Table 1. Means and standard errors for coefficients of variation of oral temperature, hum frequency, hum intensity, and the sodium and potassium concentrations in urine, sweat, and saliva.

Item	Coefficient of variation (%)
Urine (Na)*	9 ± 3
Urine (K)*	11 ± 3
Sweat (Na)*	33 ± 7
Sweat (K)*	20 ± 5
Saliva (Na)*	22 ± 2
Saliva (K)*	8 ± 1
Oral temperature†	0.6 ± 1
Hum frequency‡	8 ± 1
Hum intensity‡	101 ± 27

*From 6. †As evaluated from readings or oral temperature studies (see 5). ‡As calculated from readings from 33 female subjects taken over periods up to 179 days.

intensity (101 ± 27 percent) is much higher than that for frequency (8 ± 1 percent), and this suggests that the relatively large fluctuations of intensity tend to mask subtle changes brought about by physiological mechanisms.

In a study to explore the diurnal fluctuation of the hum frequency, 18 female subjects telephoned the laboratory at three specified times during the day—(i) in the early morning, immediately after awakening (6:30 to 7:45 A.M.); (ii) at 12 noon, before lunch; and (iii) at the end of the day, before retiring for the night. The telephone calls were answered automatically and recorded on a Western Electric telephone-answering set, type I-BA, which made the following prerecorded announcement: "Please be seated; when you hear the beep tone at the end of this announcement please say your telephone number, the time, then hold the telephone close to your mouth, keep your lips pressed together in a comfortable way, and hum one note continuously for about 5 seconds. Thank you."

An analysis of variance of the data obtained for these 18 subjects showed that a definite diurnal fluctuation of the hum frequency occurred ($P < .001$). Subsequent tests revealed that the hum frequency was significantly higher at noon (241 ± 11 cy/sec) than it was in the early morning (208 ± 7 cy/sec; $P < .001$). Moreover, the noon reading was significantly higher in frequency than the night reading (212 ± 8 cy/sec; $P < .001$). No significant difference was found between the night reading and the early morning reading ($.70 > P > .60$). This finding is undoubtedly influenced by restricting the various vocal parameters so that the acoustical signal is modulated solely by physiological change.

The diurnal fluctuation of the hum frequency suggests that this variable is associated with the sleep-wake cycle, as are many other physiological funtions. This can be deduced from studies by Carhart (*2*) who concluded that the increased breath pressure and increased tension on the vocal cords produce a rise in laryngeal frequency. Mitchinson's x-ray studies (*3*), showed that in humming the vocal folds become elongated with an increase in vocal pitch, while Sonninen (*4*) showed that a lengthening of the external laryngeal muscles and the cricothyroid muscle occurs when there is a rise in the pitch of the singing voice.

From the studies of Mitchinson and Sonninen and from those reported here it can be assumed that during the day there is a rise in breath pressure, with a consequent rise in tension of the vocal cords. There is also a lengthening of the laryngeal muscles and the cricothyroid muscle, all this resulting in a rise in the hum frequency (*7*).

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Localized Cooling in the Brain

Abstract. A slender refrigeration probe for the production of reversible discrete lesions within the central nervous system of man and experimental animals is described. Cooling, in the region of the third nerve nucleus in cats, produced pupillary dilatation which was quickly reversed when the temperature around the third nerve nucleus returned to normal.

Localized cooling of structures deep within the brain is a relatively easy, inexpensive, and effective method of producing reversible brain lesions. The widespread use of stereotactic surgical techniques for the treatment of Parkinson's disease in man has made it imperative to find a safe, effective method of producing reversible brain lesions to guide the surgeon in placing his permanent therapeutic lesions in the thalamus and basal ganglia. A refrigeration probe seems to be one answer to this problem. Furthermore, this probe could give animal neurophysiologists a dramatic new tool for the investigation of the central nervous system. This is particularly true if it could provide the experimenter with one probing electrode that could record information, stimulate the brain, and make both reversible and permanent lesions. It was with both clinical and experimental objectives in mind that we designed a long, slender refrigeration probe.

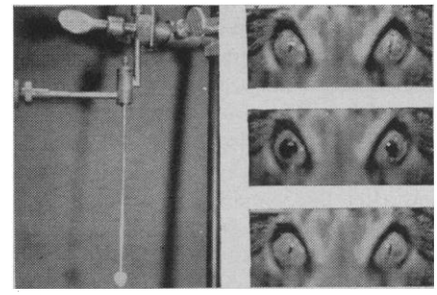

Fig. 1. (Left) Refrigeration probe with ice sphere around its tip. (Right) Pupillary size of the cat's eyes before (top), during (middle), and after (bottom) cooling produced by the refrigeration probe, 4 mm from the third nerve nucleus.

The probe (Fig. 1, left) made for us by John Chato of Massachusetts Institute of Technology (*1*) consists of two stainless-steel needles. The outer needle is 125 mm long with an outside diameter of 1.6 mm. Its distal tip, containing a 5-mm-long cooling chamber, is rounded for insertion into the brain. Its proximal end is attached to a small chamber which serves as an inlet for the liquid refrigerant (Freon 12). A smaller needle of 1 mm outside diameter lies within the larger needle; its distal tip has a beveled shoulder, which is elevated and lowered against the inlet to the cooling chamber by a knurled thumb screw at its proximal end. This device controls the inflow of refrigerant from the outer needle into the cooling chamber. The inner needle also serves as an exit for the expanded gas from the cooling chamber; it carries this cold gas up to the center of the probe and thus prevents cooling of the outer walls of the probe which carry down the uncooled refrigerant.

Our next problem was to see whether this probe would produce reversible lesions under experimental conditions. For this purpose, we did a series of ex-

periments with cats, stereotactically placing the probe within 3 or 4 mm of the third nerve nucleus on the right side. Thermocouples were attached to the refrigeration probe at 1 and 3 mm away from the tip. We then photographed the cat's eyes before, during, and after the temperature of the probe was lowered to about 5°C (Fig. 1, right). We did not reduce the temperature of the probe to 0°C for fear of producing irreversible lesions about the tip of the probe. (*2*). Bright illumination of both pupils was constantly maintained throughout the experiments. Within 20 seconds, the ipsilateral pupil fully dilated and the contralateral pupil partially dilated. Within 45 seconds after the probe was turned off, the pupils returned to normal size. This process of cooling and warming was repeated in each cat at least three times (with cooling periods of up to 10 min) without altering the physiological results or time course of the localized brain cooling. In three cats with similar electrode placements near the third nerve nucleus, the results obtained were exactly the same.

For clinical use, Cooper and his associates (*3*) have introduced a small balloon into the tip of their brain probe. They feel that they can make temporary brain lesions by expanding the balloon and mechanically compressing brain tissue within the thalamus and basal ganglia. They have used this successfully in many hundreds of cases. The expanded balloon, however, has caused hemorrhage in some clinical cases, and thus, whether it can produce temporary lesions within the brain safely is in some doubt. Procaine injections have also been used to produce temporary interruptions of brain function in man. The injection of procaine into the thalamus or basal ganglia has two disadvantages. First the diffusion of a liquid in the center of the brain mass is somewhat unpredictable, and the physiological results of such interruptions are difficult to interpret. Secondly, the seepage of procaine or other local anesthetic agents into the brain ventricles may produce a clinical catastrophe. The use of a single beam of ultrasound for the production of reversible brain lesions has been described (*4*). This is an expensive and complicated tool for routine clinical use, and in experimental work it precludes the use of electrical recording devices at the site of the intended lesion. It is, however, another promising method of producing reversible brain lesions.

Although the brain tolerates heat very poorly (irreversible lesions can be made in the brain substance by heating it to 55° or 60°C), cold is tolerated more readily. The entire body temperature during surgery has been reduced to as low as 10° or 15°C for more than 44 minutes without discernible impairment in brain function (*5*). A localized decrease in brain temperature and its effect on conduction times and somatic and synaptic potentials will be a subject of continuing investigation in this clinic. We are also attempting to build a more slender semiconductor probe for brain cooling (*6*).

Note added in proof: It has come to our attention that a cooling probe was used to make lesions in the cerebral cortex of cats by Balthasar in 1957 [E. Balthasar, *Deut. Z. Nervenheilk.* **176**, 173 (1957)].

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19 June 1961

Functional Effects of Focused Ultrasound on Mammalian Nerves

Abstract. Differential blocking of conduction in mammalian nerve fibers has been produced by irradiation of the whole nerve with focused ultrasound. The smallest (C) fibers are the most sensitive; the largest (A-alpha) fibers are the least vulnerable. Fully reversible blocking can be obtained with carefully graded doses of ultrasound.

Studies of frog sciatic nerve have revealed that the alpha, beta, and gamma fibers in the nerve are differentially sensitive to focused ultrasound (*1*). The effects of ultrasound upon fibers in a wider size range have now been investigated (*2*), in studies of the saphenous nerve of the cat. This is a skin nerve containing the alpha and delta subgroups of the A fibers (with diameters of 6 to 14 and 1 to 5 μ, respectively) and a good representation of C fibers (of 1 μ or less).

In cats anesthetized with pentobarbital sodium, the saphenous nerve was exposed for 8 to 10 cm. Near its origin in the upper thigh and in the middle of the leg it was severed and freed from surrounding connective tissue, so that it could be lifted on stimulating and recording electrodes. Ultrasound (*3*) was directed at the midportion of the nerve. The ultrasound was administered in pulses of 0.4- to 0.9-second duration with a 2- to 3-second interval between pulses.

Action potentials were recorded monophasically and after amplification were displayed on an oscilloscope. In each experiment the intensity (plate voltage of the ultrasonic generator) and duration of irradiation were increased gradually until alterations in the action potentials were noted. Before each irradiation several compound action potentials, with alpha, delta, and C fiber deflections, were photographed as controls. Records were also taken during the period of irradiation and afterwards during recovery from it.

As in the experiments on frog nerve fibers (*1*), it was found that focused ultrasound would abolish conduction of impulses completely and irreversibly if irradiation was sufficiently intense or prolonged. Fully reversible effects could be obtained with graded doses of lower intensity. Experiments were devoted chiefly to producing differential blocking of fibers of different sizes. To this end the administration of ultrasound was deliberately varied in order to explore the effects of different combinations of intensity, duration, pulse interval, and train length.

Figure 1 illustrates the results obtained in one of the most successful attempts to block differentially. Four columns of records are shown (Fig. 1, *A* to *D*). The upper and lower pairs of tracings in each were obtained before and after irradiation, respectively. The upper channel in each pair was recorded at high amplification.

Figure 1, column *A*, shows the effect of a train of 20, 0.5-second pulses of ultrasound at a plate voltage of 700. The C fiber deflection (*4*), indicated by the arrow, in the upper tracing was abolished during the course of this ir-