost total loss varies only slightly from that for the cases with at least 50% cell loss. Ischemic neuronal alterations first increase markedly after 48 h, but even then only 40% of the cases show a total loss.

Lower Brain Stem. Partially, the amount of ischemic neuronal alterations at the level of the inferior olive was impressive because of the glaring contrast to the low number or total absence of the alterations in the cerebral cortex and other regions of the brain. These alterations decreased rostral (i.e., pons, cerebellum) as well as caudal (lower level of the medulla, first cervical segment) and were not related to pontine hemorrhages or primary infratentorial processes (not included in this study). In contrast to the cortex, these alterations (Table 1, Fig. 2) increase continually and rapidly in relation to the duration of the interval; a total loss, however, is present after 48 h in only 62% of the cases.

The total case incidence of isolated as well as total cell loss in the medulla is significantly higher than in the cortex (χ^2 test, $P < 0.001$).

Hemorrhagic-meningoencephalitic Reactions

Summing up the clinical course and the pathoanatomic findings the inflammatory alterations present in some cases could not be referred to the primary disease. Moreover, the pattern of the local findings itself was different from that of most inflammations. Mainly, a partly fresh emigration of granulocytes was found throughout the pial and superficial arteries and arterioles (Fig. 3a–c). The vessels themselves, moreover, showed some necrotic alterations; the tunica muscularis of other vessels was still distinct; some contained rim-like thrombi (Fig. 4a). The walls of some pial veins were also infiltrated by granulocytes, although this finding did not predominate. The granulocytes spread into the subarachnoid space and peri-

1 Medical records were generously provided by Prof. R. A. Frowein (Director of the Dept. of Neurosurgery), Prof. E. Gladtke (Director of the Dept. of Pediatrics), Prof. R. Gross (Director of the Medical Dept.), Prof. H. Pichlmaier (Director of the Dept. of Surgery), and Prof. A. Stammler (Director of the Dept. of Neurology, University of Cologne)

Interval	Cerebral cortex		Medulla oblongata	
	≥ 1%	> 90%	≥ 1%	> 90%
1–6 h	8/29 = 28%	0/29 = 0%	8/24 = 33%	2/24 = 8%
7–12 h	12/41 = 29%	1/41 = 2%	18/38 = 47%	4/38 = 11%
13–24 h	19/52 = 37%	0/52 = 0%	27/44 = 61%	8/44 = 18%
25–48 h	15/32 = 47%	1/32 = 3%	26/26 = 100%	9/26 = 35%
49 h–6 days	12/15 = 80%	6/15 = 40%	13/13 = 100%	8/13 = 62%
All cases	66/169 = 39%	8/169 = 5%	92/145 = 63%	31/145 = 21%

Table 1. Frequency of cases with neuronal cell loss (≥ 1% or > 90% of the neurons, respectively) in groups with different time intervals of the brain death syndrome, in cerebral cortex and medulla oblongata

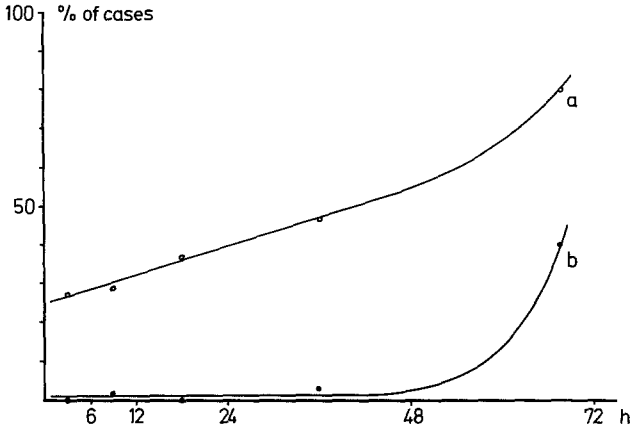

Fig. 1. Frequency of cases with about ≥ 1% (*a*) or more than 90% (*b*) neuronal cell necroses within the *cerebral cortex* in the time course of brain death, divided into groups corresponding to the time scale in Table 1

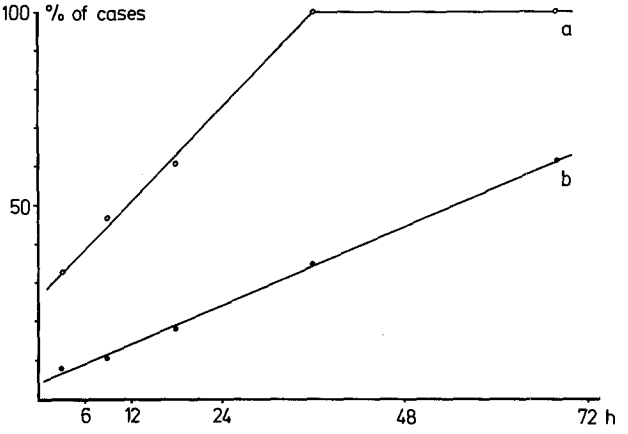

Fig. 2. Frequency of cases with about ≥ 1% (*a*) or more than 90% (*b*) neuronal cell necroses within the *medulla oblongata* in the time course of brain death, divided into groups corresponding to the time scale in Table 1

arteriolarly into the parenchyma or infiltrated diffusely the outer cerebral structures from the surface (Fig. 3a, b). The alterations were found in extensive parts, but generally not in all regions. Frequently, they were accompanied by smaller, irregular limited hemorrhages and sporadic vascular ruptures (Fig. 4b). Hemorrhages and thrombi were also found outside the inflammatory areas.

The alterations were clearly related to particularly long brain death intervals. They were found only after the brain had been dead for at least 4 days in all but one case (ventricular puncture-induced decompression of acute obstructive hydrocephalus caused by colloid cyst in the third ventricle during intracranial circulatory arrest; this case was excluded). In the total material, they were observed in six of eight cases with intervals of 4–13 days. This picture occurred in two cases only in the lower brain stem and cerebellum after 4 days and also supratentorially in the remaining four cases after 4–13 days.

No intracranial interventions had been undertaken in any of these cases. A review of the medical records revealed that temporary systolic values of 200 mm Hg or higher were recorded at hourly blood pressure measurements during the brain death period in only two of the six cases. By comparison, similar systolic values were recorded in three of 20 inflammation-free cases with intervals exceeding 48 h. The difference in the incidence is not statistically significant (exact test of Fisher, $P > 0.20$). No primarily hypoxidotic tissue damage with the possibility of symptomatic inflammation was detected in two of the six cases with inflammatory alterations (tumor and hypertonic mass hemorrhage, respectively).

Marginal hemorrhages in the cortex and lower brain stem (Fig. 5), however, were also found in cases without signs of inflammation; for the first time after 48 h. On the whole, there was a tendency toward a time-related, but not statistically significant, increase of hemorrhages (Table 2; exact test of Fisher, $P > 0.20$).

Washed-out Cell Picture

A characteristic washed-out tissue picture with shadowed neuronal cell nuclei and karyorrhectic glial cells

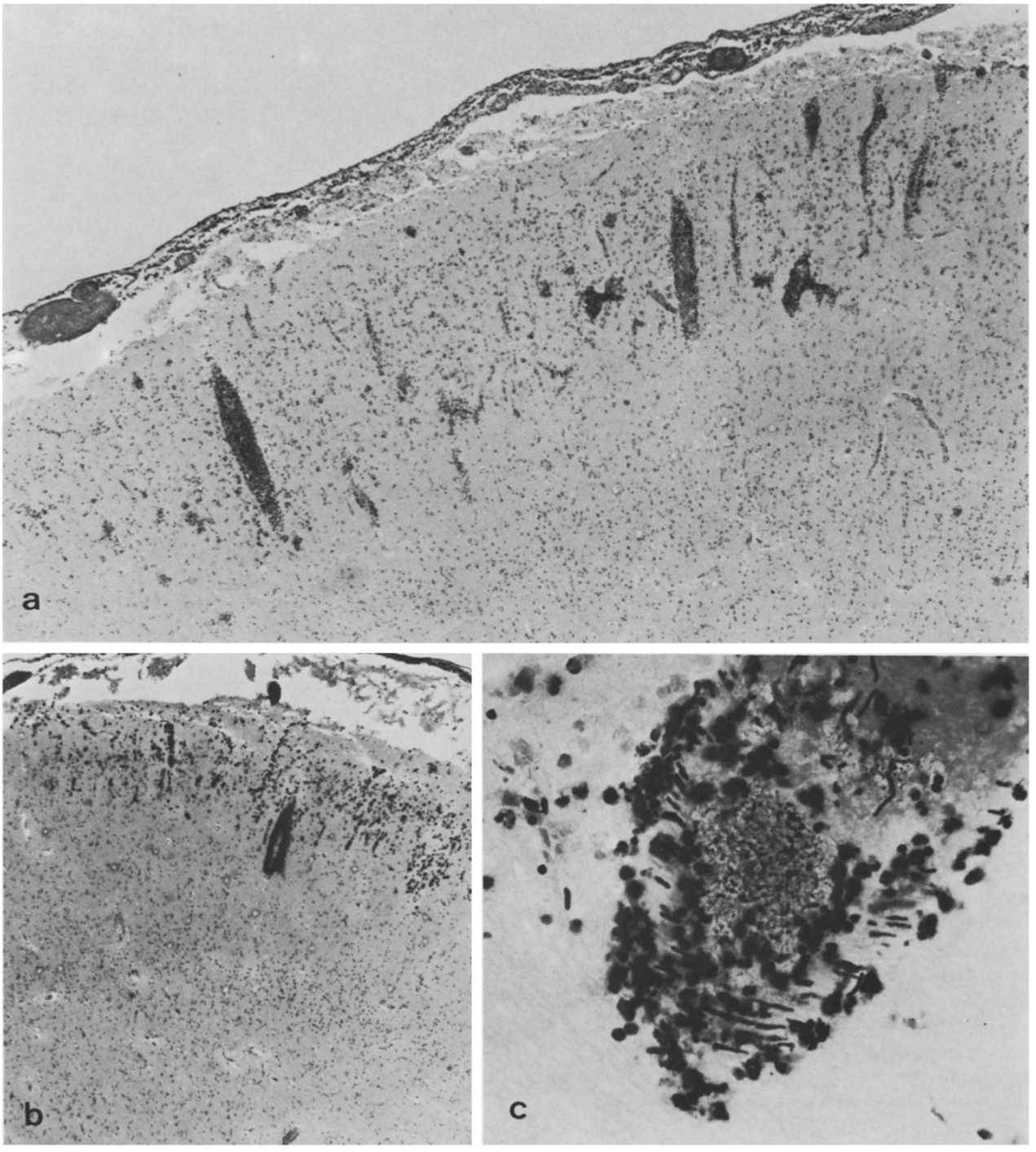

Fig. 3. a, b Meningoencephalitic reaction with meningial, periarteriolar and diffuse cortical granulocytic infiltration in a case of 7 days duration of brain death; **a** HE, × 50; **b** chloroacetate esterase, × 35. **c** Granulocyte emigration from an intraparenchymatous artery of the pons, 4 days of brain death syndrome; chloroacetate esterase, × 330

was found in the cortex and/or lower brain stem of some cases. The alterations sometimes extended perivascularly and sometimes into the superficial tissue layers.

This alteration, which was found in 11 cases, first appeared after an interval of 24 h. It was combined with the inflammatory picture in only one case and with hemorrhages in four cases. Its incidence rose signifi-

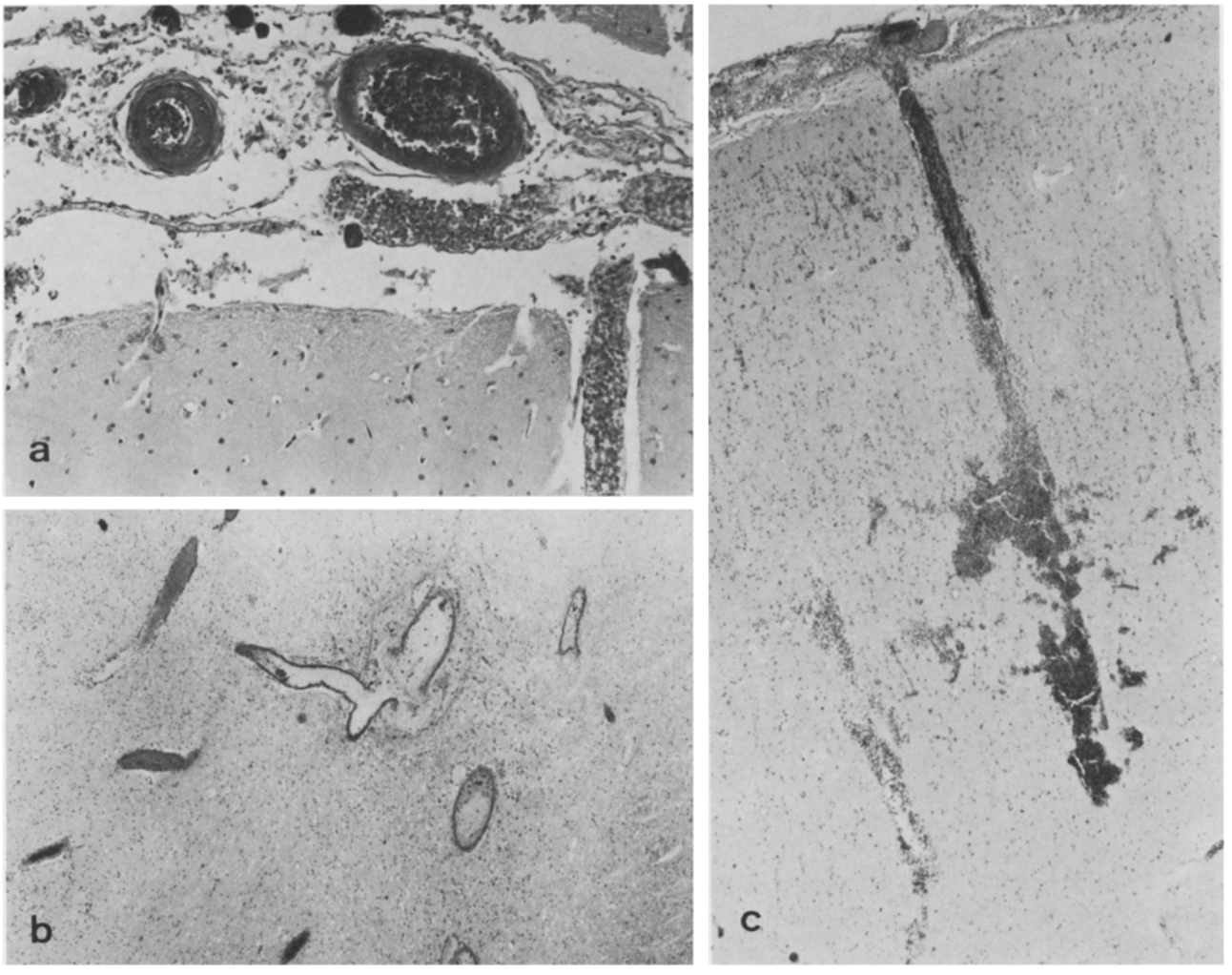

Fig. 4. a Rim-like thrombosis of pial arteries, 4 days of brain death; HE, ×115. **b** Ruptured small artery of the denate region; HE, ×30. **c** Irregular cortical bleeding in the course of a granulocytically infiltrated arteriole; HE, ×40. In **b** and **c** 7 days of brain death

Table 2. Frequency of cases with marginal bleedings, partially associated with meningoencephalitic changes

Time interval	Frequency
48–72 h	3/17 = 18%
> 72 h	6/12 = 50%

Table 3. Frequency of cases with the washed-out picture of the nuclei

Time interval	Frequency
24–47 h	3/39 = 8%
> 48 h	8/29 = 28%

cantly as the time interval increased (Table 3, χ^2 test, $P < 0.05$).

Changes in Spinal and Optic Nerve Border Zones

Myelin paling in both the spinal and optic nerve border zones was already detectable after 8 h. Only some cases, however, showed signs of hematogenous and vascular reactions. These reactions increased very gradually and were found less often in the optic nerve. Granulocyte diapedesis, therefore, was first observed after 12 h; thereafter, it was found in the cervical region of the spinal cord in 24% of the cases and in the optic nerve in 13%. The incidence was time-dependent in the spinal border zone, but not in the optic nerve. Diapedetic hemorrhages were similar. The number of microthrombi and macrophages increased markedly after 48 h, but they appeared only in the lower marginal zone.

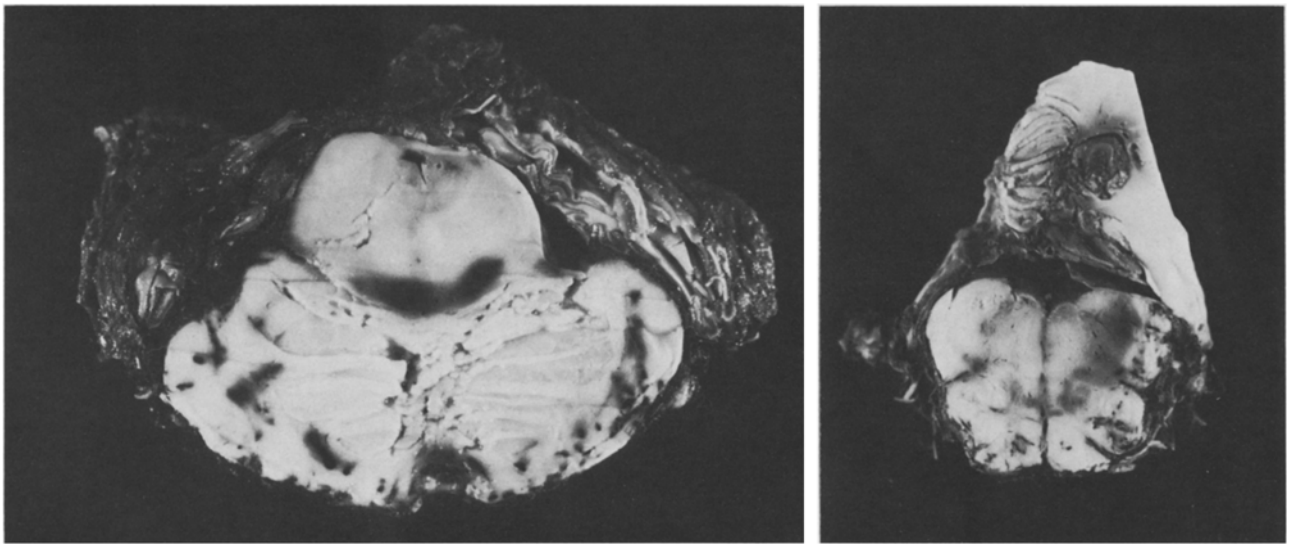

Fig. 5. A 66-year-old man with hypertonic mass bleeding in the right cerebral hemisphere; brain death period 3 days, 16 h. Multiple marginal hemorrhages in pons and medulla

The border zones were only observed twice in the cases with hemorrhagic-meningoencephalitic alterations. Since reactions were markedly lower in the optic nerve than in the spinal cord, only the cervical region of the spinal cord is described here. Subpial and partly diffuse granulocyte and macrophage infiltration of the necrotic region, corresponding vasculitis of the pial arteries and veins, rim-like thrombi in pial arteries with beginning endothelialization, hemorrhages, and fibrin-rich exudation were present, i.e., alterations corresponding to the cerebral changes.

Discussion

In most of the cases studied cerebral circulatory arrest was directly established by angiography and/or histopathologic examination of the border zones of the cerebral total infarction, in the others this situation was ensured clinically supplemented by proof of an isoelectric EEG. In all cases, therefore, complete cerebral ischemia can be presupposed. Since the formation of necrosis generally implies vital surroundings with the possibility of diffusion from intact circulation (and enough time for manifestation), whereas the maximally increased intracranial pressure in this state prevents any kind of streaming into the cerebral organ infarction, the question arises for the reason of the observed cerebral neuronal necroses.

Basically, ischemic nerve cell alterations may develop in three different phases of the disease in brain death cases. (1) Alterations induced by the initial lesion; they were essentially excluded by eliminating diffuse, primarily necrotizing injuries. (2) Development during a protracted herniation phase; an even distribution over all brain death intervals can be expected, but our findings do not generally confirm this. This interpretation, however, is applicable in cases with almost total loss in the cortex for intervals of up to 48 h, i.e., 1 % of the cases in this limited period (or 6 % with more than 50 % cell loss). The incidence of the most minor nerve cell damage pior to the onset of intracranial circulatory arrest can be estimated by the group with the shortest brain death intervals. This amounts to about one third of the cases.

All other necrotic nerve cell alterations must (3) be manifest during the phase of cerebral circulatory arrest, since they increase in relation to the duration of the brain death syndrome. However, their extraordinary delayed increase in the cerebral cortex is striking, compared to the manifestation time of 4–5 h in local infarctions (as established by other authors and confirmed by us), and also the fact that only a part of the cases with unquestionable cell death are involved, even after intervals of more than 48 h. Walker (1981), in particular, referred several times to this variability of the findings, a variability which seems widely unrelated to the time interval. Moreover, the different development of these alterations in the cerebral cortex and the medulla oblongata is characteristic. Only a few authors have reported this sort of discrepancy (Mohandas and Chou 1971; Nedey et al. 1974).

Is it possible that these alterations could be explained by an intravital autolytic process in which histolysis is produced exclusively by inherent enzymes of the local cells? During brain death, however, the

temperature of the brain is almost the same as that in the rest of the body (Quaknine et al. 1973); the process, therefore, can proceed more rapidly than postmortal processes.

The fact that signs of shrinkage are often absent in the cytoplasm and nucleus of these ganglion cells, signs which are otherwise a typical characteristic of neuronal necrosis, could indicate an analogy with pictures similar to necrosis in advanced autolysis. Using morphologic as well as enzyme histochemical methods, Oehmichen and Gencic (1980) observed that autolytic neuronal alterations appear somewhat earlier in the lower brain stem than in the cerebral cortex. These phenomena, however, are early alterations. The experimental findings on postmortal ganglion cell alterations at 37°C reported by Lindenberg (1956, 1963) compare better with the neuronal picture in brain death described in the present study (see also Pearson et al. 1978). The nerve cells showed no signs of morphologic alterations up to 24 h of postmortal incubation after a longer period of preceding hypoxia; stainability first declined after 36–48 h, but the picture of ischemic cell alterations was not yet present. Lindenberg (1971), however, compared neuronal alterations in brain death with those of "morphotropic necrobiosis", which developed much more rapidly after a short period of hypoxia in his experiments under the same postmortal conditions. These alterations correspond to a large extent to ischemic cell alterations, but the distribution pattern is reversed. In contrast to the findings in brain death, they appear later in the lower brain stem than in the cerebral cortex and do not explain the long absence of the alterations in the cortex.

As an autolytic phenomenon may be interpreted, at best, the increase in the incidence of nerve cell alterations in the cortex after more than 48 h. Nevertheless, the reason for the absence of the alterations in other cases from the group exposed to the same conditions remains unclear. The higher incidence and earlier appearance of neuronal necroses in the lower brain stem, and then in strictly limited localization, on the other hand, certainly cannot be related to the same autolytic process. Here as well, only some cases show a subtotal loss after more than 48 h. Rather, these findings can only be interpreted as a vital reaction with individually and locally varying intensity.

In the knowledge of general pathology, coagulation necrosis – and this is the neuronal ischemic cell change – in the center of a large infarction can develop much later than in the periphery because of the hindrance of fluid permeation. This was also confirmed in extensive cerebral infarctions, where the manifestation time in central regions was delayed for as long as 36 h (Schröder 1983). Similar time intervals therefore can be expected under conditions of complete intracerebral circulatory arrest with damage of the whole organ. Apparently the cerebral cortex behaves similarly; the medulla oblongata, however, does not, probably because of local diffusion from the vessels into the infarction site. This explanation, however, is plausible only if ischemia in the lower brain stem is not entirely complete or is not entirely complete for only a short period of time.

Clinical-radiologic observations indicate that circulatory arrest at the onset of brain death is often delayed in the posterior cranial fossa (see, e.g., Heiskanen 1964). This finding is morphologically confirmed by comparing the beginning of demarcation in the border zones of extracranial blood supply in the optic nerves and the upper cervical cord (Schröder 1978). The differing appearance of vascular and hematogenous reactions in both marginal areas further indicates that tissue pressure differs in both locations later as well, for higher levels better prevent these reactions than lower. In addition, an individually different pressure gradient at the craniospinal junction is possible because of the partial absence of spinal dislocation of cerebellar tissue (absent in our material even after intervals of $\geqq 48$ h in four of 20 cases = 20 %). In spite of angiographically demonstrated cessation of cerebral circulation, the supratentorial pressure-systemic blood pressure ratio can also vary considerably, as measurements by de Rougemont et al. (1974) have shown. The possibility of minimal leakage, which naturally is not sufficient to preserve the vitality of any individual cell, therefore cannot be excluded in the posterior cranial fossa.

Inflammatory alterations also begin in the posterior cranial fossa. They most certainly presume partial recirculation. Fuchs and Schneider (1975, 1978) reported the same findings in brain death after an artificial increase of blood pressure; reperfusion was even angiographically demonstrable in some cases. Comparative pressure measurements under the same conditions by Langfitt and Kassel (1966), however, showed that an increase of blood pressure is accompanied by a parallel rise in intracranial pressure, thus eliminating the possibility of perfusion pressure production. Our cases with hypertonic periods during the brain death state also did not correlate with the observed inflammatory changes. Reperfusion due to hypertonia therefore seems to be possible only in some cases, probably in those cases, as cited above, with a lower intracranial pressure-blood pressure ratio. In such cases, circulatory arrest may be surmounted.

The hemorrhagic-inflammatory phenomena in our material are clearly related to very long brain death intervals (at least 4 days). Regular reperfusion after this time can only be due to a diminution of the high intracranial pressure, first in the posterior cranial fossa and then also in the supratentorial region. Radiologists have put forth similar hypotheses based on angiographic observations, but no systematic studies are available (Penin and Käufer 1969; Lehmann 1975). As an observation reported by Parisi et al. (1982) after a 2-month interval impressively shows, at last pronounced resorptive reactions apparently can develop in brain death syndrome of extremely long duration. Here massive amounts of macrophages, recanalized arteries, veins, and sinus as well as revascularization of outer layers are found with an areactive necrotic decomposition of the central parts of the brain.

Since, however, the decrease of intracranial pressure is certainly not sudden, it is reasonable to assume that the inflammatory phenomena are not the first signs

of a vital reaction to tissue death. Subsequently, superficial hemorrhages appear in some cases as early as after 48 h. Neuronal cell alterations also increase markedly in the cerebral cortex at this time. They, therefore, are certainly not an autolytic phenomenon, but rather true necrosis in the general pathology sense. The "maturation" of the neuropathologic findings assumed by the authors cited above consequently tends to indicate the end of complete ischemia and therefore designates a new situation. The frequent absence of neuronal necroses in brain death cases, on the other hand, is probably best interpreted as a sign of the completeness of ischemia, an interpretation which is also in agreement with the experiments of Matakas et al. (1973) that extend up to 48 h. The occasional appearance of a washed-out tissue structure, however, is more difficult to explain. Nevertheless, the increasing incidence with time and the frequent vascular relationship tends to indicate a recirculation phenomenon that may well be transitory.

The reactive alterations that initially develop gradually in the spinal border zone of the total infarction (Schneider et al. 1969) also increase markedly after 48 h. After 4 days, signs of recirculation corresponding to the cerebral phenomena are present, but they are more pronounced.

A gradual reperfusion of the initially total ischemic brain due to diminution of the high intracranial pressure explains several impressive morphological phenomena associated with brain death. The flow velocity, however, must be so low after 2–4 days and probably so locally, and if possible temporally limited, that the vessel content undergoes the regularly observed autolytic alterations, i.e., it must be a very slow creeping flow. Subsequently, cellular and thrombotic reactions preceding tissue removal predominate after intervals of more than 4 days. Complete intracranial ischemia in brain death is therefore a transitory phase.

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