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THE PATHOGENESIS OF SECONDARY BRAINSTEM HEMORRHAGES AS STUDIED IN AN EXPERIMENTAL MODEL

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Secondary brainstem hemorrhages are common and ostensibly the immediate cause of death in many patients with supratentorial expanding lesions. Owing largely to the difficulty in studying hemodynamic phenomena after death, however, their pathogenesis remains obscure. Not only are the sequential changes which precede these hemorrhages unknown, but their primary site of bleeding has yet to be established. Some investigators have maintained that such hemorrhages are due to arterial rupture,[1-11] while others have insisted that they result from disruption of veins,[12-19] arteries and veins,[20-22] or arterioles, capillaries, and veins.[23]

In order to obtain more precise information regarding this phenomenon an experimental model was designed wherein it would be possible to reproduce these lesions under controlled conditions.

MATERIAL AND METHODS

Over 100 mongrel dogs (11 to 29 kg) were anesthetized with pentobarbitol sodium (60 mg per kg body weight). A single 2 cm trephine hole was made at different sites in the calvaria. A Foley catheter with a balloon was inserted into the subdural or epidural space. The balloons were inflated in most experiments with water, and occasionally with a radio-opaque solution. The location of the latter inflated bags was checked radiologically. Balloons were expanded by continuous inflation or in gradual increments. Some of the latter inflated bags were completely deflated between each progressively larger increment. Balloons were inflated with a perfusion-withdrawal pump to varied sizes (0 to 25 ml), and at variable rates (0.0017 ml per minute to

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58.2 ml per minute). The volume and situation of the intracranial balloon was checked at the end of each experiment. The blood pressure, heart and respiratory rates were monitored continuously during the experiments. Pupillary size and reaction to light was recorded at regular intervals during balloon inflation. In some animals the carotid or vertebral artery blood flow was determined using an electromagnetic flow meter.

Brains were removed from the cranial cavity immediately after death without perfusion and fixed in 10 per cent formaldehyde for 2 days. All brains were examined grossly and microscopically. The brainstem of each animal was embedded in paraffin after being sectioned coronally through its entirety at a thickness of 0.5 cm. All paraffin blocks were sectioned at a thickness of 10 μ and stained with hematoxylin and eosin. Representative sections were also stained with the techniques of Verhoeff-Van Gieson, Masson trichrome, Wilder, periodic acid-Schiff (PAS),[24] luxol fast blue-PAS,[25] and Lepehne-Pickworth.[26] Serial sections of occasional brainstems were examined after being cut at 7 μ, and mounted in their entirety on 35 mm motion picture film and stained with hematoxylin and eosin or PAS using the method of Pickett, Greene and Sommer.[27]

The morphologic and sequential changes which preceded secondary brainstem hemorrhages were studied in some animals sacrificed by instantaneous decapitation at different stages of experiments.

Results

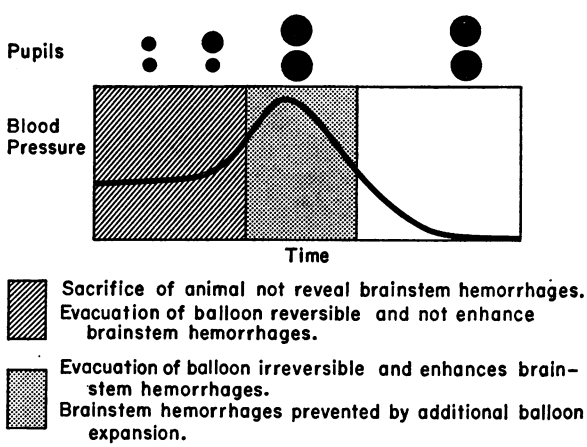
During the course of balloon inflation the systemic blood pressure could generally be subdivided into 3 distinct phases, namely, an initial period of relative blood pressure stability, a phase of hypertension and a terminal period during which the blood pressure gradually fell to zero (Graph 1). The degree of hypertension was directly proportional to the rate of balloon inflation, being greatest with rapidly expanding lesions and least when the balloon was slowly inflated. Respirations generally increased prior to the hypertensive phase and then ceased, sometimes being preceded by periodic respiration. Pupillary dilatation was initially almost invariably ipsilateral to the intracranial lesion and was generally bilateral by the time the maximum blood pressure was reached. The cerebral blood flow generally tended to parallel the systemic blood pressure and often decreased substantially prior to the phase of hypertension.

A direct relationship was established between the ensuing brainstem lesion and the volume and rate of expansion of the intracranial balloon. The accomplished volume of balloon inflation was related to the volume of the intracranial cavity, the size of the dog and the rate and duration of balloon inflation. Secondary brainstem hemorrhages (Fig. 1) could be reproduced consistently only when the balloon was inflated in such a manner that intracranial volumes of 5 to 17 ml were present prior to the attainment of maximum blood pressure. When intracranial balloon expansion continued and was retained throughout the hypertensive phase no brainstem hemorrhages occurred. Under these circumstances transverse ventral brainstem clefts were common (Fig. 2). Such clefts appar-

ently resulted from the mechanical shearing of the brainstem during downward displacement by the supratentorial mass as the degree of cleft formation was directly proportional to the final volume of the inflated balloon. Moreover, they were often absent with smaller intracranial masses which had nevertheless been fatal. If the intracranial balloon was partially or completely removed during the hypertensive phase, extensive secondary brainstem hemorrhages invariably ensued provided that the intracranial mass was more than 5 ml prior to the onset of decompression (Figs. 3 and 4) (Text-fig. 1).

The balloon could often be inflated to volumes as large as 10 ml by relatively slow expansions. Although such masses tended to be fatal they did not produce midbrain or pontine hemorrhages (Fig. 5). With extremely rapid balloon inflation it was often possible to introduce more than 20 ml into the cranial cavity prior to death. Under such circumstances the brainstem tended to be severely damaged as a result of mechanical displacement and compression. When the final intracranial balloon volumes were less than 5 ml brainstem hemorrhages were not observed unless there was an associated intracranial hemorrhage.

Experimentally produced secondary brainstem hemorrhages ranged in severity from microscopic petechiae to extensive gross hemorrhages



TEXT-FIG. 1. Summary of experimental observations showing the period during which secondary brainstem hemorrhages do not occur, as well as the phase when the production of such lesions can be enhanced by balloon evacuation or prevented by additional enlargement of intracranial mass.

with considerable destruction of surrounding brain tissue. Although hemorrhages manifested a predilection for the midbrain and pons (Fig. 1) they commonly involved other areas such as the medulla oblongata, hypothalamus, thalamus and cerebellum when the intracranial balloon was evacuated under circumstances which predisposed to hemor-

rhages (Figs. 3, 4 and 6). Hemorrhages were frequently periarterial or perivenous but were sometimes intimately related to capillaries. Vascular engorgement of arteries, veins and capillaries was almost uniformly observed within the involved areas. Occasionally the cerebral aqueduct was obliterated by brainstem edema. A cellular reaction was invariably absent in the vicinity of the hemorrhages.

The sequential sacrifice of animals under circumstances which consistently resulted in secondary brainstem hemorrhages revealed that they occurred uniformly during the hypertensive phase, that venous congestion was not a constant early phenomenon and that the site of initial bleeding appeared to be dependent upon the volume of the intracranial balloon, namely, with smaller volumes, capillary, while larger ones were predominantly arterial but also venous and capillary.

Discussion

The present investigation shows an apparent relationship between the volume and rate of expansion of the intracranial mass and the presence or absence of secondary brainstem hemorrhages. In order for the latter to become manifest the supratentorial mass must apparently reach a threshold size by the time disturbances in the systemic blood pressure become apparent. Should the size of the intracranial lesion pass beyond this threshold, secondary brainstem hemorrhages do not normally occur but can be induced readily by restoring the intracranial mass to within the volume threshold.

Although the pathogenesis of secondary brainstem hemorrhages is obscure most recent investigators generally agree that the phenomenon is related to the displacement or compression of structures in the region of the tentorial notch. A current popular hypothesis suggests that the hemorrhages result from compression of veins draining the rostral brainstem.[12,14,18,19] In support of this belief is the occasional observation of venous congestion at the tentorial notch in patients with supratentorial expanding lesions; the common association of microscopic venous congestion with secondary brainstem hemorrhages; the perivenous situation of many such hemorrhages; the occasional association of brainstem edema with some secondary brainstem hemorrhages; the anatomic fact that veins are thin-walled and hence more prone to compression or rupture than the thicker-walled arteries; and the actuality that veins draining the upper brainstem can be compressed at the tentorial notch.

Some investigators have pointed out that the vast venous anastomoses of the brainstem make it unlikely that venous obstruction *per se* can cause more than venous congestion.[10,23] Furthermore, the venous obstruction hypothesis has difficulty in explaining the variable incidence

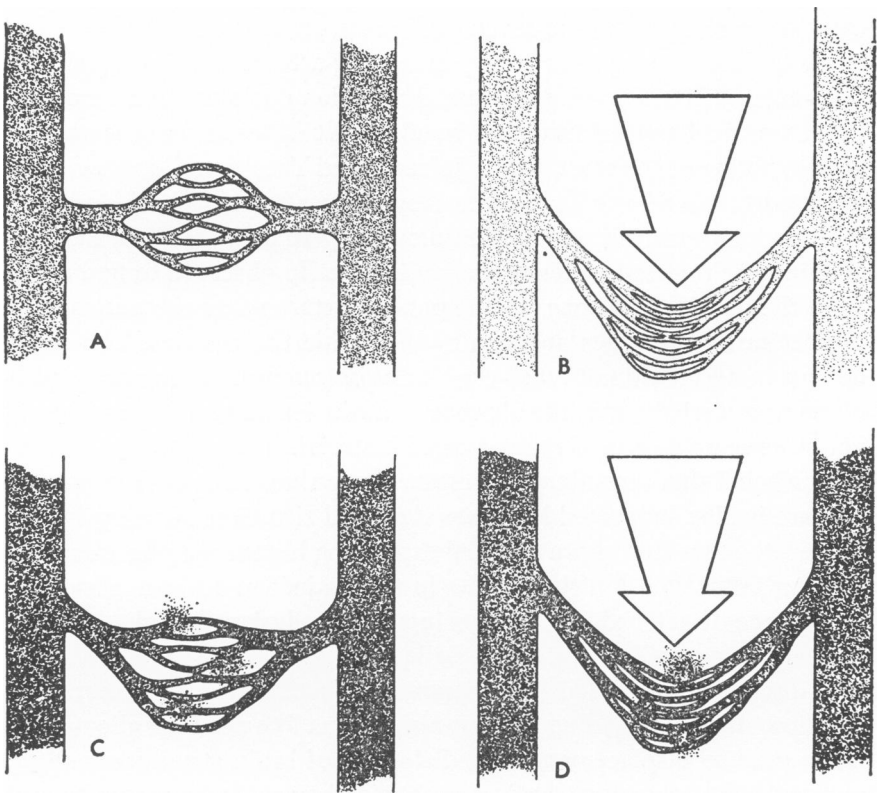
of secondary brainstem hemorrhages with different supratentorial expanding lesions as well as other clinico-pathologic observations concerning this phenomenon.

Dott and Blackwood[4] suggested that as the upper end of the basilar artery is well anchored to the tentorial edge by its posterior cerebral branches and via the posterior communicating arteries to the internal carotid arteries fixed in the cavernous sinuses, a downward displacement of the brainstem would cause the penetrating arteries to lie obliquely and be elongated. They postulated that the tension during such a maneuver to the terminal arterial branches would result either in vasospasm or in active rupture of the vessel walls. Johnson and Yates[6] produced evidence to support such a hypothesis when they perfused the cerebral blood vessels at necropsy with warm saline followed by 10 per cent silver iodide in gelatin. The injected material was radiologically observed to find egress from the terminal branches of the pontine arteries into the antemortem brainstem hemorrhages and to flow alongside the arteries. The radio-opaque material did not reach capillaries or venules. When such a technique was carried out in the absence of brainstem hemorrhages they did not observe an escape of radio-opaque material.

The belief that secondary brainstem hemorrhages result from arterial rupture is also supported by the periarterial situation of many hemorrhages, the fact that supratentorial expanding lesions may be associated with an infarction in a similar site in the brainstem and the occasional occurrence of arterial thromboses in the later lesions.[10] Using this hypothesis, it would be difficult to explain why some massive rapidly expanding supratentorial lesions do not manifest brainstem hemorrhages, and how slowly expanding intracranial lesions like cerebral gliomas can cause marked displacements and distortion of brain structures and yet not manifest secondary brainstem hemorrhages. It is generally well known that slowly expanding lesions do not manifest secondary brainstem hemorrhages unless accompanied by a relatively sudden change in intracranial hemodynamics.

Although the present study does not evaluate all factors which might be cogent to the pathogenesis of secondary brainstem hemorrhages, it is possible to offer a tentative hypothesis to explain the observations (Text-fig. 2). The fact that secondary brainstem hemorrhages can consistently be made to extend beyond regions having a particular venous drainage strongly argues against the hypothesis that this vascular phenomenon is secondary to venous obstruction. Furthermore, the observation that evacuation of the intracranial mass during a critical period accentuates the degree and distribution of secondary brainstem hemorrhages rather than prevents them strongly suggests that the hemorrhages are depen-

dent upon an active circulation and that they result from blood forced in the usual direction of blood flow. It seems probable that an acute rapidly expanding supratentorial lesion causes brainstem ischemia as it displaces the latter structure downwards and that although blood vessels may become severed death follows without brainstem hemorrhages, if



TEXT-FIG. 2. Schematic summary of a postulated explanation for the observed data. The brainstem vasculature is shown with blood potentially reaching it from a rostral or caudal direction and venous drainage likewise proceeding upwards or downwards (A). If a large rapidly expanding supratentorial lesion displaces the brainstem downwards but results in death during a period of brainstem ischemia, secondary brainstem hemorrhages will not take place even if blood vessels are severed (B). Should such a supratentorial lesion, however, be evacuated after downward displacement of the brainstem but while the blood pressure is maintained, brainstem blood flow will be restored and hemorrhages will ensue through damaged blood vessels (C). If an acute rapidly expanding supratentorial lesion displaces the brainstem downwards, traumatizing blood vessels, but permitting physiologic restoration of brainstem blood flow, secondary brainstem hemorrhages will occur (D).

the brainstem blood flow is impeded. Should such a supratentorial lesion be partially or completely evacuated, however, while the systemic blood pressure is elevated, brainstem blood flow will be restored and hemorrhages ensue through the damaged vessels. If a rapidly expanding supratentorial lesion displaces the brainstem downwards, damages blood ves-

sels, and yet, permits physiologic restoration of brainstem blood flow, hemorrhages will occur. Slowly expanding supratentorial lesions presumably do not manifest secondary brainstem hemorrhages as they probably result in gradual downward displacement and ischemia of the brainstem. Furthermore, they do not appear to manifest the same capacity for rapid restoration of cerebral blood flow, as mediated via the vasopressor responses, as acutely expanding masses.

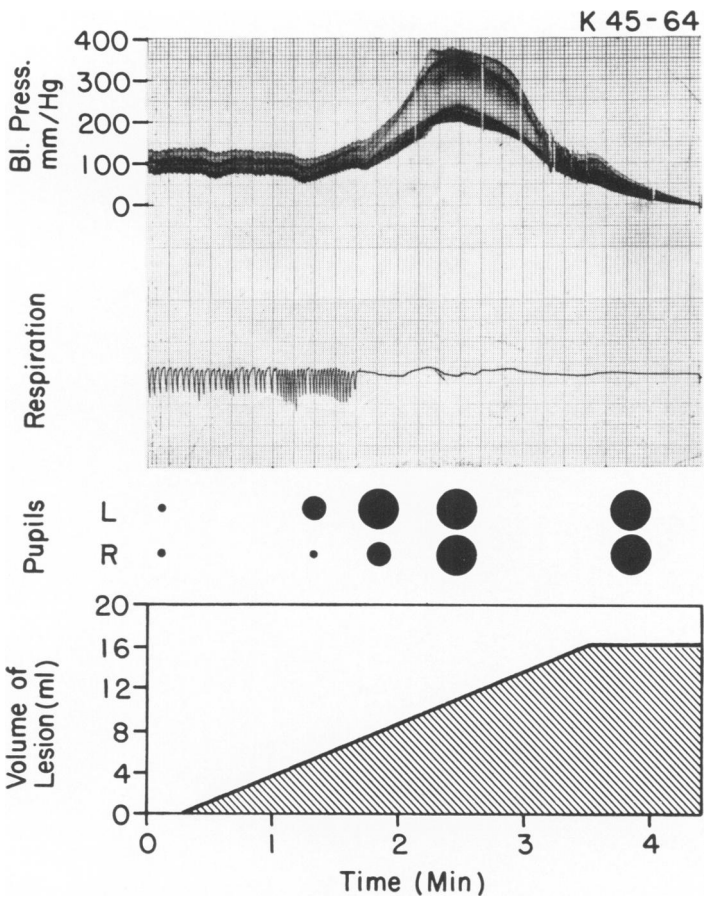
Summary

In order to obtain more precise information regarding secondary brainstem hemorrhages an experimental model was designed wherein it was possible to consistently reproduce secondary brainstem hemorrhages under controlled conditions in the dog. The occurrence of secondary brainstem hemorrhages coincided with alterations in the systemic blood pressure and was apparently dependent upon the volume and rate of expansion of the intracranial lesion. The alleviation of intracranial pressure during a particular period in physiologic decompensation invariably accentuated brainstem hemorrhages and was often critical to their production. Although the present study does not evaluate all factors which might be cogent to the pathogenesis of secondary brainstem hemorrhages the experimental data strongly suggests that the hemorrhages are dependent upon an adequate blood flow through a downward displaced brainstem. The present study also demonstrates that supratentorial expanding lesions may be fatal and yet not manifest secondary brainstem hemorrhages.

References

1. Bannwarth, A. Zur Pathologie des Hirntumors. Diagnostische Irrtümer unter besonderer Berücksichtigung der Klinik des Schläfenlappen-und Kleinhirnbrückenwinkeltumoren. *Arch. Psychiat.*, 1935, **103**, 471–509.
2. Blackwood, W.; Dodds, T. C., and Sommerville, J. C. Atlas of Neuropathology. E. & S. Livingstone, Ltd., Edinburgh, 1964, ed. 2, 234 pp.
3. Blackwood, W. In: Greenfield's Neuropathology. Blackwood, W.; McMenemey, W. H.; Meyer, A.; Norman, R. M., and Russell, D. S. (eds.). The Williams & Wilkins Co., Baltimore, 1963, ed. 2, 679 pp.
4. Dott, N., and Blackwood, W. Mechanism of midbrain haemorrhage. Communication to the Society of British Surgeons, 1951.
5. Greenacre, P. Multiple spontaneous intracerebral hemorrhages. A contribution to the pathology of apoplexy. *Bull. Hopkins Hosp.*, 1917, **28**, 86–88.
6. Johnson, R. T., and Yates, P. O. Brain stem haemorrhages in expanding supratentorial conditions. *Acta Radiol.*, 1956, **46**, 250–256.
7. Moore, M. T., and Stern, K. Vascular lesions in the brain-stem and occipital lobe occurring in association with brain tumours. *Brain*, 1937–38, **60–61**, 70–98.
8. Weintraub, C. M. Bruising of the third cranial nerve and the pathogenesis of midbrain haemorrhage. *Brit. J. Surg.*, 1960, **48**, 62–68.

9. WILSON, G., and WINKELMAN, N. W. Gross pontile bleeding in traumatic and nontraumatic cerebral lesions. *Arch. Neurol. Psychiat.*, 1926, **15**, 455–470.
10. WOLMAN, L. Ischaemic lesions in the brain-stem associated with raised supratentorial pressure. *Brain*, 1953, **76**, 364–377.
11. ZÜLCH, K. J. Störungen des intrakraniellen Druckes. In: Handbuch der Neurochirurgie 1/1. Grundlagen 1, Springer-Verlag, Berlin, Gottingen, Heidelberg, 1959.
12. CANNON, B. W. Acute vascular lesions of the brain stem; a complication of supratentorial space-occupying lesions. *Arch. Neurol. Psychiat.*, 1951, **66**, 687–696.
13. ECHOLS, D. H., and RICKLES, J. A. Herniation of the temporal lobe into the cerebellar fossa. *New Orleans M. S. J.*, 1945–46, **98**, 408–411.
14. EVANS, J. P., and SCHEINKER, I. M. Histologic studies of the brain following head trauma. III. Post-traumatic infarction of cerebral arteries with consideration of the associated clinical picture. *Arch. Neurol. Psychiat.*, 1943, **50**, 258–278.
15. GUIOT, G., and JANNY, P. La réduction chirurgicale de la hernie temporale. *Sem. Hop. Paris*, 1947, **23**, 748–758.
16. LE BEAU, J.; GRUNER, J., and MINUIT, P. Remarques sur une série de 400 traumatismes cranio-cérébraux graves. *Neurochirurgie*, 1955, **1**, 117–126.
17. PIA, H. W. Die Schädigung des Hirnstammes bei den raumfordernden Prozessen des Gehirns. Ein beitrag zur Pathogenese, Klinik und Behandlung der massenverschiebungen des Gehrins. *Acta Neurochir. (Wien)*, 1957, suppl. iv, 182 pp.
18. SCHEINKER, I. M. Transtentorial herniation of the brain stem. A characteristic clinicopathologic syndrome, pathogenesis of hemorrhages in the brainstem. *Arch. Neurol. Psychiat.*, 1945, **53**, 289–298.
19. SCHEINKER, I. M. Neurosurgical Pathology. Charles C. Thomas, Springfield, Ill., 1948, 370 pp.
20. DILL, L. V., and ISENHOUR, C. E. Etiologic factors in experimentally produced pontile hemorrhages. *Arch. Neurol. Psychiat.*, 1939, **41**, 1146–1152.
21. DUKHIN, A. L., and TUSHEVSK, V. F. [Pathogenesis of brain stem symptoms tumors of the cerebrum.] *Inst. for Teach. & Res. in Neurosurg.*, Vrach. Delo., Kiev, 1962, **6**, 40–46.
22. POPPEN, J. L.; KENDRICK, J. F., and HICKS, S. F. Brain stem hemorrhages secondary to supratentorial space-taking lesions. *J. Neuropath. Exp. Neurol.*, 1952, **11**, 267–279.
23. LINDENBERG, R. Compression of brain arteries as pathogenetic factor for tissue necroses and their areas of predilection. *J. Neuropath. Exp. Neurol.*, 1955, **14**, 223–243.
24. MCMANUS, J.F.A., and MOWRY, R. W. Staining Methods: Histologic and Histochemical. Paul B. Hoeber, Inc., New York, 1960, 423 pp.
25. MARGOLIS, G., and PICKETT, J. P. New Applications of the luxol fast blue myelin stain. *Lab. Invest.*, 1956, **5**, 459–474.
26. DOHERTY, M. M.; SUH, T. H., and ALEXANDER, L. New modifications of the benzidine stain for study of the vascular pattern of the central nervous system. *Arch. Neurol. Psychiat.*, 1938, **40**, 158–162.
27. PICKETT, J. P.; GREENE, W. B., and SOMMER, J. R. Improved film strip technique for the laboratory. *Arch. Path. (Chicago)*, 1964, **77**, 429–433.



GRAPH 1. Blood pressure, respiration, relative pupil size and volume of intracranial balloon during a representative experiment. Secondary brainstem hemorrhages were not manifest in this animal.

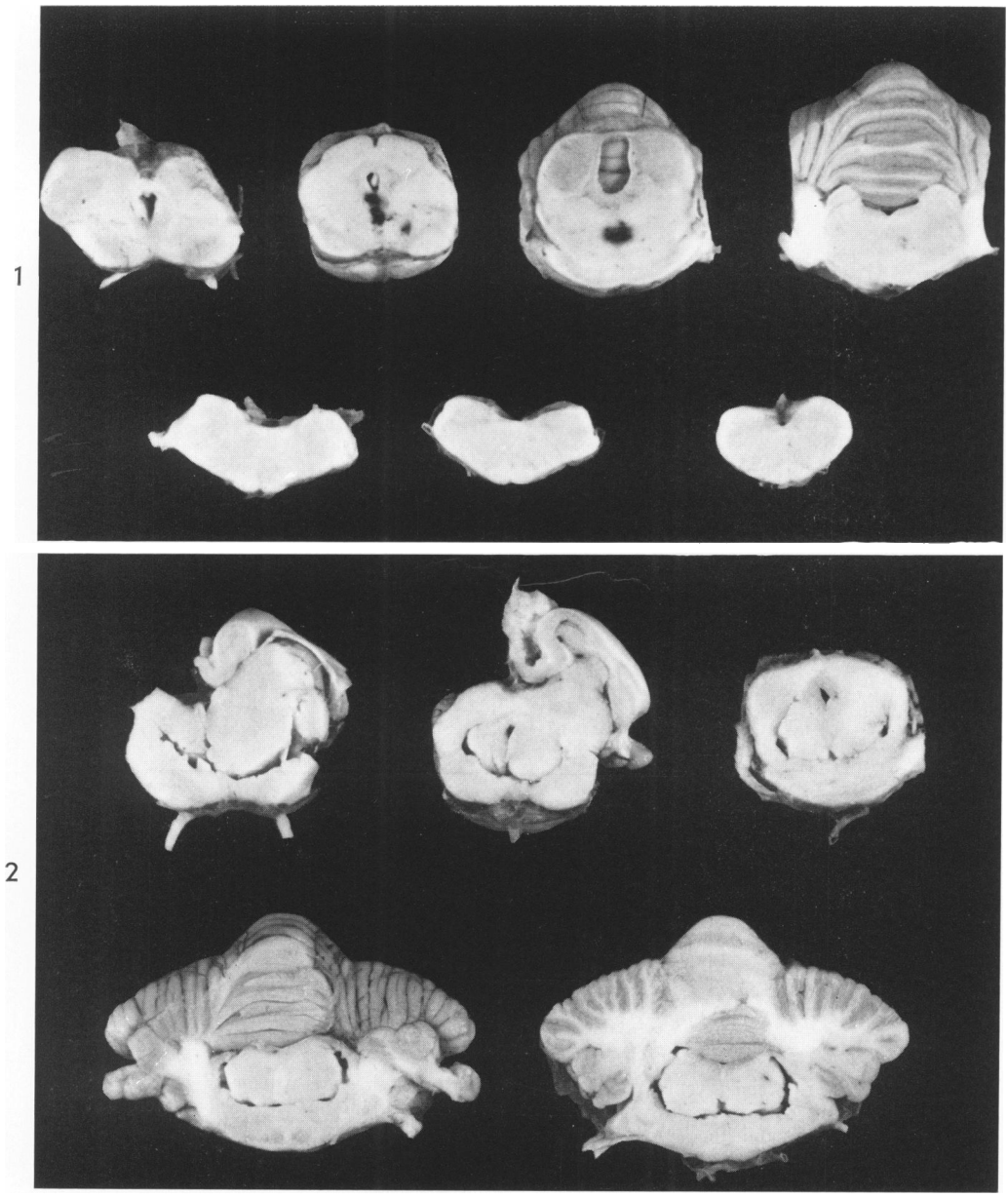
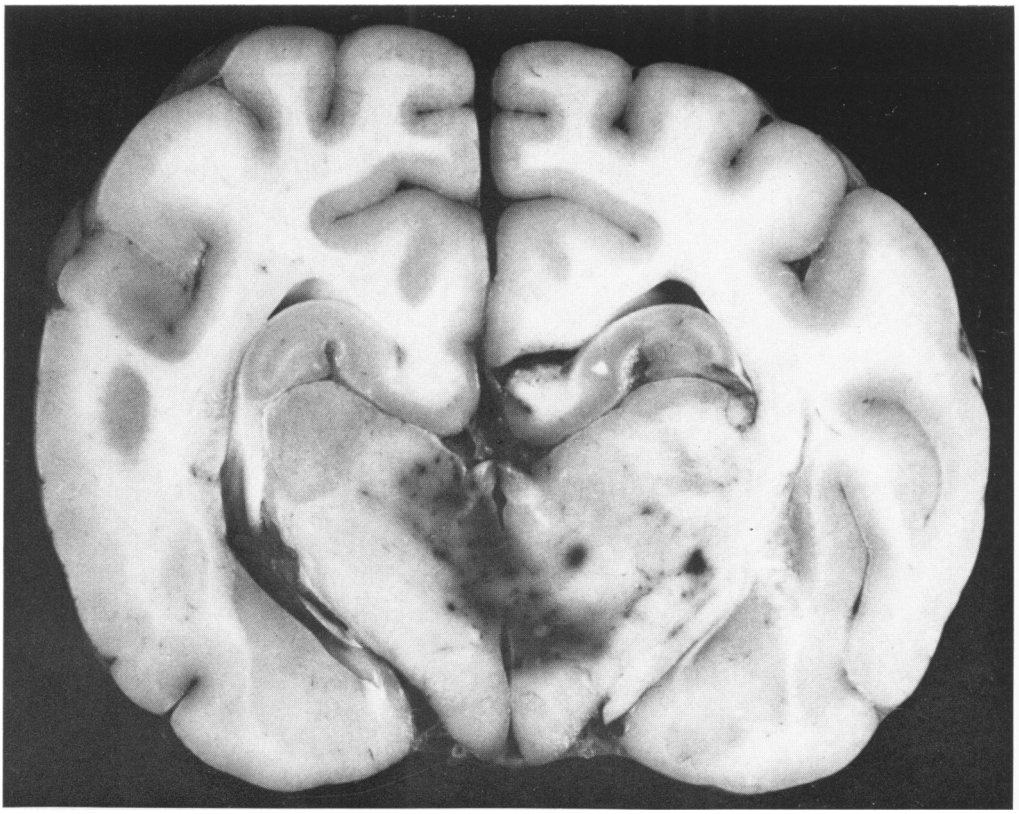


FIG. 1. Coronal sections of the brainstem show secondary midline midbrain and pontine hemorrhages in a representative experimental animal in which an intracranial balloon was continuously inflated at 5.82 ml per minute to 7 ml and maintained at that size until death. In this dog inflation ceased prior to the attainment of maximum blood pressure. Secondary brainstem hemorrhages generally manifested a predilection for this location.

FIG. 2. Brainstem sections from an animal in which balloon inflation continued until death. In this particular dog the intracranial balloon was inflated to 18 ml at 5.82 ml per minute. The transverse ventral brainstem clefts, which apparently resulted from the mechanical shearing of the brainstem during downward displacement by the supratentorial mass, are unassociated with secondary brainstem hemorrhages.



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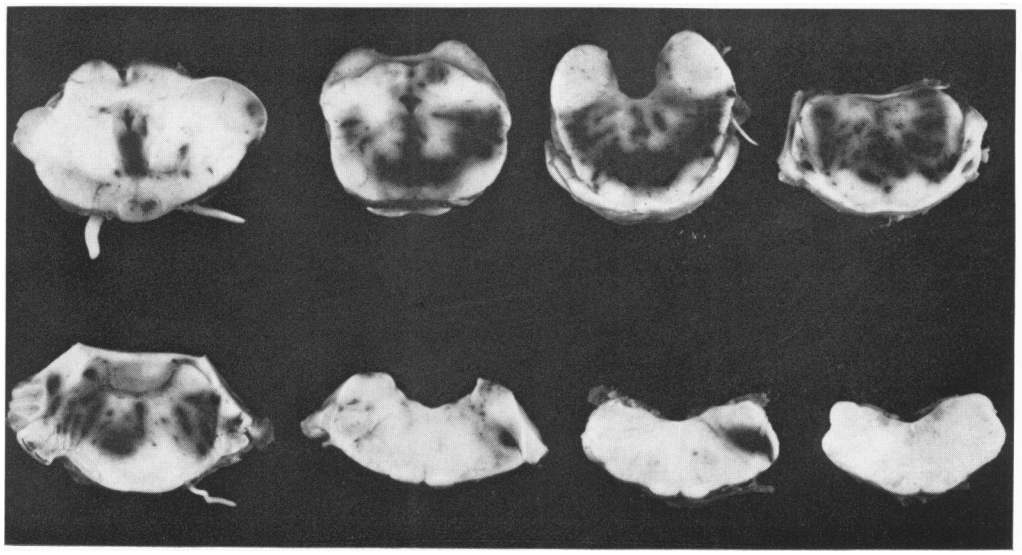

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FIG. 3. Total evacuation of intracranial balloons during the hypertensive phase commonly results in hemorrhage in sites other than the brainstem. The cerebrum here shows secondary hemorrhages within both thalami and adjacent structures in a dog that had a subdural balloon continuously inflated at 5.82 ml per minute to a volume of 12 ml and then completely deflated during the hypertensive phase, at the same rate.

FIG. 4. The brainstem from the same experimental animal shown in Figure 3. The extensive nature that secondary brainstem hemorrhages may manifest following evacuation of a large intracranial mass during the phase of physiologic decompensation is shown.

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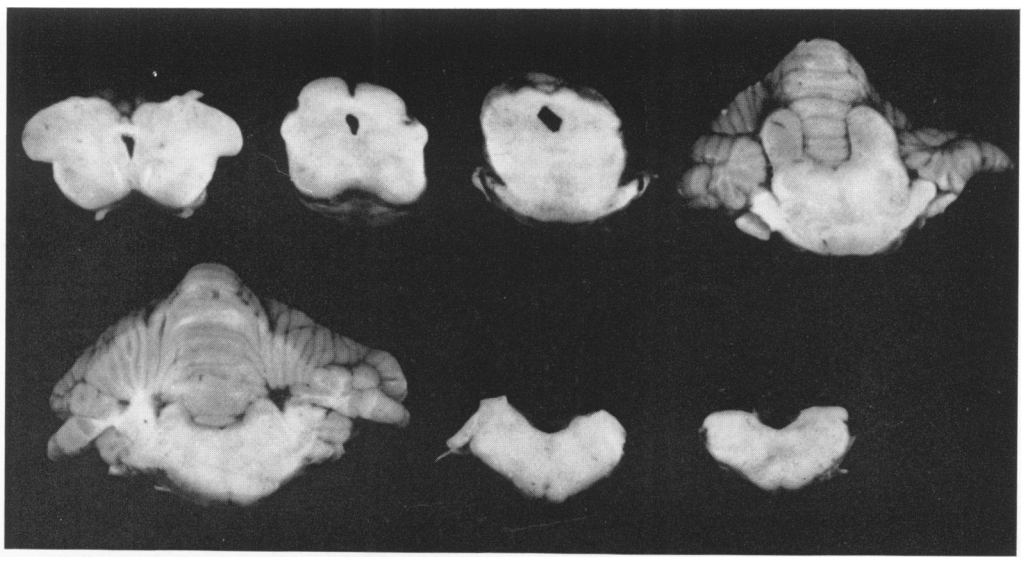

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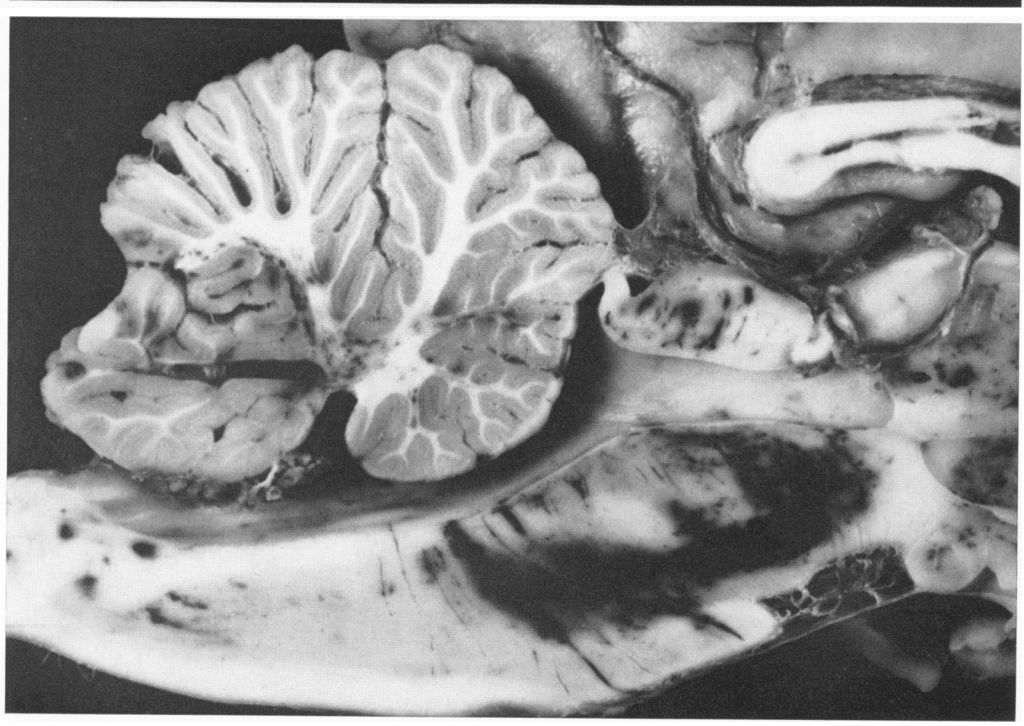

FIG. 5. No gross morphologic lesions are evident in this brainstem. Such a finding was encountered if the intracranial balloon was inflated relatively slowly, or when animals with intracranial masses were instantaneously sacrificed prior to the attainment of a significantly elevated blood pressure.

FIG. 6. A sagittal section of the brain shows extensive secondary brainstem hemorrhages which are predominantly located within the midbrain and pons but which are also present in the medulla, thalamus, hypothalamus and cerebellum. In this particular animal 8 ml was inflated supratentorially at 5.82 ml per minute and then withdrawn at the same rate.