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Lost in Translational Neurology: From Anemic Decerebration to Anoxic-Ischemic Brain Injury

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Experiments in which animals were exposed to interruption of blood flow were far removed from the bedside evaluation of patients with anoxic-ischemic brain injury. In the early 1900s, laboratory scientists created "acute anemia" (through ligation of major arteries or removing large volumes of blood) to study the resuscitation of the central nervous system of mammals; they labeled the resulting presentation "anemic decerebration." Sherrington's intercollicular lesion decerebration model looked identical to the anemic decerebration model. Clinicians had to wait for a 1946 paper that described a complete neurologic examination, including cranial nerves, motor function, tone, and reflex pattern, along with comprehensive autopsy results showing extensive changes in the basal ganglia, particularly in the caudate nucleus, putamen, and the temporal lobe (cornu ammonis).

The study of the pathophysiology of brain damage has a long history starting with animal experiments and cumulating in autopsy descriptions of patients who died after some days of support. Unsurprisingly, the research tracks of animal experiments and bedside evaluation of anoxic-ischemic brain injury were far apart. However, each provided a foundation for our clinical understanding of what we now know is the most severe type of injury to the brain [1].

Animals First

As early as the early 1900s, scientists created "acute anemia" to study the resuscitation of the central nervous system of mammals. Often, they passed ligatures around the cerebral arteries. A 20-min interruption would not result in full recovery, but some animals were able to make a full recovery after a maximal 10-min interruption [2]. As cited by Hill, Astley Cooper performed the first important experiment on a dog by tying the vertebral arteries at their origin from the innominate and left subclavian arteries and, at the same time, ligating the carotids [3]. The resulting posturing was reminiscent of Sherrington's classic decerebration-induced immediate spasms [4]. Some concluded that 10 to 15 min of cerebral anemia was sufficient to damage the brain permanently [5]. Previous investigators did not recognize the importance of spinal arteries in maintaining some cerebral circulation after all other vessels had been tied, and thus, the capacity of neurons to endure cerebral anemia was overestimated. The occasional recovery of cats after a 15-min anemic episode could be explained by the presence of unusually good anastomosis.

Gildea and Cobb found frequent anatomic variations and concluded that the symptoms produced were the best indicators of whether a severe anemia occurred. The two most reliable were cessation of respiration minutes after ligature of the arteries and seizures or posturing during or after the period of arterial occlusion. They appreciated the difficulty of producing anemia severe enough to induce structural brain injury without causing the death of the animal. Gildea and Cobb reported that only 20 of 90 cats survived for 24 h or more. They either failed to resume breathing or died with continuous convulsions [6].

Pollock and Davis devised a 2-step method of producing decerebrate rigidity by anemia (Fig. 1). First, they performed ligation of the basilar artery at any desired point

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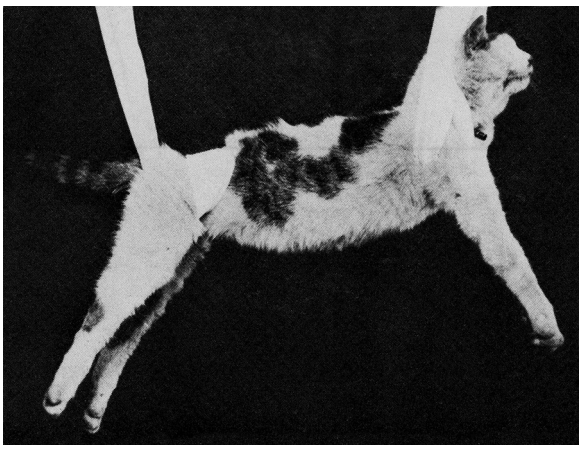

Fig. 1 Decerebrate cat, American Medical Association [8], used with permission

and, second, the ligation of the carotid arteries [7, 8]. They found the following:

> *Shortly after the ligature of both carotids and the basilar artery, the animal assumed the characteristic posture of decerebrate rigidity. The forelegs were thrust backward, the elbows were rigidly extended, and the hindlegs were usually not as completely involved in the rigidity as were the forelegs. The tail was invariably curved stiffly upward. The head was lifted and retracted on the neck. The mouth was tightly closed. If the legs, tail, or head were moved from the attitude assumed they would immediately spring back into the position of extensor rigidity. While this posture would be assumed with the animals lying on the side, the suspended position and fixed supine position favored the early production of rigidity.*

In another experiment, Stewart et al. interrupted the cerebral circulation for periods of 3 to 81 min by ligation of the innominate and left subclavian arteries proximal to the origin of the vertebral, in 93 cats. The eye reflexes disappeared very quickly, and a period of high blood pressure immediately followed the occlusion. Vagus inhibition caused cardiac slowing and a drop in blood pressure, followed by a second rise after the vagus center succumbed to anemia. Respiration stopped temporarily (20–60 s) after the beginning of occlusion and resumed in a series of strong gasps of the Cheyne–Stokes type, after which it stopped until after the restoration of the cerebral circulation. The respiratory and vagus centers lost their power of functioning at approximately the same time. Asphyxial slowing of the heart would occur without the agency of the vagus center. The blood pressure slowly fell to a level that was maintained throughout the remainder of the period of occlusion [2].

These prominent researchers were interested in how specific injury, predominantly the link between nuclei and critical traits, could lead to specific clinical signs and, thus, how the central nervous system was integrated. Sherrington's intercollicular lesion decerebration model looked identical to their anemic decerebration model.

These animal experiments, including the development of animal models to understand and treat human diseases, were very common in the early and mid-1900s. Some experimental procedures involving animals were filmed. Jean Painlevé filmed anemic decerebration in his unnerving documentary, *Experimental treatment of a hemorrhage in a dog* [9]. The 4-min film shows bloodletting from a cannula placed in the carotid artery of a large, unanesthetized canine strapped to an operating table. Dr. Leon Normet exsanguinates the dog until the front legs acutely stretch (anemic decerebration). The objective of the experiment is, presumably, to determine the amount of blood loss (1400 cc, apparently) that an animal can sustain. A large volume of serum citrate is returned to the animal through a vein, after which he gets off the table, wagging his tail, and drinks. The dog is shown again on the following day with no apparent injury. This dog was 1 of 100 subjected to this experiment (with a 95% success rate), and the serum was considered a "miraculous" blood transfusion surrogate. The documentary confirmed what many researchers observed independently during their experiments.

Humans Second

Pathologists and neurologists in the early 1950s became interested in anoxic-ischemic injury to the brain after cardiac arrest [1]. Some of the attention was directed to the differing vulnerability of gray and white matter, and it became clear that ischemia affected the cerebral and cerebellar cortices more than the basal ganglia—with the reverse in hypoxemia. The paper on neuronal damage from cardiac arrest by Howkins et al. can be considered one of the first comprehensive papers on the evaluation of a patient with successful cardiac massage [10]. The report was published before cardiopulmonary resuscitation (CPR) became commonplace. The patient was a 32-year-old woman who, after surgery was almost completed, had a sudden cardiac failure and received transdiaphragmatic cardiac massage, which lasted 7 min. She also received intracardiac adrenaline. A regular pulse was felt that then normalized. Six hours later, her neurologic examination showed absent corneal reflexes, increased knee jerk, clonus, extensor plantar responses, and significant decerebrate rigidity (Fig. 2). Lumbar

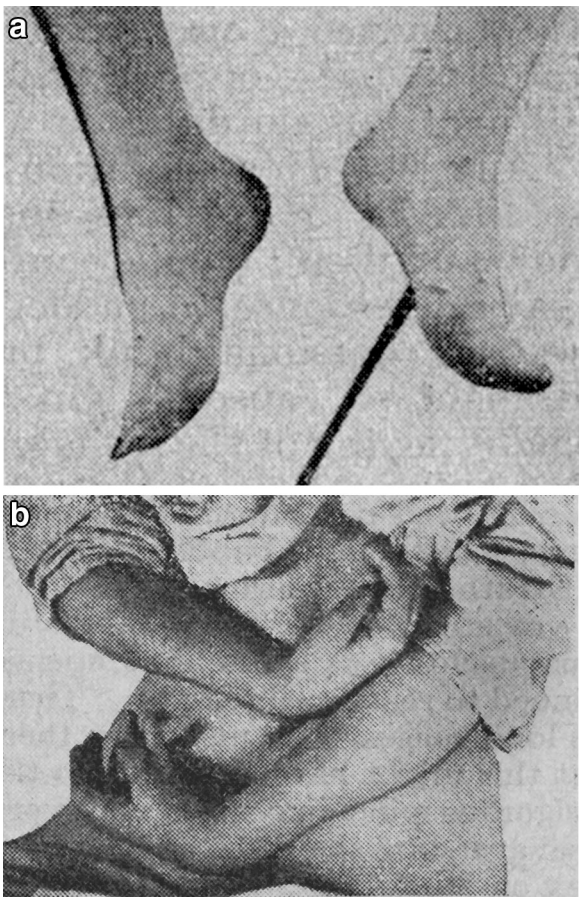

Fig. 2 Posturing and plantar response of a comatose patient after cardiopulmonary resuscitation, *Lancet*, Elsevier Publishing [10], used with permission

puncture showed normal pressure. She remained comatose. The case report describes a rather complete neurologic examination with examination of the cranial nerves, motor function, tone, and reflex pattern. The electroencephalography report showed very low voltage waves. In addition, at autopsy, many of the anterior horn cells were shrunken and stained darkly on the lumbar cord. The midbrain showed little abnormality, and the medulla and pons were also largely spared with a few shrunken cells. The Purkinje cells in the cerebellum were reduced in number with many empty baskets. The basal ganglia showed extensive and severe changes, particularly in the caudate nucleus and putamen. Great loss of pyramidal cells was also found in the cornu ammonis.

Conclusion

When the heart stops and cerebral blood flow is interrupted during a cardiac arrest, patients lose consciousness and may remain comatose after resumption of circulation. Such a global injury to the brain is understandably profound. When the standstill is unwitnessed by others or discovered much later, more than 2/3 of the patients die or remain comatose even after successful CPR. When the standstill is an unshockable rhythm, the outcome is even worse. Anoxia describes the complete lack of oxygen delivery; hypoxia describes what may occur during times of decreased oxygen delivery but with some degree of continued blood flow during resuscitation. Hypoxic brain injury—albeit less well-defined and less clearly understood than anoxic-ischemic injury from cardiac arrest—occurs in patients with respiratory arrest, severe hypoxemia (e.g., asphyxia) but no appreciable hypotension. Success of intervention in these conditions may be predicated on early correction of hypoxemia and critical blood pressure.

How long the brain can sustain injury from anoxic injury has remained unresolved; some patients, in the words of Kramer, went from "reanimation to deanimation" [11]. Others recovered even after brief periods of decerebration. Reflexive motor responses and abnormal brainstem reflexes remain key clinical findings in assessment of damaged brains after successful CPR. Both bench work and keen clinical observation resulted in understanding of the effects of marginal or no flow to the brain and to determine how long the brain could sustain injury from anoxic injury. This opened an interest in the brain's resilience to anoxia and anemia which yet has remained unresolved. Kouwenhoven, the father of cardiac resuscitation, showed blood flow during cardiac massage and sternal pressure in their dogs with ventricular fibrillation. This was encouraging, but they did not know how much was enough [12, 13].

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