The Isolated Monkey Brain: Operative Preparation and Design of Support Systems*

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MULTICELLULAR tissue aggregates and small whole organs have been successfully maintained in isolated viable states for intensive investigation. The pioneer work of Carrel and Lindberg in the 1940's first demonstrated the practicability of supporting these tissues for protracted periods of time via their own intrinsic vasculature, with the aid of artificial circulatory systems. Cerebral tissue, however, until very recently,24,25 has been maintained in a separated, living state only as small tissue explants,2 slices,13 or single cells;1 its nutrient support has been derived from the immersing media, but its normal mode of metabolic exchange across the blood-brain barrier has not been possible.

In spite of recent advances in the field of isolated organ preparation and perfusion technique,10,18 permitting sophisticated biochemical and physiological measurements under absolute control of environment,14,27 the brain has steadfastly resisted all surgical attempts to be prepared and supported as an isolated organ.

This state of affairs has existed for three reasons: 1) the complexity of the intracranial circulation and its innumerable anastomotic relationships; 2) the extreme dependence of brain tissue on an uninterrupted supply of oxygen and glucose; and 3) the surgical difficulty of isolating and removing the brain without seriously compromising the function of the total organism.

Previous attempts to study the metabolism and physiology of the isolated brain have utilized either isolated head preparations6,11,12 or in situ preparations in which the competing cephalic vasculature was eliminated by ligation6,10 or differential perfusion

Received for publication January 13, 1967.

* Presented at the meeting of the Harvey Cushing Society, April 21, 1964, in Los Angeles, California. Supported by U. S. Public Health Service Grant NB-08859.

pressure techniques.17 Unfortunately, in none of these biological models does the brain approach an isolated organ state. To produce a truly isolated organ, we have felt it mandatory for the circulation to enter and leave the brain through totally isolated vessels. In addition, we have insisted that all contiguous tissues competing with brain metabolism be ablated. These absolute requirements have necessitated the development of new operative methods and equipment.

In this first report, we describe in detail our operative technique for preparing the isolated monkey brain as well as the extracorporeal perfusion systems (donor and mechanical) that we use to maintain this biological model in a viable state. In a future report we shall present the metabolic and neurophysiological data derived from studies of the isolated monkey brain.

Operative Method

Monkeys were selected as the experimental subjects because previous work had suggested that the anastomotic associations within the extracranial circulation were limited and it was known that sufficient blood could be provided to brain through the posterior (vertebral-basilar) circulation.21 To reduce the length of surgery, small animals weighing 6 to 8 pounds were used.

Anesthesia was induced and continued throughout the procedure with intravenous Nembutal (25 mg/kg of body weight). Following careful shaving of the entire head, neck, and both groins, the head was placed in a fixation (orbital-oral) unit (Fig. 1) which provided three points of cranial contact including the roof of the mouth and both infraorbital ridges. A femoral artery and vein were cannulated with appropriately sized polyethylene catheters to monitor blood pressure and to provide for fluid and blood replacement. Each animal was wrapped in a...
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 thermo-regulated blanket to maintain an even temperature, which was continuously recorded via a rectal thermistor. EKG monitoring was accomplished with suitable limb leads.

Operative Procedure in the Ventrall Position. Initially, the monkey was positioned on its back on a light-weight, adjustable, miniature operating table with the head hyperextended by means of the orbital-oral fixation unit. The skin and subcutaneous tissues were incised in the midline from the manubrium to the angle of the jaw. The trachea was elevated into the wound and divided between large cotton ligatures after the insertion of a wire spiral endotracheal tube.

The following major operative steps were then performed:

1. All the anterior neck muscles including the strap muscles and the muscles immediately associated with the anterior and lateral surfaces of the cervical bodies were completely removed.

2. The severed trachea together with a ligated and divided esophagus were elevated as a single block of tissue, permitting removal of all muscles associated with the base of the skull including the pharyngeal structures, and permitting the ligation and removal of all components of the external carotid arteries and internal jugular veins.

3. The mandibular joint was exposed, and the tissues of the mouth were incised to provide direct communication from the oral cavity to the mandibular joint on each side.

Operative Procedure in the Dorsal Position. The monkey was next rotated onto its stomach and the scalp and tissues of the neck divided in the midline from the nasium to the spinous process of T-1. Six stainless steel paired electrodes were positioned extradurally in small openings in the skull in the frontal, parietal, and occipital areas. They were cemented in place with quick-setting dental acrylic (Fig. 2).

The following major operative steps were then performed:

1. All the tissues and muscles of the skull (temporalis muscles, etc.) and neck muscles associated with the spinous processes and lamina of the upper five cervical vertebrae were totally removed.

2. Both orbits were exenterated, and the fleshy components of the nasal and facial structures were sacrificed.

3. Large bilateral craniectomies were performed, leaving only a bony support for electrodes. In addition, the bone was totally removed from the posterior fossa, exposing the dura covering the cerebellum and lateral sinuses.

4. A generous laminectomy from C-1 through C-5 was accomplished with great care to avoid entering the vertebral venous sinuses (Fig. 3).

Second Operative Procedure in the Ventrall Position. The animal was again rotated onto its back, and following stabilization of arterial pressure, the ventral dissection was completed. The following steps were performed:

1. The lower jaw was removed, with careful control of the volume drainage from the veins associated with the cranial nerves in the base of the skull.

2. After heparinization (3 mg/kg of body weight) the common carotid arteries were cannulated with specially designed silicone coated metal "T" cannulae (Fig. 4). The cannulae were properly located in position by means of "stirrups" constructed from heavy malleable wire.

Second Operative Procedure in the Dorsal Position. The animal was then rotated onto its stomach, its final operative position, and the dorsal dissection and isolation completed. The carotid cannula system was connected to the extracorporeal perfusion system so that the preparation could be instantaneously transferred to extracorporeal perfusion. The isolation of the brain then was carried out as follows:

1. The spinal dura was opened wide in the midline, and with the Ferguson ligature car-