secretory responses to gastrin, increasing amounts of gastrin were added to the nutrient solution. After the maximal response to each dose had been recorded, the nutrient solution was exchanged. The results of a typical experiment are shown in Fig. 2. In no case did a dose of 2.5×10^{-10} M elicit a response. In the experiment illustrated, the threshold dose was 2.5×10^{-9} M and the peak response occurred at 2.5×10^{-8} M.

The secretory responses to 71 doses of gastrin in 30 bullfrog mucosae are shown in Fig. 3. The response to each dose is expressed as the ratio of the stimulated rate of secretion to the basal rate just prior to addition of gastrin. The threshold dose in all cases was 2.5×10^{-9} M and the maximal response occurred at 2.5×10^{-8} M or 2.5×10^{-7} M. By comparison, the response of 12 mucosae to 31 doses of histamine indicated that the threshold dose of histamine was 2.5×10^{-7} M and the maximal secretory dose was 2.5×10^{-4}. Therefore, the threshold dose of gastrin is 1/100 the threshold dose of histamine, and the dose of gastrin required to achieve a maximal secretory response is 1/1000 or 1/10000 the corresponding dose of histamine.

Addition of supramaximal doses of gastrin, *i.e.*, 2.5×10^{-4} M, stimulated acid secretion and did not inhibit basal or previously established gastrin- or histamine-stimulated secretion. Secretory inhibition following supramaximal doses of gastrin has been observed in the intact dog(1).

The mucosal content of histamine declined gradually during the course of 6 experiments (Fig. 4). No significant differences in histamine content were observed between the gastrin-stimulated and the non-stimulated mucosae.

Summary. Gastrin stimulates the secretion of acid by the isolated gastric mucosa of the bullfrog. The threshold dose is 2.5×10^{-9} M and the maximal secretory response occurs at 2.5×10^{-8} or 2.5×10^{-7} M. Supramaximal doses of gastrin failed to inhibit gastric secretion. Gastrin has no effect on the levels of endogenous mucosal histamine.

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Temperature Gradients Between Arterial Blood and Brain in the Monkey.* (30827)

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Blood serves as a common carrier of heat from one area of the body to another. In the homeotherm it provides the thermal stimulus for specialized thermosensitive receptors in the preoptic-anterior hypothalamic region and additionally removes the heat produced by neuronal and glial metabolism(1,2). While such generalizations are well established, a number of specific aspects of the thermal relationships between the brain and blood are

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still uncertain. Several groups have observed fluctuations in brain temperature associated with behavioral changes related to sleep and arousal(3-8). These temperature shifts occur simultaneously throughout the hypothalamus and in the cerebral cortex without a change in deep body (rectal) temperature(4-7). The physiological basis for these temperature fluctuations is not known. Another unexplained observation is the presence of temperature gradients in different brain areas. For example, the anterior hypothalamus is cooler than the posterior hypothalamus and warmer than the cerebral cortex(2-4). To explore further the relationship between blood and brain temperatures we measured arterial blood temperature simultaneous to the temperature of a variety of cerebral sites in the unanesthetized monkey. The level of alertness was also noted. Changes in arterial blood temperature were found to follow within 2 to 10 seconds changes in the level of alertness as indicated by overt behavior, EEG and EMG recordings. The arterial blood temperature shifts were followed somewhat later (within 10 to 90 seconds) by changes of similar direction and magnitude in brain temperature. Temperature gradients of 0.2 to 0.6°C were found between the arterial blood and the selected cerebral sites. While these gradients were different for each site they were nonetheless usually constant over several hours recording and could be repeatedly demonstrated on the various days of testing.†

Materials and methods. All measurements were made during 30 experiments on 5 adult female monkeys *(Macaca mulatta)* of 4 to 6 kg body weight. Two to four weeks prior to study the animals were adapted to a primate restraining chair in a thermoregulated chamber with 12 hours of artificial light and 12 hours of darkness. Under pentobarbital anesthesia and with sterile operative technique, glass-enclosed thermocouples (OD, 0.84 mm) were stereotaxically implanted in deep brain areas. Other thermocouples sealed in polyethylene tubing (OD, 0.61 mm) were implanted 0.5 to 1 mm into the cerebral cortex through the subarachnoid space. Still other thermocouples in polyethylene tubing were passed through a branch of the external carotid artery or the common carotid artery to the arch of the aorta without occluding the internal carotid artery. Epidural silver ball electrodes were implanted over the biparietal cortex. Insulated stainless steel wires with bared tips were fixed in the orbicularis oculi muscles. Lead wires were threaded under the skin of the neck and attached to brass connector pins (EEG, EMG) and to copper-constantan plugs (temperature) which were cemented to a lucite platform on the skull. This lucite platform either replaced the scalp (10) or was elevated 2 cm on 4 posts to allow an intact hair bearing scalp over the skull and brain. Post-operatively the monkeys were treated with penicillin and streptomycin for 3 days and allowed 1-2 weeks of trauma free recovery time.

Recordings were made on healthy, afebrile monkeys eating at a preoperative level. Animals were studied at rest behind a one-way glass mirror window in a primate restraining chair in a lighted, sound-attenuated chamber with a controlled environmental temperature between 23-30°C ± 0.5°C and at approximately 50% relative humidity. Recordings were made with an Offner Type-R ink-writing oscillograph which provided continuous and simultaneous EEG, EMG and temperature records. Thermocouples were made from enameled arc-welded 100 micron copper-constantan wires (Sigmund Cohn Corp.). Thermopotentials were amplified with a DC amplifier (Offner 481 B preamplifier and 9806 A coupler). A distilled water, crushed ice reference junction was used. This recording system had a response time of 1 second and a maximum sensitivity of 0.25°C/cm. The accuracy of the thermocouples after calibration was ± 0.05°C. At the end of the study the monkeys were sacrificed with an overdose of pentobarbital and the brains perfused and fixed in 10% formalin. Brains were frozen, serial sections cut at 80 μ, and the sections stained with thionin. Thermocouple positions were determined by gross and microscopic examination.

Results. Arterial blood temperature and arousal. Temperature measurements at the

† Some of these results have been described in abstract form(9).

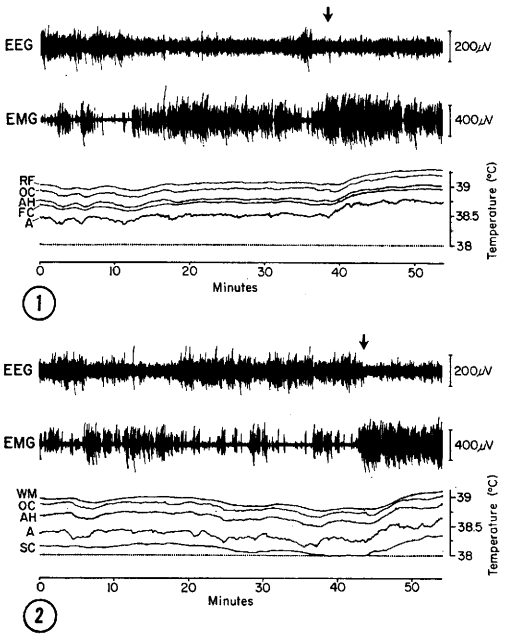

FIG. 1. Blood and Brain Temperatures and Arousal. Fluctuations in blood and brain temperatures are shown in relation to changes in the EEG and EMG in the chamber isolated (24°C) resting monkey. Loud tap on the chamber at the arrow. Abbrev.: EEG, biparietal electroencephalogram; EMG, orbicularis oculi electromyogram; RF, midbrain reticular formation; OC occipital cortex; AH, anterior hypothalamus; FC, frontal cortex; A, arterial blood at the arch of the aorta.

FIG. 2. Blood and Cranial Temperatures during Drowsiness in the Monkey. Continuous and simultaneous recordings of temperatures of the brain, subcutaneous tissue of the scalp and arterial blood as compared with electrical activity in the cerebral cortex and in the periorbital muscles. Chamber temperature 24°C. Buzzer sounded at the arrow. Abbrev.: WM, subcortical white matter; SC, subcutaneous tissue of the scalp. Other abbreviations as in Fig. 1.

arch of the aorta have been used as an index of core temperature in the calf(11). In our monkeys, the mean temperature of the circulating blood measured at this site proved to be a rapidly changing and sensitive parameter. Changes ranged from small dips of 0.03 to 0.08°C and of 10 to 20 seconds duration to larger 0.1 to 0.2°C shifts that occurred over a period of 30 to 90 seconds. These latter shifts were closely related to changes in overt motor activity and the patterns of EEG and EMG recordings. During periods of sustained and "spontaneous" wakefulness, oscillations at a frequency of 6 cycles/minute in baseline temperature were frequently observed. These oscillations had an amplitude of 0.04°C and were not associated with any net rise or fall in blood temperature.

The monkeys commonly grew drowsy in the sound-attenuated chamber. Typically 10 to 20 minute periods of arousal were interspersed with brief 1-5 minute periods of drowsiness or sleep, at which time the EMG potentials were diminished and high voltage slow waves were manifest in the EEG recordings. Whenever the animals fell asleep blood temperature dropped 0.1 to 0.2°C. During subsequent arousal blood temperature rose again to its former level (Fig. 2). As determined at faster paper speed than shown in these records, EEG and EMG wave changes usually preceded blood temperature changes by several seconds. The magnitude and duration of the slower changes in blood temperature were relatively phase-locked to the changes in EEG and EMG recordings (Fig. 1 & 2). When drowsiness became more pronounced and prolonged, the ratio of "sleep time" to "arousal time" was increased. This meant that more cooling than warming of the blood took place with every sleep-arousal cycle and repetition of these unequal cycles over several minutes led to a slow, stepwise downward shift in blood temperature. At this stage auditory stimuli were used to induce a more sustained arousal including an orienting response, and EEG desynchronization and increased EMG activity were followed within 2 to 5 seconds by a steady warming of the arterial blood (Fig. 1 and 2).

Brain temperature and arousal. Brain temperature fluctuations were similar in direction and degree to the changes in blood temperature during sleep and arousal. Any alteration in the level of arousal was followed within seconds by a change in blood temperature and then seconds *to minutes* later by a relatively comparable shift in brain temperature. Invariably the rate of change in brain temperature was slower than the preceding blood temperature change. The shifts of 0.1 to 0.2°C and of 30 to 90 second duration in arterial blood temperature during drowsiness had their counterpart in the temperature changes of the hypothalamus and cerebral cortex. In contrast the subcortical white mat-

TABLE I. Temperature Gradients Between the Brain and Arterial Blood in the Monkey.

The simultaneous measurement of temperatures in the brain (T_B) and of the arterial blood (T_A) in 5, resting-chair restrained, rhesus monkeys in a lighted thermoregulated chamber.

Anatomical location	Brain* (T_B—T_A) (dgr C)	Blood (mean T_A) (dgr C)
Rostral diencephalon and septal area		
Diagonal band of Broca	+.22 ± .06	38.01
Preoptic area	+.25 ± .03	38.74
Anterior hypothalamus	+.30 ± .03	38.49
" "	+.34 ± .04	38.40
Caudal diencephalon and midbrain		
Posterior hypothalamus	+.39 ± .08	38.01
Midbrain RF	+.52 ± .05	38.58
" "	+.56 ± .04	38.43
Cerebral cortex		
Frontal cortex	+.23 ± .03	38.46
Occipital cortex	+.43 ± .05	38.58
" "	+.45 ± .05	38.42
Parietal white matter	+.50 ± .07	38.17
" " "	+.52 ± .05	38.49

* Values for the brain are expressed as the mean difference between temperature of the brain and arterial blood (T_B—T_A) ± S.D. in dgr C. Data tabulated for ten 5-minute intervals during 3 experiments for a total of 30 readings for each brain site.

ter could not "follow" these more rapid blood temperature changes, and it exhibited changes related only to the larger and slower shifts in arterial blood temperature. These regional differences in blood-brain thermal conductivity are illustrated in Fig. 1 and 2 to demonstrate the varying degrees of thermal inertia present in nervous tissue. Fig. 2 additionally shows that temperature changes of similar direction and degree were encountered in the subcutaneous tissue of the scalp an extracerebral cranial structure.

Gradients between brain and blood temperature. In all the monkeys brain temperature was higher than the mean temperature of the arterial blood by 0.2 to 0.6°C. As shown in Table I, temperature gradients between the arterial blood and each cerebral site we studied were maintained within narrow limits for the 1-2 hours of each experiment and on the different days of testing. Slow shifts in blood temperature which minimized the thermal inertia of the brain caused no change in these temperature gradients. During the more rapid changes in blood temperature, gradients were briefly increased or decreased between the blood and the hypothalamus and cerebral cortex. Gradients with blood temperature varied from one cerebral site to another. Temperatures at rostral sites in the hypothalamus and the frontal cortex were 0.17 to 0.22°C closer to arterial blood temperature than caudal regions of the brain stem and the occipital cortex. The only cranial structure we studied in which the temperature was lower than the blood was the subcutaneous tissue of the scalp.

Discussion. These studies have clearly shown that the arterial blood exerts a major influence on the thermal environment of the brain. Fluctuations in blood temperature were quickly followed by parallel fluctuations in brain temperature. While other investigators (3,5-8) have observed a relationship between brain temperature and arousal, they have usually attributed such brain temperature shifts to changes in neuronal metabolism or cerebral blood flow rather than the presently reported *earlier* change in arterial blood temperature. The failure to associate these brain changes with shifts in deep body temperature probably arises from the frequent use of the rectum as a reference site for core temperature. Ultimately the establishment of the physiological basis for brain temperature changes will depend upon the use of the most reliable index for deep body temperature, namely the arterial blood rather than the rectum. Moreover, changes in arterial blood temperature would appear from our present results to be a more reliable thermal correlate of behavioral changes associated with sleep and arousal than would changes in brain temperature.

Measurement of arterial blood temperature also facilitates the study of temperature gradients in the brain. Temperature differences between diencephalic and midbrain areas in the monkey are similar to those gradients described for the cat and dog in which rostral brain stem sites are cooler than caudal brain stem regions(2,4). Additionally, we found the rostral cortex (frontal) to be as warm as the anterior hypothalamus and the caudal cortex (occipital) temperature level to approach that of the midbrain reticular forma-

tion. Subcortical white matter was one of the warmest sites in the brain and also had the greatest thermal inertia of all the intracranial structures in which temperature measurements were made. The genesis and functional significance of intracerebral temperature gradients are still unknown. In the past a major problem in evaluating these intracerebral gradients has been the continuous fluctuations of brain temperature. It would now appear that simultaneous measurements of arterial blood temperature and various brain temperatures will permit a more accurate assessment of those fluctuations in brain temperature due to altered neuronal or glial metabolism, *local* blood flow and *local* blood temperature in contrast to those changes that result simply from changes in the mean temperature of arterial blood coming to the brain.

Summary. Temperature measurements were made simultaneously in the arterial blood and various brain structures in 5 chronically prepared rhesus monkeys at rest in a lighted, sound-attenuated, thermoregulated chamber. The level of alertness of the animals was also noted by observing changes in overt behavior together with EEG and EMG recordings. Spontaneous and induced shifts in the level of arousal were followed in seconds by warming or cooling of the arterial blood and seconds to minutes later by parallel shifts in the temperature of the majority of the brain sites. Arterial blood temperature was thus found to yield a sensitive index of the behavioral state of the monkey in relation to sleep and arousal. Changes in the mean temperature of the arterial blood going to the brain appeared primarily responsible for temperature fluctuations in the brain. A number of steadily maintained but differing thermal gradients were found to exist between regional brain sites and the arterial blood.

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Enhanced Bacterial Virulence in Fluids Produced in Strangulation Intestinal Obstruction.* (30828)

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Fluids accumulating in the peritoneal cavity and in the small intestine during the irreversible course of strangulation intestinal obstruction are lethal when injected into healthy animals(1). These fluids are malodorous, red to reddish black in color, and laden with bacteria. Clostridia, coliforms, bacteroides and streptococci are respectively the most numerous flora(2). Supernates from centrifuged strangulation fluids often lose lethality when sterilized by filtration. In some cases sterile fluids retain their lethality owing to the presence of preformed clostridial exotoxins(3). Bacteria exert a role in the

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