Role of cerebral arterial blood in the regulation of brain temperature in the monkey

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HAYWARD, JAMES N., AND MARY ANN BAKER. Role of cerebral arterial blood in the regulation of brain temperature in the monkey. Am. J. Physiol. 215(2): 389-403. 1968.—The major determinant of cerebral temperatures in the monkey is the temperature of the arterial blood perfusing the brain. We measured arterial blood temperatures in the aortic arch simultaneously with those at extracranial and intracranial sites in 10 chronic monkeys. Sequential thermal changes occurred in the central arterial blood, cerebral arterial blood, and in the brain during feeding, sleeping, arousal, and saline injections. Information about the thermal state of the body core is carried rapidly by the arterial blood to the thermoregulatory neural elements in the preoptic-anterior hypothalamic region of the brain. Manipulations which alter ventilation and the levels of carbon dioxide in the blood can change the tone of the cerebral vessels and cause a shift in cerebral blood flow. In our monkeys such shifts in the rate of flow of the cooler arterial blood through the warmer brain altered the convective heat transfer in the brain and predictably changed the brain blood temperature gradients. Our concept of the role of the cerebral arterial blood in homeothermy of the brain in the primate is applicable as a general approach to the study of brain temperature and temperature regulation in other mammals.

Regional cerebral temperatures in the homeotherm have been thought to be determined by local neural heat production, local blood flow, and the temperature of the arterial blood perfusing the brain (1, 7, 8, 32, 37). Several years ago when we first began to investigate brain temperature in unanesthetized monkeys, we found the temperature of the systemic arterial blood to be a major determinant of brain temperature (25). Using aortic arterial blood temperature as a steady thermal base line and as a common point of reference, we performed the series of experiments, reported here for the first time, on the effects of behavioral states and pharmacological agents on brain temperature at multiple cerebral sites. From these experiments the following view of homeo-thermy of the brain and thermoregulation in the primate derives. First, the cerebral arterial blood determines changes in brain temperature in the unanesthetized animal. Second, while the cerebral arterial blood is cooler than deep brain sites, temperatures tend to increase progressively toward the center of the brain. Third, the temperature gradient between the cerebral arterial blood and aortic arterial blood is of major importance for temperature regulation. Fourth, the shifts in temperature of the cerebral arterial blood are a sensitive index of autonomic adjustments in the behaving animal. Fifth, local changes in heat production and blood flow do not appear to contribute to thermal shifts in the brain of the unanesthetized animal.

Whatever we report here concerning brain temperature in the monkey we have found applicable to other mammalian species, once certain species' anatomical variances are taken into account. The type of vascular connection between the circle of Willis and the extracranial vessels is of primary importance. In the monkey and the rabbit the internal carotid artery provides a direct uninterrupted major vascular pathway from the intrathoracic vessels to the circle of Willis and the cerebral arterial blood is at the same temperature as systemic arterial blood in those species (3, 26). In the cat (4) and sheep (5), however, where the small vessels of the carotid rete allow heat exchange and cooling of the central arterial blood as it enters the circle of Willis, we found a dissociation between brain and body temperatures. In retrospect, we were most fortunate to have begun our studies on brain temperature in the monkey. When we turned our attention to other mammalian species (3–5, 21) we immediately recognized both the species differences and the common factors in mammalian brain temperature regulation.

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1 Some of these results have been reported at meetings of the American Association of Anatomists and the American Physiological Society and published in abstract form (18, 19).
METHODS

Sixteen adult female rhesus monkeys (Macaca mulatta) weighing 4–6 kg were used in these experiments. Each was trained to sit in a primate chair within a sound-attenuated chamber in which environmental temperature was maintained at 28–32 ± 0.5 °C, 30–50% relative humidity, with 12 hr of artificial daylight supplied by an overhead neon tube. The animals were fed a balanced diet of dry crackers (Chimcrackers, Old Mother Hubbard, Inc.) supplemented with fresh fruit, vegetables, and vitamin C, and with access to water at all times.

Each trained animal was anesthetized with pentobarbital (35 mg/kg) in order that a Lucite platform could be fixed by sterile operative technique to its head with four stainless steel Sheatz screws (39). In eight animals this platform replaced the scalp over the cranial vault (23). In the remaining eight, the hair-bearing scalp was left intact and the Lucite platform was suspended above the skull by four vertical Lucite posts, thus maintaining nearly normal ventilation over the entire head. The addition of front, back, and side pieces of perforated Lucite to this elevated platform kept the monkey from removing any of the thermocouples or cannulae that ran between the skin and the platform. Fine holes were drilled in the platform and skull with a stereotaxic drill, and glass-enclosed thermocouples (o.d., 0.8 mm) and bipolar concentric stainless steel insulated electrodes (o.d., 4 mm) were implanted in deep brain arcs using the stereotaxic coordinates of Olszewski (33). Other thermocouples sealed in polyethylene tubing (o.d., 0.6 mm) were threaded both under the scalp and through T slits in the skull into the subarachnoid space and superficial cerebral cortex. Two or three junctions were fixed in the same glass or polyethylene tube for measurements of temperatures at different vertical levels in the same frontal plane or at different distances along the subarachnoid space. These serial junctions allowed evaluation of thermal conduction along the wires as well as serial tissue thermal gradients. In eight animals thermocouples in polyethylene tubing were passed through a branch of the external carotid artery. In the remaining eight animals thermocouples went from the common carotid artery into the arch of the aorta without occluding the flow of the blood in the internal carotid. In some animals polyethylene-enclosed thermocouples were threaded up the internal jugular vein to the superior jugular bulb or down the internal jugular vein to the right atrium. Epidural silver ball electrodes were implanted over the biparietal or bifrontal cerebral cortex. Insulated stainless steel wires with bared tips were fixed in the periorbital cone rubber cannulae (Becton-Dickinson Co., o.d., 1.6 mm) were introduced into the right atrium through the right internal jugular vein and into the aortic arch (o.d., 1.2 mm) through the common carotid artery and fixed in situ. Lead wires and cannulae were threaded under the skin of the neck and head and attached to brass connector pins (EEG, EM), miniature copper-constantan plugs (temperature, Thermoelectric Co., Nr. MSJ-TX), and hypodermic needles (blood pressure and venous cannulae) capped with Luer-Lok rubber diaphragm connectors (2). All of these were cemented to the Lucite platform on the skull. Postoperatively the monkeys were treated with either penicillin, streptomycin, or chloromycetin for 3 days and allowed 1–2 weeks of trauma-free recovery time. All measurements were made on healthy, afecrile monkeys eating and drinking at a preoperative level.

An Offner type-R ink-writing oscillograph provided continuous and simultaneous EEG, EM, temperature, and blood pressure records. Thermocouples were made from enameled arc-welded 100-μ copper-constantan wires (38 gauge, Sigmauul Colun Cypa,) for small probes and minimal conduction. Thermopotentials were amplified with a chopper-stabilized d-c amplifier. A distilled water-crushed ice reference junction was used. This recording system had a response time of less than 1 sec for 90% deflection and a maximum sensitivity of 0.25 C/cm. Thermocouples were calibrated over the expected temperature range against a Bureau of Standards thermometer in a 38 C constant-temperature bath. The overall accuracy of the thermocouples after calibration was ±0.05 C. All values in this paper will be expressed as the mean, to be followed by the range and the number of experiments in parentheses.

In eight of these chronically prepared animals, at repeated weekly intervals of several hours each and in an environmental chamber at 35 C, the trachea was intubated through the mouth with a soft plastic tube (without a pressure cuff) and ventilation controlled with a Harvard pump at 20–25/min with the end-expired CO2 adjusted to 4–5%. A rapidly acting infrared CO2 analyzer (Goddart, Copenhagen), calibrated against gases of known chemical composition, was used to determine end-expired CO2. Gallamine triethiodide (Flaxedil, American Cyanamid Co., 3–8 mg/kg) and pentobarbital sodium (5–10 mg/kg) were given to obtain full respiratory control. The immobilized monkey was comfortably positioned and padded with towels on top of a table in the environmental chamber with lubricating ointment on the conjunctival sacs and the eyelids closed. These animals were exposed to gases of different compositions from a Douglas bag with gas flow through the respiratory pump.

At termination of the experiments the animals were placed under pentobarbital anesthesia, their hearts perfused first with saline and then with 10% formal saline. Thermocouple and electrode positions were determined by gross inspection and microscopic examination of serial sections of frozen tissue which had been cut at 80 μ and stained with thionin.

RESULTS

We compared the temperature of the arterial blood at the aortic arch in 16 monkeys with temperatures at 29 other sites located within the arteries, veins, right atrium,
BRAIN TEMPERATURE AND THE ARTERIAL BLOOD

TABLE 1. Intracranial and extracranial temperatures in the monkey

<table>
<thead>
<tr>
<th>Site</th>
<th>(T_x - T_d)</th>
<th>Range</th>
<th>No. Exp</th>
<th>No. Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central arterial blood</td>
<td>0.00</td>
<td>-0.03-0.03</td>
<td>31</td>
<td>7</td>
</tr>
<tr>
<td>Cerebral arterial blood</td>
<td>0.09</td>
<td>-0.03-0.07</td>
<td>40</td>
<td>4</td>
</tr>
<tr>
<td>Venous blood, rt atrium</td>
<td>-0.09</td>
<td>-0.40-0.01</td>
<td>32</td>
<td>5</td>
</tr>
<tr>
<td>Racket</td>
<td>0.10</td>
<td>0.00-0.35</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Esophagus, stomach</td>
<td>0.03</td>
<td>-0.10-0.25</td>
<td>31</td>
<td>5</td>
</tr>
<tr>
<td>Precentral muscle, cervical</td>
<td>0.12</td>
<td>0.09-0.15</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Subcutaneous scalp</td>
<td>0.45</td>
<td>1.40-0.32</td>
<td>102</td>
<td>18</td>
</tr>
<tr>
<td>Subcutaneous car pinna</td>
<td>-2.30</td>
<td>-7.00-1.00</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>Ventral hypothalamus (4-4 mm)</td>
<td>0.27</td>
<td>0.15-0.39</td>
<td>136</td>
<td>15</td>
</tr>
<tr>
<td>Dorsal hypothalamus (5-8 mm)</td>
<td>0.40</td>
<td>0.33-0.50</td>
<td>43</td>
<td>5</td>
</tr>
<tr>
<td>Midbrain tegmentum</td>
<td>0.50</td>
<td>0.40-0.63</td>
<td>81</td>
<td>8</td>
</tr>
<tr>
<td>Inferior colliculus</td>
<td>0.50</td>
<td>0.26-0.39</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Pontine reticular formation</td>
<td>0.44</td>
<td>0.37-0.52</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Thalamus</td>
<td>0.43</td>
<td>0.36-0.50</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Superficial cortex and white matter (1-3 mm)</td>
<td>0.10</td>
<td>0.00-0.20</td>
<td>49</td>
<td>5</td>
</tr>
<tr>
<td>Deep cortex and white matter (4-3 mm)</td>
<td>0.27</td>
<td>0.15-0.42</td>
<td>54</td>
<td>6</td>
</tr>
<tr>
<td>Lateral deep subcortical white matter (lat 8-10 mm, 6-12 mm deep)</td>
<td>0.50</td>
<td>0.36-0.65</td>
<td>53</td>
<td>7</td>
</tr>
<tr>
<td>Intact scalp</td>
<td>0.24</td>
<td>-0.60-0.38</td>
<td>34</td>
<td>3</td>
</tr>
<tr>
<td>Scalp replaced</td>
<td>0.40</td>
<td>0.99-0.57</td>
<td>70</td>
<td>10</td>
</tr>
<tr>
<td>Parasagittal deep subcortical white matter (lat 0-4 mm, 6-12 mm deep)</td>
<td>0.53</td>
<td>0.36-0.68</td>
<td>68</td>
<td>10</td>
</tr>
<tr>
<td>Basal ganglia, internal capsule</td>
<td>0.34</td>
<td>0.18-0.48</td>
<td>79</td>
<td>8</td>
</tr>
<tr>
<td>Hippocampus, amygdala</td>
<td>0.02</td>
<td>-0.12-0.15</td>
<td>49</td>
<td>11</td>
</tr>
</tbody>
</table>

* At an ambient temperature of 28-32 C.  † Ex vivo arterial blood samples were used.  ‡ Extreme upper and lower values observed.  § Number of experiments, each number representing a separate experiment.

Intravascular Temperatures

Arterial sites. Temperatures of the arterial blood at the arch of the aorta was studied in 16 monkeys and proved to be a rapidly changing, sensitive measure of the mean temperature of the blood. The simultaneous comparison of intrathoracic arterial blood with 12 other sites in the arterial system at the aortic arch, common carotid, basilar artery, anterior cerebral artery, and abdominal aorta revealed nearly identical absolute temperatures (Table 1 and Fig. 1), with similar oscillations and "thermal inertia." From these intra-arterial studies we conclude that after the mixed arterial blood is ejected from the heart its temperature tends to remain steady, with little heat transfer occurring on the way to sites as distant as the anterior cerebral artery, the basilar artery, or the abdominal aorta.

Venous sites. A comparison of brain and arterial blood temperatures in seven monkeys with eight sites in the intracranial and extracranial temperatures revealed wide variations in steady-state temperatures of the venous blood (Table 1, Fig. 1). During feeding and sleeping, the changes in venous temperature usually did not parallel the changes in arterial blood and brain temperatures (Fig. 1). While measurements in the right atrium did indicate thermal oscillations due to respiratory and cardiac cycles as well as the fastest shifts in blood temperature during feeding, sleeping, and arousal, these changes were too unpredictable and varied to be used as a reliable baseline reference in the study of cerebral temperature.

FIG. 1. Brain cooling during feeding. Air 30 C. Animal rapidly fills cheek pouches in 4 min, as shown by arrows, with two 70-g bananas chilled to 2 C, and then eats them. Note the cooling of right atrial venous blood to a maximal level 0.28 C below that of arterial blood, followed subsequently by return to control A-V thermal relationships. Thermal inertia lag in both magnitude of response and time of peak response is seen in two brain sites and under the scalp. Venous blood cools by 1.4 C in 6 min; arterial blood 1.12 C in 6 min; ventral blood 0.96 C in 7.5 min; RA, right atrium; SC, subcutaneous tissue of frontal scalp.

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Extravascular Temperatures

In nine monkeys temperature in nine sites in the rectum, esophagus, stomach, and cervical prevertebral muscle were compared with simultaneously measured brain and arterial blood temperatures (Table 1). These extravascular locations were warmer than the moving blood stream and showed a variety of independent local thermal shifts. In several instances, both rectal and esophageal temperatures changed over several hours to levels either warmer or cooler than arterial blood, although blood-brain thermal relationships remained steady.

Thermal Effects of Feeding

Thirty experiments were performed in seven monkeys to determine a physiological basis for the effects of feeding on brain temperature (14). Given a banana, a hungry monkey quickly stuffs its cheek pouches full, chews, and swallows this food at its leisure. This type of behavior can provide an abrupt transfer of heat by conduction between the food and the mouth of the monkey, with rapid cooling of the blood even before the food is swallowed. Ingestion of two cold bananas (each 70 g chilled to 5°C) over a 5-min period produced a mean drop of 0.8°C in all brain sites (Fig. 1) with a maximal rate of fall in eight experiments. Two neutral bananas (34°C) caused no consistent change in brain temperature in four experiments. Filling the cheek pouches and eating two warm bananas (40°C) caused a mean rise in brain temperatures of 0.2°C in four experiments. Simultaneous measurement of temperature of venous blood in the right atrium and of arterial blood in the aorta also showed warming and cooling during feeding (Fig. 1). Within 20 sec after the monkey began to fill its cheek pouches with 5°C bananas, the right atrial blood began to cool, and within 30 sec, arterial blood temperature dropped. Not until 40-70 sec after ingestion did brain sites begin to cool. The peak right atrial temperature drop was 0.2-0.3°C greater than that measured in the arterial blood in three experiments (Fig. 1), but both of these cooling curves reached their low points at about the same time. In five experiments arterial blood cooled 0.1-0.2°C more than three deep brain sites, and maximal rate of fall being 0.2°C/min. The extracerebral nonvascular tissues showed the most thermal lag following feeding. For example note the subcutaneous tissue of the scalp in Fig. 1 where there was a 4-5 min time lag in comparison to the response of the arterial blood. Brain and blood temperatures usually returned to control levels within 30 min following eating. There was no persistent change in the difference in temperature between blood and brain.

Thermal Correlates of Sleep-Walking Cycles

The resting monkey, isolated in a lighted, sound attenuated chamber at 28-32°C, alternates brief episodes of slow sleep which are associated with hypothalamic cooling with episodes of arousal which are associated with hypothalamic warming (Fig. 2) (14, 13). As we noted in a preliminary report (26), these cyclic hypothalamic temperature changes that occur throughout the brain and in extracerebral tissues are the direct result of arterial blood temperature changes. In the present studies we found that similar thermal shifts were also directly related to cooling and warming in the venous blood in the right atrium and to inverse thermal shifts on the skin of the ear (15). During 20 experiments on four monkeys at 30°C air temperature in 10 episodes of drowsiness, skin temperatures rose by 3°C, blood cooled by 0.3°C, and the hypothalamus cooled 0.2°C. Four episodes of "spontaneous" arousal were accompanied by ear pinna cooling of 4.5°C, blood and brain warming of 0.2°C and 0.15°C, respectively.

In four experiments in one monkey, shifts in the baseline temperature at the external nasal meatus were inversely related to shifts in blood and brain temperatures and directly correlated with sleep-waking cycles. In an air temperature of 32°C and a relative humidity of 30%, a nasal thermocouple recorded the oscillations of the respiratory cycle as well as the basal temperature at this site (Fig. 2). During waking the respiratory rate was 30/min with a half-cycle (inspiratory or expiratory) excursion of 2°C. With the onset of drowsiness this respiratory rate dropped to 24/min, half cycle temperature fell to 1°C, and the base-line temperature rose 2°C over 5 min. After the initial 1°C warming at the nose and
about 30 sec after the onset of sleep, the arterial blood and the brain began to cool to a peak level of about 0.3 C in 5 min. Arousal was signalled by a reversal of these thermal events, with cooling at the nose and warming of the blood, hypothalamus, and other brain sites. During eight episodes of drowsiness and sleep, the nasal temperature rose 1.8 C over 3.5 min; blood cooled 0.3 C over 4.6 min; the hypothalamus cooled 0.15 C in 5 min. During five episodes of arousal, nasal temperatures fell 1.6 C in 4 min, while the blood rose 0.2 C in 4.4 min and the hypothalamus warmed by 0.15 C in 5 min. During periods of sudden change in the level of illumination in the chamber (lights-off or lights-on) or during episodes of induced arousal, the respiratory rate changed from 20–25/min to 30–40/min without any consistent change in base-line temperature in the nose, blood, or brain. Cooling the chamber from 32–20 C eliminated this cyclic nasal and blood oscillation completely, even though sleep-waking cycles persisted.

Visual stimuli By opening the chamber door and confronting the monkey, we produced a rapid rise in blood and hypothalamic temperatures of 0.2–0.3 C in 3–5 min at a rate of 0.06 C/min, which returned rapidly to base line when we closed the door. Turning off the lights during the day (10 AM–2 PM), we found we could elicit several different responses, such as a rise, a fall, or no change in blood and brain temperatures. On two occasions, mid-afternoon darkness produced blood cooling of 0.25 and 0.3 C in 60 and 90 min, respectively, at a rate of 0.004 C/min.

Cyclic patterns of sleep behavior, EEG, and hypothalamic and rectal temperature in the monkey have been described by other workers (11, 14, 15, 27, 34, 42). In our calm, trained monkeys conditioned to expect the lights to be shut off automatically at 6 PM, the abrupt onset of darkness at this time was followed by a predictable sequence of events. Initially, there was some increased eye movements, perhaps even a slight rise in blood temperature and low-voltage EEG. Within 2–3 min after the onset of darkness, temperatures of the ear increased, venous blood cooled rapidly, to be followed in seconds by a falling arterial blood temperature, and seconds to minutes later by cooling of the various brain sites. Detailed analysis of these rapidly changing initial thermal events required a faster time base than was required for the studies shown in Fig. 3. During 17 all-night studies in four monkeys, blood and brain temperatures fell in a parallel manner from about 38.5 C just prior to light out at 6 PM, to a low of 37.1 C at 5 AM in the dark, for an over-all cooling of around 1.4 C. Brain and blood cooling occurs in two phases: first, after the onset of darkness, there is an initial rapid temperature drop for 15–30 min at rates of up to 0.07 C/min. This accounts for about 60% of the nocturnal temperature change and is associated with continuous eye movements, low-voltage EEG, and continued blood oscillations (Fig. 3). Thus there is a dissociation between these thermoregulatory events and the EEG and behavioral signs of the onset of sleep. This initial phase is followed by a slower degree of blood and brain cooling for the remaining 11.5 hr of nocturnal darkness, at the rate of 0.007 C/min, accounting for the rest of the total diurnal cooling and associated with absent or greatly diminished eye movements, high-voltage EEG, and absence of blood oscillations (Fig. 3).

During several all-night experiments in two monkeys, repeated 2– to 10-min bursts of eye movement, lower voltage EEG, and 0.1–0.15 C elevations of brain and blood temperature occurred about every 20 min from midnight to 6 AM in the dark. These thermal changes with apparent paradoxical sleep in the monkey were less marked than those we observed in other species (3–5). If, after 2–4 hr of slow sleep in the dark and with blood cooling of about 1.3 C, we turn the lights on and open the chamber door, the blood and brain temperatures in the monkey rise rapidly at a maximal rate of 0.07 C/min with return toward control daytime levels in 10–15 min. If we failed to turn off the lights at 6 PM the monkey's brain and blood cooled slowly and steadily at a rate of approximately 0.002 C/min during the first 2 hr (30% of total drop) and at a rate of about 0.005 C/min (70% of total drop) during the last 9 hr of the lighted night, with an over-all cooling of 1 C. There was no evidence of consistent change in the brain-blood temperature gradients between daytime and night-time studies on 10 monkeys over 64 experiments.

**Fig. 3.** Visual triggering of brain cooling preceding sleep. Air 30 C, 6 PM. Arrow lights out. Note the initial few minutes of rise (0.1 C) in blood and brain temperatures followed by first, a 10- to 15-min precipitous drop in blood and brain temperatures at the rate of 0.07 C/min in the presence of eye movements, blood oscillations, and lower voltage EEG; and second, by a slower rate of cooling at the rate of 0.007 C/min in the absence of eye movements and with a higher voltage EEG. Brain temperatures parallel the blood without significant changes except during the rapid downward shift with some thermoregulation of the brain. Abbreviations: EEG, biparietal electroencephalogram; EM, eye movements; OC, occipital subcortical white matter; AH, ventral hypothalamus, mid-III ventricle; FC, deep frontal cortex; otherwise the same as in previous figures.
Deep cerebral temperatures in the unanesthetized monkey were warmer than the arterial blood perfusing the brain. Thermal shifts in the brain were preceded by similar changes in the arterial blood during feeding (Fig. 1), sleeping (Figs. 2 and 3), and arousal. The exact determination of brain-blood temperature differences (\(T_b - T_a\)) was made only after several minutes of steady blood temperatures in order to avoid the effects of thermal inertia at deep brain sites (Figs. 1–3). The use of the freely flowing aortic arterial blood as a common-thermal base line is contingent upon the absence of thermal gradients in the arterial blood as it travels from the aortic arch to the intracranial vessels. A clotted arterial reference site (Table 2) or an environmental heat sink (see later discussion of the scalp) can disturb the normal brain-blood temperature gradients.

In over 300 experiments at 100 intracranial sites in 16 unanesthetized monkeys, we found continuous gradients of increasing temperature from the subarachnoid space to the central regions of the cerebral hemispheres and the brain stem (Table 1, Fig. 1). The temperature of the subarachnoid space over the cerebral cortex, in the basal

**Table 2. Thermal-dilution curves in three monkeys**

<table>
<thead>
<tr>
<th>Anatomical Location (No.)</th>
<th>(T_x - T_{ac} ) °C</th>
<th>(\Delta T ) (Range), °C</th>
<th>(\Delta S ) (Range), sec</th>
<th>No. of Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial blood-aortic arch (3)</td>
<td>0.25</td>
<td>(0.5-1.0)</td>
<td>(15-40)</td>
<td>62</td>
</tr>
<tr>
<td>Clotted blood-common carotid (1)</td>
<td>0.25</td>
<td>0.24</td>
<td>36</td>
<td>1</td>
</tr>
<tr>
<td>Inferior colliculus (1)</td>
<td>0.30</td>
<td>0.27</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>Ventral hypothalamus (1)</td>
<td>0.97</td>
<td>(0.20-0.29)</td>
<td>(24-38)</td>
<td>4</td>
</tr>
<tr>
<td>Dorsal hypothalamus (2)</td>
<td>0.40</td>
<td>0.20</td>
<td>62</td>
<td>14</td>
</tr>
<tr>
<td>Amygdala-medial, lateral (6)</td>
<td>0.30</td>
<td>(0.10-0.28)</td>
<td>(36-120)</td>
<td>30</td>
</tr>
<tr>
<td>Parasagittal white matter (6)</td>
<td>0.40</td>
<td>(0.10-0.28)</td>
<td>(24-132)</td>
<td>29</td>
</tr>
<tr>
<td>Midbrain reticular formation (2)</td>
<td>0.48</td>
<td>0.16</td>
<td>70</td>
<td>12</td>
</tr>
<tr>
<td>Globus pallidus (5)</td>
<td>0.50</td>
<td>0.16</td>
<td>96</td>
<td>21</td>
</tr>
<tr>
<td>Rectum, 13 cm (3)</td>
<td>0.10</td>
<td>0.12</td>
<td>106</td>
<td>11</td>
</tr>
<tr>
<td>Subcutaneous scalp (3)</td>
<td>-0.29</td>
<td>0.04</td>
<td>125</td>
<td>24</td>
</tr>
<tr>
<td>Cerebral cortex (1)</td>
<td>0.10</td>
<td>(0.03-0.13)</td>
<td>(48-200)</td>
<td>4</td>
</tr>
<tr>
<td>Cerebral cortex (2)</td>
<td>0.14</td>
<td>0.17</td>
<td>39</td>
<td>17</td>
</tr>
<tr>
<td>Subarachnoid space (5)</td>
<td>0.00</td>
<td>0.16</td>
<td>(20-28)</td>
<td>28</td>
</tr>
</tbody>
</table>

* All cold saline injections reported in this table were standardized: 10 ml of 5% isotonic saline intra-atrially in 20 sec, at ambient temperatures of 28–32 °C.  

Cerebral hemispheres. The superficial levels of the cerebral hemispheres (1–3 mm deep) at two frontal and three temporal sites in two monkeys were warmer than the arterial blood by 0.1 °C. At deeper levels (4–5 mm deep) in the frontal, parietal, temporal, and occipital regions in five monkeys, temperatures were 0.27 °C warmer than the incoming arterial blood. Further into the lateral subcortical white matter (6–12 mm deep and lateral 8–10 mm) under an intact scalp, seven sites in four monkeys were 0.5 °C warmer than the blood. Parasagittal subcortical sites (6–12 mm deep and lateral 0–4 mm) in the corpus callosum and lateral ventricles in proximity to anterior cerebral arteries in five monkeys were 0.4 °C above the blood (Fig. 5). Central locations in the nuclear masses of the cerebral hemispheres in the globus pallidus (six sites), putamen (one site), and head of the caudate (one site) in five monkeys were about 0.5 °C warmer than the arterial blood. In two animals the internal capsule between upper caudate and putamen was 0.6 °C warmer than the blood. The basal hemispheric structures in four monkeys were 0.35 °C above the arterial blood temperatures including eight sites in medial and lateral amygdala, uncus of hippocampus, and deep temporal lobe. A complete listing of mean temperatures, range of measurements, and anatomical locations is found in Table 1 and Fig. 4.
while the most rapid response in a deep brain site was in the inferior colliculus with a 0.27°C cooling in 36 sec. Generally, there was an inverse relationship between the degree of warmth of a particular deep brain site above the blood and the speed and amount of heat transfer. The most rapid cooling obtained in all the intracraniac sites in these three monkeys was in the cerebral cortex adjacent to a cortical arteriole with roughly 50% of the aortic blood cooling response and only a 5-sec greater delay (Table 2).

Role of Air Temperature and the Scalp in Homeothermy of the Brain

We found that shifts in air temperature from 5–7°C on either side of the neutral zone (28–32°C) could increase or decrease the temperature difference between superficial cerebral sites with arterial blood. As noted in a preliminary report (18) and as shown in Fig. 6, environmental temperature can influence intracranial temperatures.

Deep brain sites with intact scalp. In five experiments in four monkeys with elevated platforms measurements at the basal subarachnoid space were at the level of arterial blood temperature. Ventral regions of the hypothalamus (1–4 mm deep) at 15 sites in 14 monkeys, as far rostrally as the preoptic-septal region and as far caudally as the mammillary bodies, were 0.27°C warmer than the blood. Five dorsal hypothalamic sites (5–8 mm deep) in five monkeys were 0.4°C warmer than the arterial blood. Two sites in the thalamus (lateral geniculate and pulvinar) were 0.4°C above blood temperature levels. More caudally in the central brain stem in the midbrain reticular formation at eight sites in eight monkeys, temperatures were 0.5°C above arterial blood.

Brain Cooling After Intravenous Cold Saline

In 148 experiments in nine monkeys we used a standard thermal-dilution test with intra-arterial cold saline while measurements of the degree (°C) and speed (sec) of cooling were made simultaneously in the arterial blood, the brain, and in other body sites (Table 2). A 20-sec bolus injection of 10 ml of chilled (5°C) isotonic saline into the right atrium was chosen as a standard test for evaluation of convective heat transfer at 41 sites in 110 experiments in three monkeys (Table 2, Fig. 5). Arterial blood cooled 0.8°C in 22 sec
four lateral subcortical sites (6–12 mm deep), the control gradients between brain and blood of 0.45 C at air temperature of 30 C were decreased by 0.23 C at air temperature of 20 C and further dropped toward the blood by 0.32 C at air temperature of 10 C. Air warming to 40 C increased these brain-blood temperature gradients by 0.13 C. Rather similar and parallel cooling and warming of the subcutaneous tissues of the frontal scalp occurred.

Deep brain sites with scalp replaced. We first recognized the importance of an intact scalp for homeothermy of the brain during our experiments with eight monkeys in which the scalp was replaced with a Lucite platform cemented to the cranial periosteum (23). In these animals, air temperatures of 20–23 C caused cooling 6–8 mm deep in the subcortical structures to as much as 0.4 C cooler than the blood (control values 0.3 C warmer than the blood), although neither blood nor hypothalamic sites were affected.

Superficial brain sites with intact scalp. To eliminate the possibility of direct conductive effects of extreme air temperatures along thermocouple wires, which in model experiments indicated was limited to a maximum of 0.05 C for 10 mm distance under these physiological conditions, polyethylene-enclosed thermocouples were threaded 30–50 mm subdurally into the superficial cortex and the subarachnoid space through occipital T slits. At five sites 4–5 mm deep in the brain in four monkeys at 30 C air temperature, temperature gradients with the arterial blood were 0.25 C. Air cooling to 20 C resulted in cooling of these cortical sites with a decrease in the temperature difference with the arterial blood by 0.15 C. At 10 C air temperature, further cooling of the brain resulted in an over-all decrease of the temperature gradients with the blood of 0.22 C, with these sites just slightly above the arterial blood temperature (see control values given earlier). In heated air at 40 C, these five 4- to 5-mm-deep subcortical sites exceeded control (30 C air temperature) levels by a temperature difference of 0.1 C. Five locations in the subarachnoid space over the cerebral cortex of two monkeys had control temperatures just above the arterial blood at 0.02 C in air temperature of 32 C. Environmental cooling to 20 C cooled the scalp and cooled these subarachnoid sites well below the arterial by 0.25 C (Fig. 6). These sites in the cerebrospinal fluid of the subarachnoid space were located at the basal temporal lobe, temporal pole, and orbital surface of the frontal lobe as shown in Fig. 6. Deeper brain sites in the hypothalamus, midbrain reticular formation, and middle of the cerebral hemispheres, as well as the arterial blood, were unaffected by this amount of environmental cooling. The specialized role of the scalp and its profuse blood supply for thermal protection of the brain has been suggested in studies of man (12).

**Thermal Effects of Anesthesia on the Brain**

We performed 40 experiments on 11 monkeys under barbiturate anesthesia in order to test the hypothesis that the temperature difference between the cooler arterial blood and the warmer brain sites results in part from the algebraic sum of heat produced from neural metabolism and heat cleared by cerebral blood flow.

Cool air. In an air temperature of 20–25 C in 15 experiments in five monkeys, administration of graded doses of sodium pentobarbital into the right atrium produced three phases of blood cooling. At the lowest dosage range of 5 mg/kg in six experiments, the blood cooled by 0.8 C. A larger amount of pentobarbital of 15 mg/kg in two experiments resulted in blood cooling of 1.5 C. Peak dosage of 45 mg/kg in six experiments caused 3.2 C cooling of arterial blood. Plummeting blood temperatures were associated with abolition of spontaneous thermal oscillations. Brain temperatures followed the blood almost immediately, with slightly greater cooling and narrowing of the brain-blood thermal gradients. During the experiment shown in Fig. 7, repeated doses of barbiturate were administered continuously over a 2- to 3-hr period in order to maintain an isoelectric EEG and mean blood cooling of 3.3 C. Four brain sites cooled
0.3 °C toward the arterial blood temperature (decrease in $T_b-T_a$) after anesthesia. The depressant effect of barbiturates on the hypothalamus and the disruption of autonomic outflows for maintenance of body temperature are well known (38, 41).

Warm air. The question of whether these selective decreases in brain-blood temperature gradients ($T_b-T_a$) were due to scalp cooling (19), blood cooling, or intracerebral changes in blood flow (29, 31, 40) or heat production (10, 30) could not be answered conclusively from this data alone. Therefore, 14 experiments were performed on seven monkeys at an air temperature of 35 °C. Under these conditions (Fig. 8), barbiturate (24-30 mg/kg) produces an isoelectric EEG, abolishes arterial blood temperature oscillations without significant change in blood or scalp temperature levels, and selectively cools the brain. In five experiments, brain temperature in nine brain areas dropped toward the blood temperature by 0.22 °C or a mean drop from the control $T_b-T_a$ pressure lowered; still brain temperatures were not affected (Fig. 9).

**Thermal Effects of Carbon Dioxide on the Brain**

Cerebral cooling under barbiturate anesthesia in the spontaneously breathing monkey appeared to be the result of respiratory depression and increased heat removal from the elevated cerebral blood flow secondary to hypercapnia and hypoxia (29, 38, 40). These doses of barbiturate anesthesia may also depress oxygen consumption and neuronal metabolic heat production in the brain (10, 29), yet our thermal method detected no change in brain-blood temperature difference during controlled ventilation. This suggests that deep barbiturate anesthesia produces a parallel depression of heat production and heat removal in cerebral tissues with no net change in the thermal balance. In order to examine the effects of carbon dioxide at more normal levels of cerebral heat production, we performed 53 experiments on eight chronic monkeys under controlled ventilation. We observed 23 hypercapnic periods, ranging from 10-60 min in length, of inhalation of 8-10% carbon dioxide in air, and 10 hypocapnic periods, each 10 min long, of hyperventilation to an end expired CO₂ level of 1-2%.
<table>
<thead>
<tr>
<th>Anatomical Location</th>
<th>Control (T_{b,c} \ (^\circ\text{C}))</th>
<th>Pentobarbital Na (\Delta(T_{b} - T_{a}, ^\circ\text{C}))</th>
<th>Hypercapnia (8-10% CO(<em>2)) (\Delta(T</em>{b} - T_{a}, ^\circ\text{C}))</th>
<th>Hypocapnia (1-2% CO(<em>2)) (\Delta(T</em>{b} - T_{a}, ^\circ\text{C}))</th>
<th>Limbic Lobe Stimulation With Apnea (\Delta(T_{b} - T_{a}, ^\circ\text{C}))</th>
<th>Cessation of Cerebral Blood Flow (\Delta(T_{b} - T_{a}, ^\circ\text{C}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventral hypothalamus</td>
<td>0.27 (0.25-0.30, N = 5)</td>
<td>0.13 (0.10-0.18, N = 11)</td>
<td>0.21 (0.13-0.24, N = 2)</td>
<td>0.15 (0.08-0.22, N = 2)</td>
<td>-0.20 (0.14-0.28, N = 2)</td>
<td>0.28 (0.25-0.32, N = 5, 30-50 C)</td>
</tr>
<tr>
<td>Dorsal hypothalamus</td>
<td>0.40 (0.28-0.50, N = 5)</td>
<td>0.26 (0.20-0.34, N = 10)</td>
<td>0.20 (0.12-0.31, N = 2)</td>
<td>0.20 (0.14-0.28, N = 2)</td>
<td>-0.26 (0.19-0.36, N = 2)</td>
<td>0.10 (0.23-0.35, N = 4, 35-50 C)</td>
</tr>
<tr>
<td>Midbrain reticular formation</td>
<td>0.50 (0.22-0.60, N = 5)</td>
<td>0.30 (0.20-0.43, N = 10)</td>
<td>0.30 (0.10-0.46, N = 2)</td>
<td>0.30 (0.10-0.46, N = 2)</td>
<td>0.00 (0.16-0.44, N = 2)</td>
<td>0.00 (30-35 C, N = 3)</td>
</tr>
<tr>
<td>Lateral subcortical white matter</td>
<td>0.50 (0.20-0.44, N = 5)</td>
<td>-0.26 (0.10-0.46, N = 2)</td>
<td>0.20 (0.17-0.44, N = 2)</td>
<td>0.20 (0.17-0.44, N = 2)</td>
<td>-0.20 (0.14-0.28, N = 2)</td>
<td>0.10 (35 C)</td>
</tr>
<tr>
<td>Parasagittal subcortical region</td>
<td>0.40 (0.16-0.22, N = 5)</td>
<td>0.19 (0.25-0.30, N = 3)</td>
<td>0.14 (0.10-0.20, N = 10)</td>
<td>0.14 (0.10-0.20, N = 10)</td>
<td>0.10 (0.15-0.25, N = 10)</td>
<td>0.15 (35 C)</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>0.50 (0.16-0.33, N = 5)</td>
<td>0.34 (0.22-0.44, N = 35)</td>
<td>0.19 (0.12-0.25, N = 33)</td>
<td>0.19 (0.12-0.25, N = 33)</td>
<td>0.10 (0.15-0.25, N = 33)</td>
<td>0.15 (35 C)</td>
</tr>
<tr>
<td>Medial amygdala</td>
<td>0.27 (0.71-0.94, N = 5)</td>
<td>0.12 (0.71-0.94, N = 5)</td>
<td>0.25 (0.10-0.40, N = 2)</td>
<td>0.25 (0.10-0.40, N = 2)</td>
<td>0.10 (0.15-0.25, N = 33)</td>
<td>0.15 (35 C)</td>
</tr>
<tr>
<td>Lateral amygdala</td>
<td>0.40 (0.14-0.20, N = 5)</td>
<td>0.22 (0.14-0.20, N = 5)</td>
<td>0.25 (0.10-0.30, N = 2)</td>
<td>0.25 (0.10-0.30, N = 2)</td>
<td>0.10 (0.15-0.25, N = 33)</td>
<td>0.15 (35 C)</td>
</tr>
<tr>
<td>Deep cerebral cortex</td>
<td>0.28 (0.15-0.18, N = 5)</td>
<td>-0.16 (0.15-0.18, N = 5)</td>
<td>0.19 (0.14-0.20, N = 5)</td>
<td>0.19 (0.14-0.20, N = 5)</td>
<td>0.15 (0.15-0.25, N = 33)</td>
<td>0.15 (35 C)</td>
</tr>
<tr>
<td>Inferior colliculus</td>
<td>0.31 (0.01-0.16, N = 5)</td>
<td>-0.16 (0.01-0.16, N = 5)</td>
<td>0.19 (0.01-0.16, N = 5)</td>
<td>0.19 (0.01-0.16, N = 5)</td>
<td>0.15 (0.15-0.25, N = 33)</td>
<td>0.15 (35 C)</td>
</tr>
<tr>
<td>Pontine reticular formation</td>
<td>0.44 (0.15-0.18, N = 5)</td>
<td>-0.33 (0.25-0.30, N = 2)</td>
<td>0.19 (0.15-0.25, N = 2)</td>
<td>0.19 (0.15-0.25, N = 2)</td>
<td>0.15 (0.15-0.25, N = 33)</td>
<td>0.15 (35 C)</td>
</tr>
</tbody>
</table>

\[^*\] T\(_b\) - T\(_a\) is the temperature difference between the brain site and the arterial blood under control conditions. \[^{\dagger}\] \(\Delta(T_{b} - T_{a})\) is the change in this difference which occurred with the experimental maneuvers; a negative value indicates a narrowing of the brain-blood temperature gradient, while a positive value indicates a widening.

\[^{\ddagger}\] Temperatures in parentheses indicate the ambient temperatures at which these experiments were conducted; the remainder of the experiments were conducted at 35 C ambient temperature.
As described in our preliminary reports (19, 20), cerebral cooling occurred at all deep brain sites, beginning 1 min after onset of 8-10% CO₂ inhalation, reaching a low point in about 4 min, and continuing at this level for the duration of exposure, usually for 10 min (Fig. 10), but in some experiments up to an hour. When the animals returned to air breathing, their brain temperatures began to increase in 1 min and had returned to control levels by 7 min (Fig. 10). During 43 periods of hypercapnia the mean level of decrease in the brain-blood temperature gradients in eight cerebral regions was 0.27°C, or a drop of 69% in Tb-Ta (Table 3). While the absolute change in Tb-Ta for regional sites ranged from 0.18 to 0.34, the percentage change from control levels were all close to the mean value of 69%. In addition, we observed the following during hypercapnia: EEG aroused patterns, elevation of arterial blood pressure, scalp cooling, and accelerated clearance of a bolus injection of cold saline (Fig. 10). Deeper levels of anesthesia abolished many of these responses to CO₂ without changing the brain cooling effect.

Changing respiratory rates from 20 to 40/min caused the end-tidal CO₂ to fall below 2% and caused an increase in all brain-to-blood temperature differences, with some delay in cold saline heat transfer and a higher voltage EEG. The mean increase in the brain-blood temperature gradient in six cerebral regions was 0.2°C or 56% increase in Tb-Ta (Table 3).

**Thermal Effects of Limbic Stimulation on the Brain**

In order to test the effects of a change in ventilation on brain temperature in the unanesthetized, moving mon-
Key we chose electrical stimulation of the limbic lobe (13, 24). We performed 22 experiments on four chronic monkeys, using usual temperature as a sensitive measure of change in ventilation. Electrical stimulation of the basal nucleus of the amygdala and the stria terminalis for 50 individual periods in two monkeys produced inhibition of respiration and generalized cerebral cooling. Analysis of this cerebral cooling showed that it was due partly to cooling of the cerebral arterial blood and partly to an increased blood flow to the brain. There was narrowing of the temperature gradients between the brain and the blood.

Cool air. In an air temperature of 20-30°C, stimulation of these limbic sites produced apnea in inspiration, elevation of arterial blood pressure by 30-40 mm Hg, tachycardia or cardiac arrhythmia, rapid cooling of the arterial blood by 0.4°C, followed by a greater degree of brain cooling. Brain-blood temperature differences were decreased below prestimulus values. We observed that the rectal temperature was increased 0.12°C, the head and eyes turned upward and toward the side opposite the stimulus site, the animal vocalized, and there were EEG arousal patterns and an occasional afterdischarge. This generalized cooling of the brain at 20-30°C air temperature was dependent upon an interruption of ventilation and was apparently caused by two factors, blood cooling and increased cerebral blood flow secondary to the apnea (13, 29).

Warm air. Warming the environment to 35-40°C warmed the skin and eliminated any source of cool blood in the periphery. Under these circumstances limbic stimulation resulted in a mild 0.1°C warming of the arterial blood in contrast to the blood cooling which occurred at cooler air temperatures (Fig. 11). Cerebral cooling due to increased cerebral blood flow continued to be a response to apnea induced by limbic stimulation (Fig. 11, Table 3). Subthreshold stimulation of limbic structures without apnea failed to produce a change in brain temperatures. Pentobarbital sodium (10-15 mg/kg) abolished both the apnea and any thermal, vascular, or behavioral responses to limbic stimulation. Electrical excitation of three control sites in two monkeys in the globus pallidus and in the temporal horn of the lateral ventricle produced minor behavioral and EEG effects without change in ventilation, blood and brain temperatures, or blood pressure.

Thermal Effects of Cessation of Cerebral Blood Flow

An abrupt cessation of blood flow to the brain and scalp was produced in six chronic monkeys with elevated platforms by rapid intra-atrial infusion of a lethal dose (20-50 mg/kg) of thiopental sodium or pentobarbital sodium, thus eliminating arterial blood pressure and respiration (38). Two animals were breathing spontaneously and four were under controlled ventilation and endotracheal intubation when the lethal dose was given. In all six monkeys, 11 sites in four deep brain regions warmed by 0.28°C during the 5-8 min after circulatory arrest (Table 3, Fig. 12). The thermal changes of the more superficial cerebral sites and scalp during the first 10 min after death and all sites after 10 min depended upon environmental temperature. In four animals at air temperatures of 30-35°C, cessation of cerebral blood flow was associated with immediate parallel cooling of two sites in the subcutaneous tissue of the scalp and six brain sites in the lateral subcortical white matter and the deep cerebral cortex (Fig. 12, Table 3). After 10 min, deep brain sites also cooled at the same rates as scalp and superficial brain sites. In one dead monkey warming of the chamber from 30 to 50°C reversed this cranial cooling and returned all sites to control levels. Two other animals...
were studied at 45 and 50°C air temperature during barbiturate-induced circulatory and respiratory arrest. Both deep and superficial brain sites warmed during the initial 10 min after death, presumably because of the continued metabolic heat production without heat removal by the blood, while scalp temperatures remained steady (Table 3). At these higher air temperatures, there was little cooling throughout the head after this initial rise in brain temperature except for some mild cooling toward scalp levels. When the air was then cooled to 30–35°C first the scalp, and then superficial brain, and finally deep brain sites began to cool. Cranial structures cooled at mean rates of 0.07°C/min at 30°C air temperature, 0.05°C/min at 35°C air temperature, and not at all at 45 50°C air temperatures. With circulatory arrest, temperatures in the brain in the aortic arch remained steady for several hours, even at 30–35°C air temperature, unless cool air was introduced into the trachea by the respiratory pump (Fig. 12). Such cooling occurred by direct conduction across the 5–8 mm from the end of the endotracheal tube to the thermocouple in the stationary blood in the aortic arch. One arterial blood site, in which the thermocouple was lying within the vessel wall (endothelium) against the pontine surface of the middle-basilar artery, reflected the continued pontine metabolic heat production after cessation of heat removal (blood flow) with a temperature rise of 0.3°C during the initial 8 min. The brain, unlike other deep heat-producing organs, is uniquely susceptible to heat exchange with the environment, both via the scalp (18) and via the nasal cavity (4–6, 21). The brain’s situation as a “superficial” organ complicates the study of brain temperature and must be recalled in any analysis of cerebral function.

**DISCUSSION**

In our studies of 16 chronic monkeys, we found that the cerebral arterial blood exerts a major influence on the thermal environment of the brain. Fluctuations in aortic blood temperature during feeding, sleeping, arousal, and saline injections were quickly followed by parallel fluctuations in cerebral arterial blood and brain temperatures. These brain temperature shifts in the primate serve to emphasize the rapidity of forced convective heat transfer by the blood from one region of the body to another, and indicate the close thermal connections that the arterial blood maintains between peripheral events and the thermosensitive zone of the hypothalamus (7, 16, 22, 41). An interesting example of this principle is the inverse relationship between heat loss through the nose and the temperature oscillations in the arterial blood and brain during sleep-waking cycles in the monkey (Fig. 2). We have recently described a similar inverse relationship between heat loss from the nasal mucosa and temperature in the hypothalamus of the sheep during paradoxical sleep (5) and during thermal polypnea (6) due to intracranial heat exchange at the carotid rete in the cavernous sinus. Whether the primate can manage a degree of “panting” by increased upper respiratory heat loss with vasodilatation in the nasal mucosa remains to be fully elucidated (8, 9, 35), but present evidence pointing in that direction provides another of the growing number of autonomic correlates of sleep-waking cycles (3–5, 27).

Our observation that the brain is warmer than the body has raised the question of the physiological basis for this phenomenon and the extent to which local cerebral function can influence brain temperature. We hypothesize that the warmth of the brain involves the dynamic interaction between local heat production and heat dissipation by blood flow. The ability of the cool blood in the cerebral arteries to remove heat from a site is closely related to the distance of that site from the subarachnoid space as well as to the local heat production and local blood flow. Whether there are actually specific local shifts in brain temperature due to primary local changes in cerebral blood flow or heat production rather than only secondary thermal shifts due to alterations in the temperature of the blood perfusing the brain, is a problem yet to be solved. It is quite obvious that a thermal solution to the problem can never be attained unless the blood perfusing the nervous site under study is used as a thermal base line for comparison (28, 32, 36). In all of our studies in unanesthetized monkeys (17, 18, 25, 26), rabbits (3), cats (4), sheep (5, 6), and dogs (21) we have yet to see an intracerebral thermal change which could not be explained by a prior shift in the temperature of the cerebral arterial blood. We have recently shown, for example, that the rise in brain temperature during paradoxical sleep, attributed by some to local increased neuronal metabolism (36) or blood flow (27, 28), was
actually due to a rise in the temperature of the cerebral arterial blood resulting from reflex vasoconstriction of the skin of the ear (3, 4) and the mucosa of the nose (5).

We have studied certain generalized primary changes in brain temperature that are independent of blood temperature. Those related to ventilatory changes or to the cessation of cerebral blood flow are cases in point. If inhalation of 8–10% carbon dioxide produces a 100% increase in cerebral blood flow, as has been shown in man and animals (29, 31, 40), and if the arterial blood is cooler than the brain, then we would expect that the increased flow of cool blood through the warmer brain would lower brain temperatures toward blood temperature. We have measured such brain cooling in our studies with hypocapnia. If hyperventilation lowers the tension of carbon dioxide in the arterial blood below 2% and decreases cerebral blood flow, as has been shown in man and animals (29, 31, 40), then we would expect that this decreased flow of cool blood through the warmer brain would elevate brain temperature further above blood temperature. Such brain warming is measured in our studies with hypocapnia. Abrupt cessation of cerebral blood flow upsets the delicate thermal balance within the cranium. While there is a drop in temperatures of the scalp and superficial brain structures after circulatory arrest, there is also a steady initial rise in temperature of deep brain structures since cerebral tissues continue to produce heat for minutes even though they are deprived of a steady supply of oxygen and glucose (10). Heat is retained when there is no clearance of heat from the brain by cerebral blood flow. The rise in brain temperatures cease when the tissue dies or when conductive cooling to the environment ensues.

We recognize that the present thermal approach has certain intrinsic limitations for the study of brain temperature changes due to local neural activity. Any functional increase in brain heat production will probably result in the simultaneous production of carbon dioxide and pH changes as by-products. These metabolic products can act on local vessels to accelerate blood flow and heat removal, thereby limiting any temperature rise that would be expected for such neural activity (10). Only a temporal dissociation of the heat-producing and heat-removal phases would allow thermal detection of such activity. While several phases of heat production are described in mammalian and in invertebrate peripheral nerves in vivo (30), whether such thermal correlates of neural activity occur in the brain with an intact circulation remains unknown at this time. Our current methodology is perhaps too insensitive to detect the degree of changes expected (30), to show local changes in heat production (32, 37) and blood flow (39, 37), to sensory and somatic stimuli. When we use the cerebral arterial blood for our thermal base line and keep in mind the complex species differences in the regulation of brain temperature (3–5, 21), we find no thermal evidence to indicate any local increases in central neural metabolism during sleep-waking cycles, feeding, or arousal.

Deep barbiturate anesthesia has a major depressant effect on oxygen consumption, heat production, and blood flow to the primate brain (10, 29, 38, 40). Still, when we controlled ventilation and apparently decreased metabolic heat production in the brain by large doses of barbiturate, we failed to see any change in brain-blood temperature gradients. Since rates of oxygen consumption and heat production in the brain are directly linked through oxidative metabolism to the rates of production of carbon dioxide, and since carbon dioxide is probably the major factor in the chemical control of cerebrovascular tone (29, 40), it is reasonable to expect a somewhat parallel reduction in both heat production (oxygen consumption) and heat removal (blood flow), with no net over-all change in the thermal balance. Our results support such a conjecture. During deep barbiturate anesthesia with controlled ventilation there was no over-all change in brain-blood temperature differences despite an isoelectric EEG (Fig. 9). Whether using a more sensitive thermal approach and the arterial blood as a common thermal base line will allow us to detect any thermal correlates of changes in neuronal heat production during anesthesia remains to be studied in the primate. Certainly, investigators using the inert radioactive gas technique with autoradiography to measure regional cerebral blood flow in the cat have found highly significant shifts in local blood flow both with visual stimuli and barbiturate anesthesia (31). Most studies on cerebral blood flow and cerebral oxygen consumption indicate a parallel change in heat-producing and heat-removing mechanisms during varying states of consciousness, anesthesia, and cerebral disease (10, 29, 31, 40), further suggesting that thermal correlates of changes in neuronal activity in the central nervous system may be nonexistent.

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BRAIN TEMPERATURE AND THE ARTERIAL BLOOD


