Discussion points submitted to members of the IACC, 25 Jan 2010

(1) Evidence that the auditory system of the brain has higher blood-flow and metabolism than any other area of the brain [1, 2]. See figures 1 and 2 below.

Note: The deoxyglucose method has been extensively used in animal research on brain activity responses to drugs and other factors. The inferior colliculus has consistently been found to have the highest rate of glucose utilization in every study.

(2) Evidence that the auditory system is susceptible to damage by circulatory arrest [3-13]. See figures 3, 4, and 5 below.

Note: Asphyxia at birth was produced in monkeys by preventing the first breath and cutting off circulation to the placenta (by clamping the umbilical cord). Ischemic bilaterally symmetric damage to brainstem nuclei resulted.

Note: Current accepted practice in obstetrics is to clamp the umbilical cord immediately after birth, whether or not the first breath has occurred [14].

(3) Evidence that the auditory system is susceptible to impairment by toxic substances [15-36].

Note: Toxic substances cause bilaterally symmetric hemorrhagic (petechial) lesions of brainstem nuclei (Wernicke's encephalopathy). The lesions are petechial, resulting from increased blood flow in response to the insult, with bursting of capillaries. Toxic substances impair aerobic metabolism.

(4) Evidence that the auditory system is susceptible to impairment by loss of aerobic enzyme function when the co-enzyme thiamine (vitamin B1) is lacking [37-49]. See figures 6, 7, and 8 below.

Note: Beriberi was once believed to be caused by a bacterial infection: "The cause of beriberi appears to be a bacillus which gains entrance to the alimentary canal in contaminated food and drink." [50, p289]

(5) Evidence that the auditory system is part of the subcortical pattern of damage found in children affected by kernicterus [51, 52]. See figure 9 below.

Note: Ranck and Windle (1959) in their paper on asphyxiation of newborn monkeys commented: "The human neuropathologic entity most closely resembling the effects of asphyxia neonatorum in the monkey is kernicterus. There are similarities in the distribution and type of nerve cell changes in both conditions. Major differences between the findings in the monkey and those in human infants with kernicterus are absence in the former of the usual history of erythroblastosis fetalis, lack of clinical jaundice, lack of pigment in the lesions, . . ." [4, p153]

(6) Evidence that bilirubin staining of the basal ganglia and other subcortical areas is secondary to impairment of the blood-brain barrier [53-57].

Note: Bilirubin is not toxic. Bilirubin staining of subcortical nuclei results from impairment of the blood-brain barrier by anoxic-ischemic injury or by a substance that disrupts aerobic metabolism.

(7) Evidence that synthetic vitamin K and sulffisoxazole antibiotic are toxic to the blood-brain barrier [58-67]

Note: Natural vitamin K is fat soluble. Synthetic versions are water soluble, thus could be given by injection. Robertson pointed out that vitamin K became the second standard treatment for all newborn infants: "The prophylactic use of vitamin K in newborns began in the early 1940s and was the second routine pharmacological treatment of newborn infants; the first being the use of silver nitrate to prevent ophthalmia neonatorum." [63, p53]

Comment: Discovery of the toxicity of synthetic vitamin K occurred at the same time that autoradiography revealed high blood-flow and metabolism in the inferior colliculi and other subcortical structures affected in kernicterus. Why have these elegant studies of brain activity been so neglected? Vitamin K continues to be part of accepted practice even though its routine administration to all newborns continues to be controversial, and rightfully so [62, 63].

(8) Evidence that damage of subcortical sites in the perinatal period leads to disruption of normal maturation of the cerebral cortex [68]. Sites of injury found in monkeys subjected to asphyxia at birth are listed in table 1 below. Sites of secondary growth failure are listed in table 2.

Note: Faro and Windle examined the brains of monkeys kept alive for many months or years after being subjected to asphyxia at birth. They noted "structural changes sequential to the initial asphyxial lesions . . . It was difficult to separate the primary effects of asphyxia from these later atrophic changes in some regions . . ." [68, p41].

"Some of these regions, such as the frontal and parietal cortex, will be recognized as locations normally receiving the terminations of tracts destroyed by the primary lesions. . . . Extensive primary damage by asphyxia at birth led to a reduction in amount of white matter, as in the corpus callosum . . . All the animals had severe brain damage, but some were worse off than others." [68, p43]

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Clamping the umbilical cord immediately after birth is accepted practice in obstetrics

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Maturation of the cerebral cortex is impaired following perinatal brainstem injury

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Table 1: Brainstem Sites Damaged by Asphyxia at Birth

- **Inferior colliculi and Superior olives**
  (acoustic processing & relay)
- **Trigeminal nerve sensory nuclei**
  (5th cranial nerve from face & jaw)
- **Gracile and cuneate nuclei**
  (lower & upper body sensory)
- **Vestibular nuclei**
  (equilibrium & reflexive orientation)
- **Ventral thalamic nuclei**
  (sensory processing & relay from brainstem & cerebellum to cortex)
- **Basal ganglia**
  (subcortical motor control)

Table 2: Areas of Dysmaturation in Brains of Monkeys Following Long-term Survival

- **Brainstem:**
  periaqueductal gray
  oculomotor nuclei
  Inferior olives
- **Cerebellum:**
  vermis
- **Subcortical sites:**
  mammillary bodies
  hippocampus
  amygdala
- **Cerebral Cortex:**
  frontal and parietal lobes
  corpus callosum
  (left/right hemisphere connection)
  ventricular enlargement

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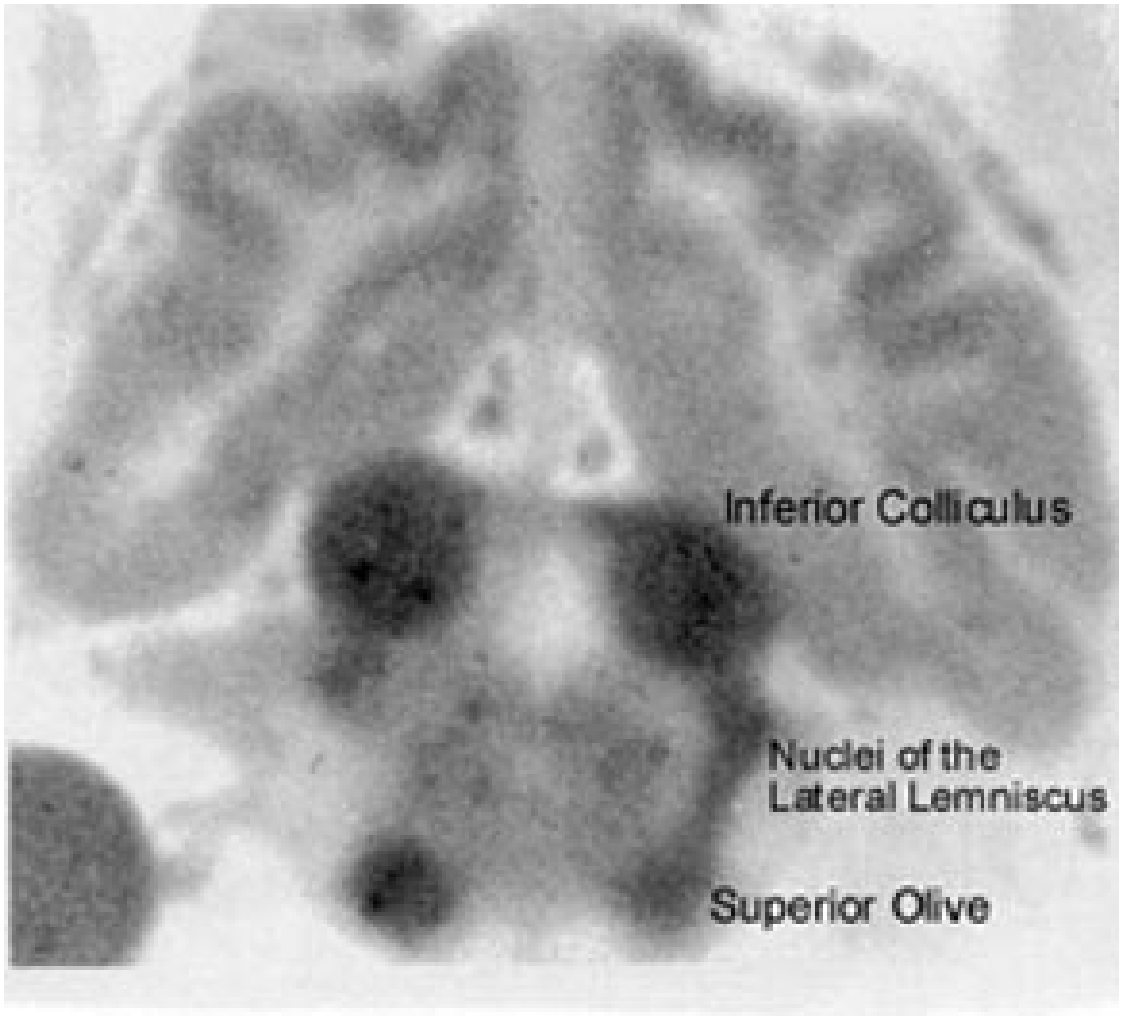

Figure 1: Blood Flow in the Brain

Autoradiogram of the brain of a cat 60 seconds after injection of a radioactive tracer shows the greatest perfusion (thus greatest blood flow) in nuclei of the brainstem auditory pathway. This technique has revealed that the highest blood flow in the brain is to structures in the auditory pathway in several other mammalian species, including monkeys. From Kety, 1962, with permission from Columbia University Press. Note: Labels for components of the auditory pathway, superior olive, nuclei of the lateral lemniscus, and inferior colliculus, were added for reference.

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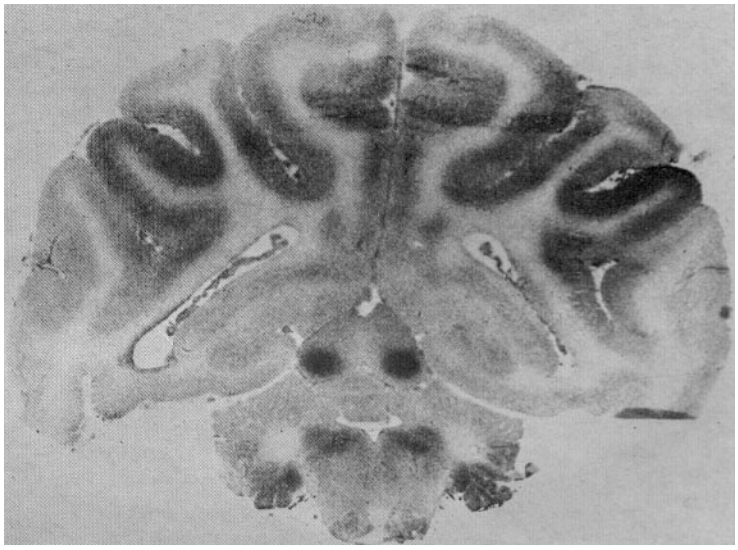

Fig. 7. Autoradiograph of coronal brain section of normal newborn monkey. Just prior to being killed, this animal sustained an intravenous infusion of ^{14}C-Iabeled antipyrine. Staining density relates to volume flow of blood per unit of tissue per unit of time. The central nuclei of the inferior colliculi stand out due to their high-volume blood flow< (Courtesy C. Kennedy and L. Sokoloff, Laboratory of Cerebral Metabolism, National Institute of Mental Health.)

Figure 2: Figure 7 from Myers (1972), p254

Autoradiograph showing blood flow in the brain of a newborn monkey. The greatest blood flow is to the inferior colliculi in the midbrain. High blood flow is also seen in other subcortical structures and inner sulci of the cerebral cortex. From Myers (1972) with permission from the American Medical Association.

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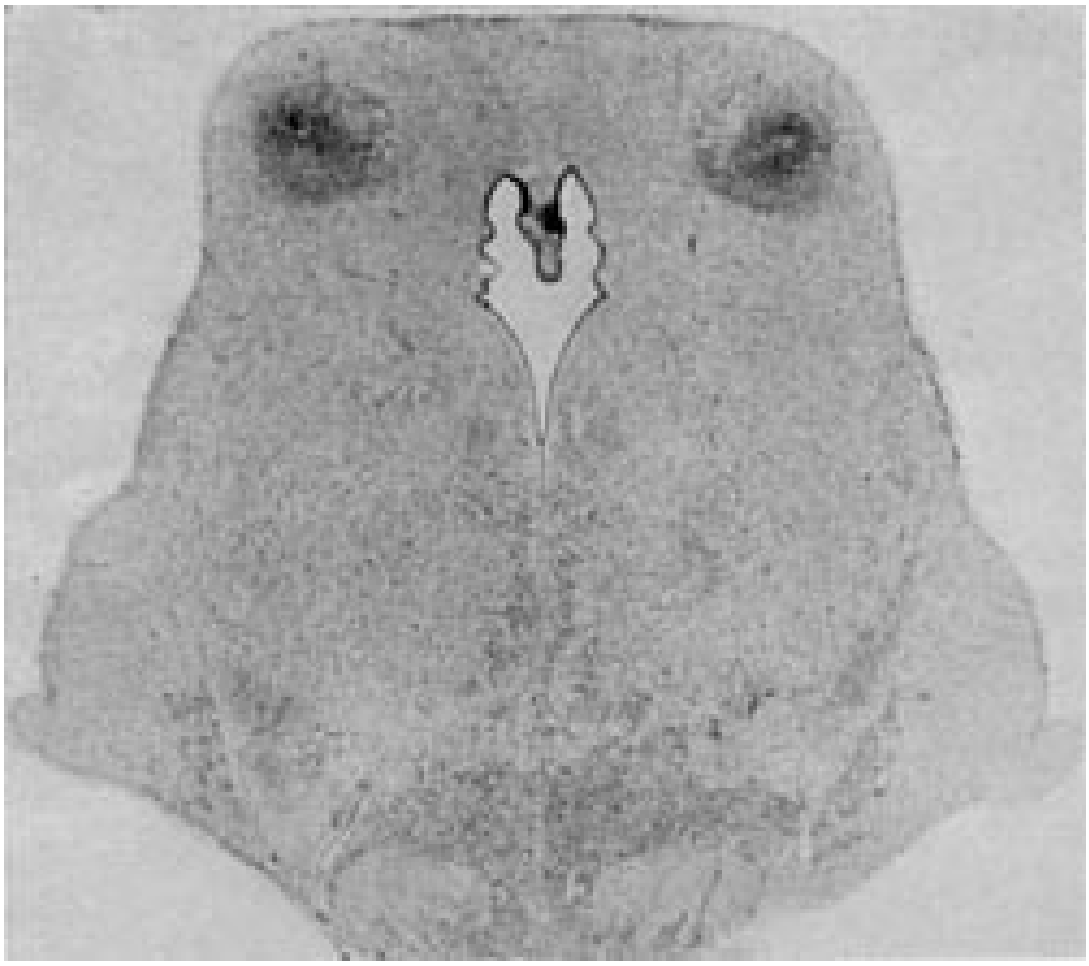

Figure 3: Damage of the inferior colliculi: Result of subjecting a newborn monkey to 12 minutes of total asphyxia. (from Myers 1972)

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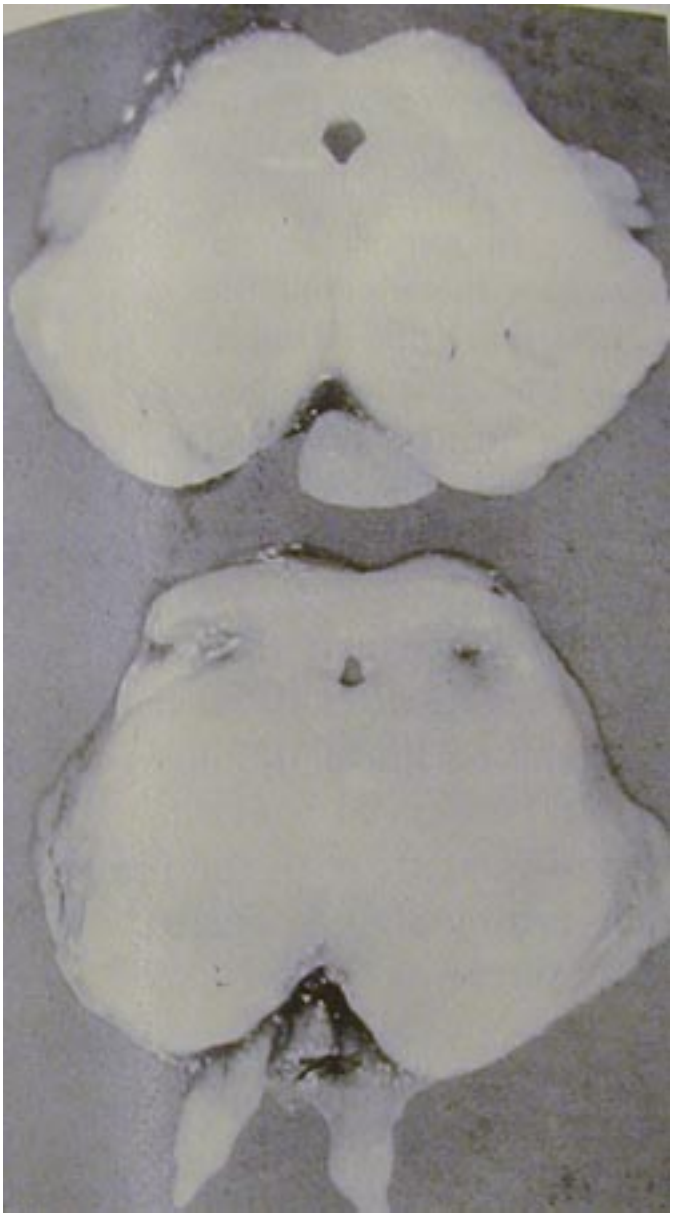

Figure 4: Brain damage in human infants also involves the inferior colliculi (bottom) following asphyxia (from Leech & Alvord 1977, with permission from the American Medical Association).

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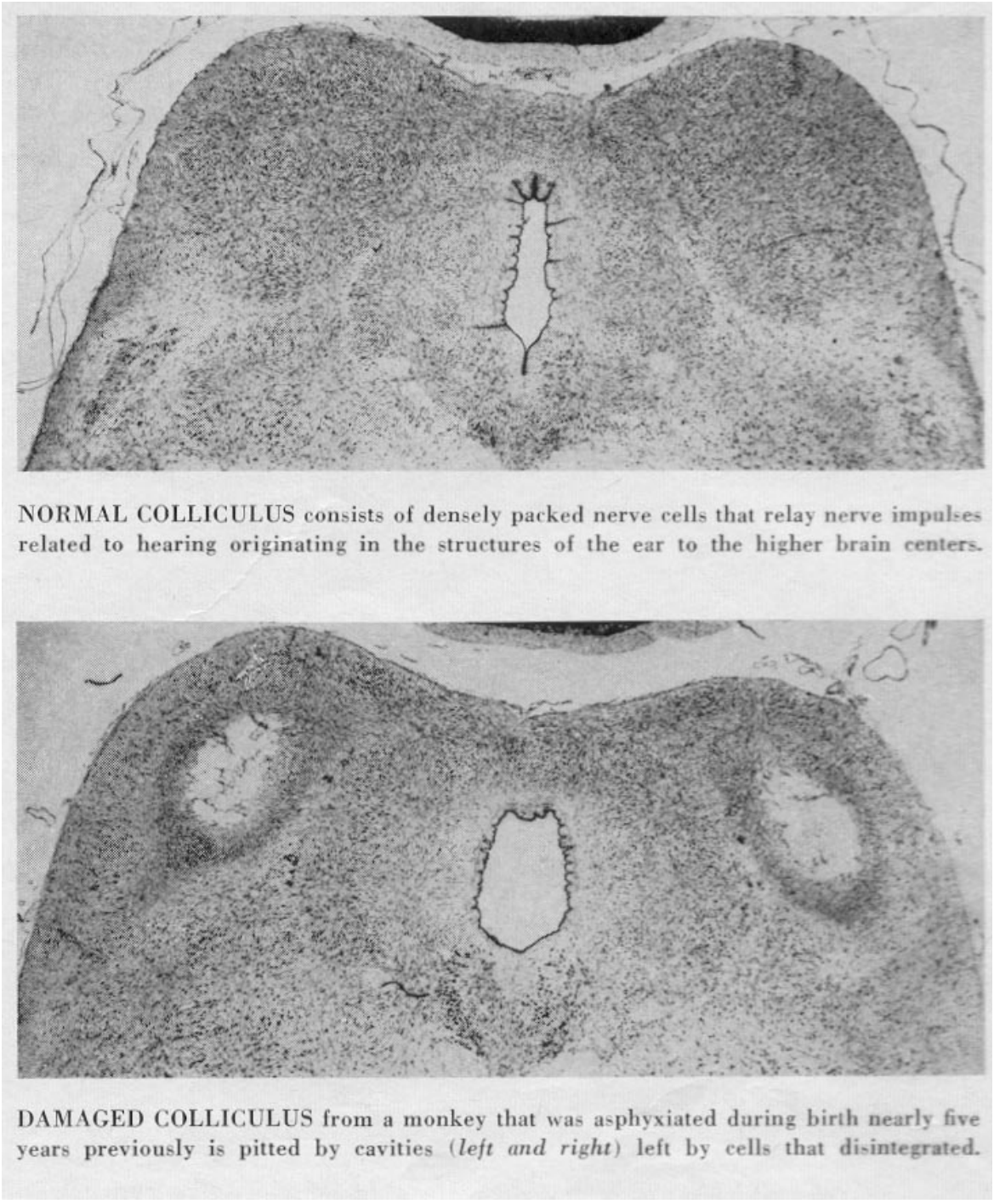

NORMAL COLLICULUS consists of densely packed nerve cells that relay nerve impulses related to hearing originating in the structures of the ear to the higher brain centers.

DAMAGED COLLICULUS from a monkey that was asphyxiated during birth nearly five years previously is pitted by cavities (*left and right*) left by cells that disintegrated.

Figure 5: Pictures from the article by William F. Windle in the October 1969 issue of the Scientific American.

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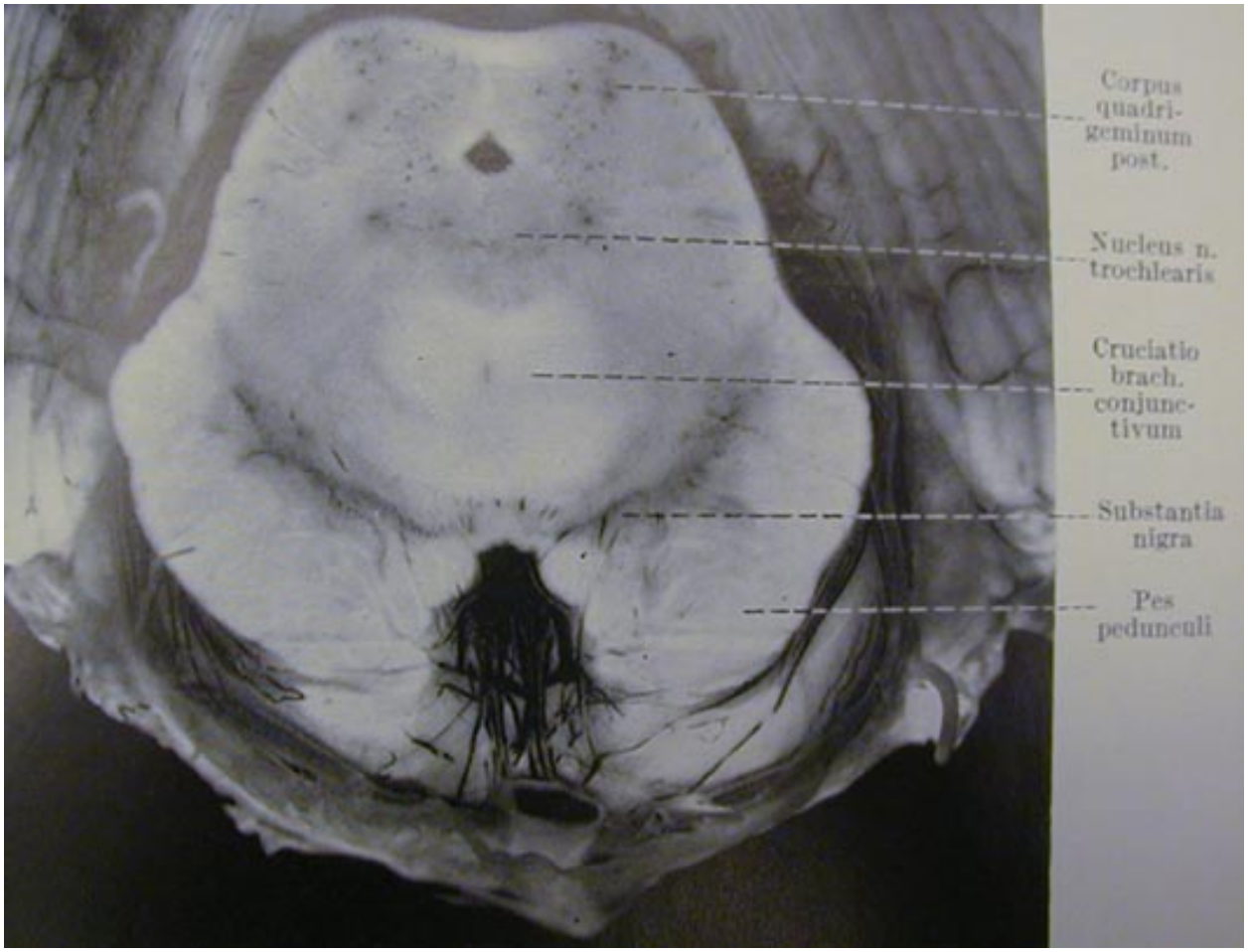

Figure 6: Wernicke's encephalopathy, caused by chronic alcohol intoxication or deficiency of thiamine (vitamin B1) deficiency, is characterized by small flea-bite size hemorrhages in the inferior colliculi (here labeled corpus quadrigeminum posterior) from dilated blood vessels that burst. From Kant (1933, with permission from Springer-Verlag).

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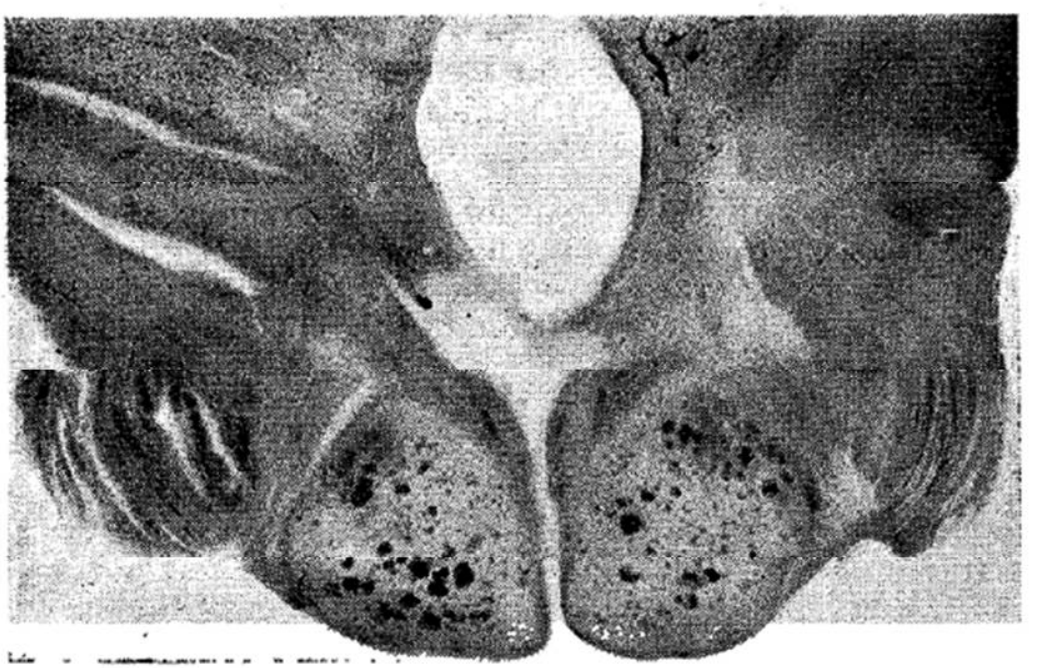

Fig. I—Frozen section through mammillary bodies showing dilated vessels and hæmorrhages, and a smaller lesion in the wall of the 3rd ventricle. (Lepehne Pickworth, $\times 4^1/_2$.)

Figure 7: Hemorrhagic damage of the mammillary bodies in Wernicke's encephalopathy. From DeWardener and Lennox (1947).

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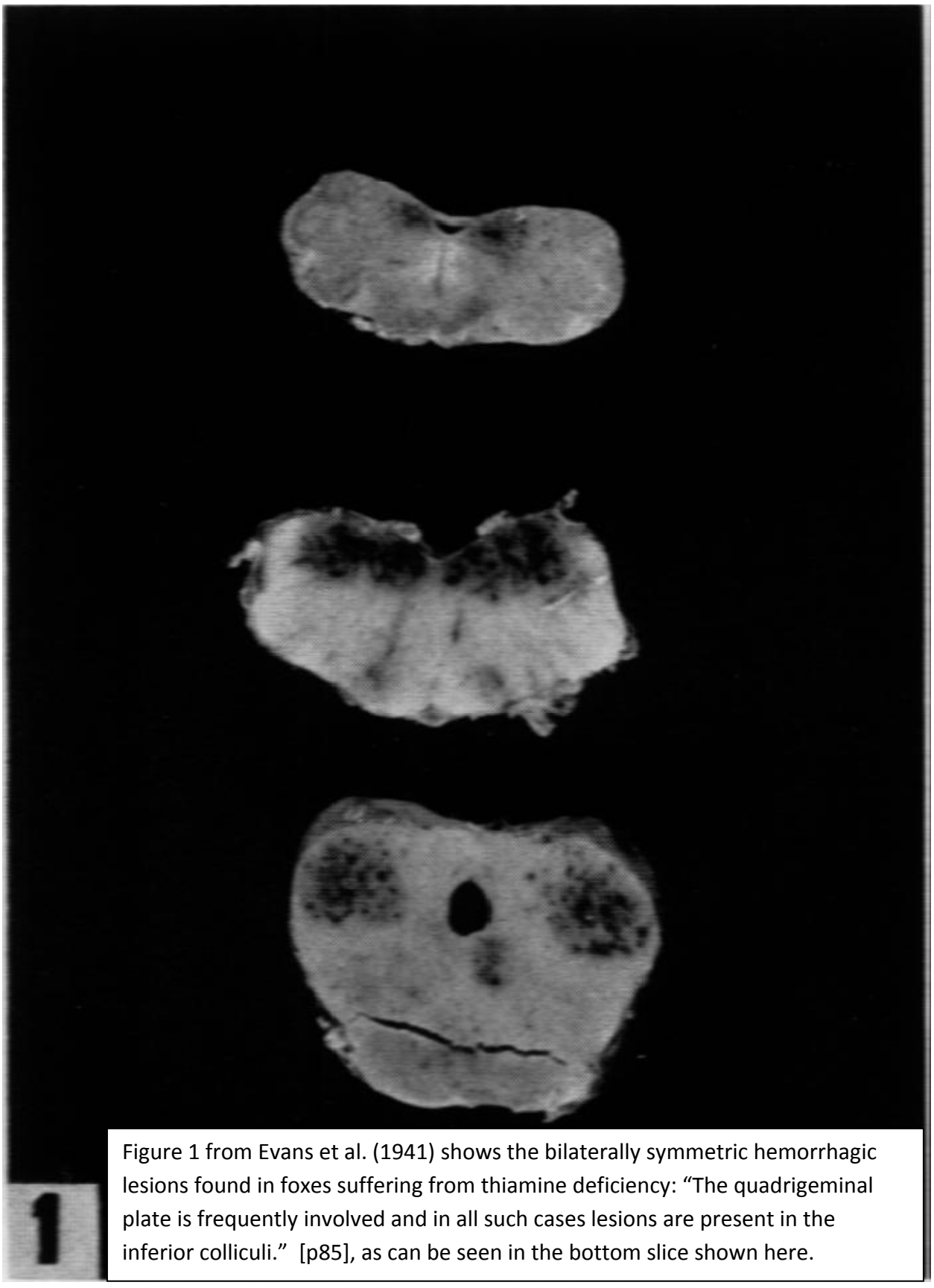

Figure 1 from Evans et al. (1941) shows the bilaterally symmetric hemorrhagic lesions found in foxes suffering from thiamine deficiency: "The quadrigeminal plate is frequently involved and in all such cases lesions are present in the inferior colliculi." [p85], as can be seen in the bottom slice shown here.

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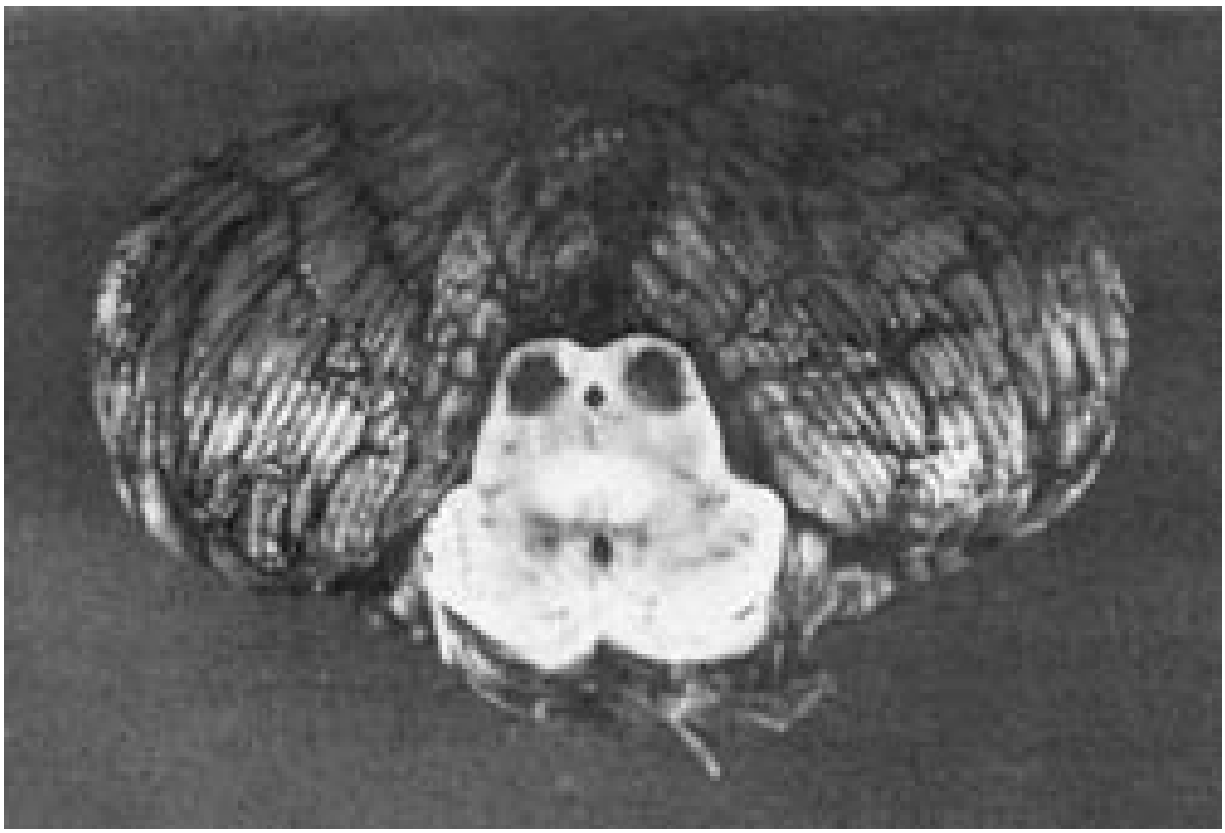

Figure 8: Hemorrhagic damage of the inferior colliculi in a human patient maintained on prolonged parenteral feeding lacking vitamin B1 (from Vortmeyer et al. 1992).

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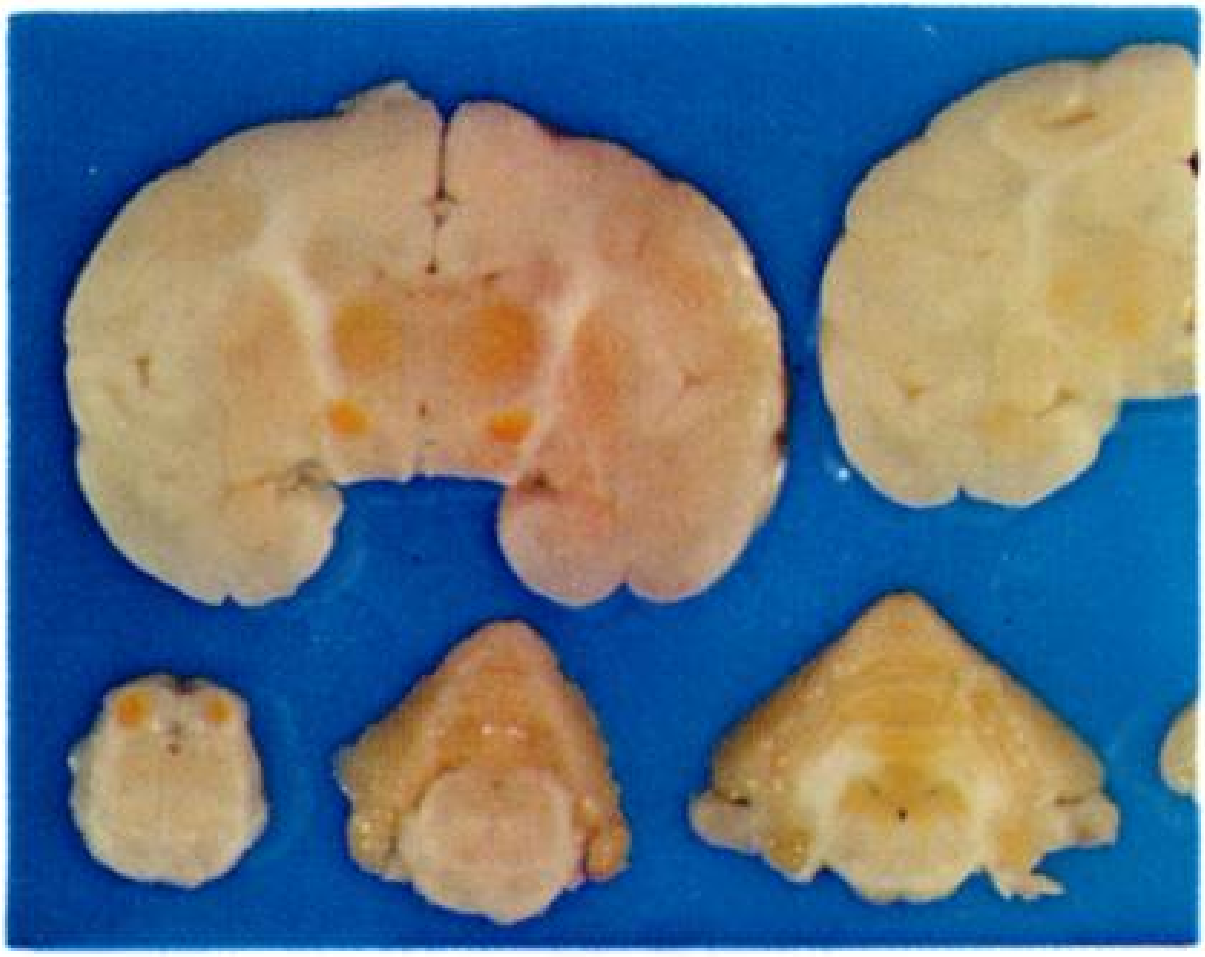

Figure 9: Picture from the the paper by Lucey et al. (1964). Note that bilirubin staining is not uniform throughout the brain. Blood flow and metabolism are not uniform throughout the brain. Brainstem nuclei of high metabolic rate are most susceptible to damage when a sudden catastrophic lapse in aerobic metabolism occurs. The inferior colliculi in the midbrain auditory pathway (lower left) are intensely stained, as are the mammillary bodies and basal ganglia (upper left).

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