articles, the 17 percent of current research attributed to the United States by this survey is undoubtedly spuriously high.

The Russian journals display a strong interest in the therapeutic aspects of sleep. Most of the German reports center on the effectiveness of various drugs in dealing with insomnia and more exaggerated sleep disturbances.

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Miniature Subcutaneous Frequency-Modulated Transmitter for Brain Potentials

Abstract. A device for broadcasting electrical signals from the brain of an animal is described. It is small enough to be implanted under the animal's skin. That signals are broadcast without distortion is shown by the comparison of a broadcast recording of an electrocorticogram of a cat with a simultaneous recording made directly with wire leads.

In recent years physiologists have been concerned with the study of the relationship between the electrical activity of the brain of an animal and its behavior. It is common practice to implant electrodes subcortically and connect them with wire leads to a sensitive recording apparatus. This technique has the disadvantage of artificially restraining the animal and impeding normal behavior. Radio telemetry can be used to eliminate the wires (*1*). A transmitter small enough to be implanted under the skin of the animal would be ideal.

Some requirements of a transmitter for this application follow:

1) The input impedance should be several times the source impedance in order to record essentially the open-circuit voltage. Measured source impedances were of the order of 15,000 ohms.

2) The frequency response should be nearly perfect in the range from 1 to 1000 cy/sec.

3) Transmitted signals with peak-to-peak magnitude as small as 50 μv should be intelligible to a good antenna-receiver system located within 100 feet of the animal.

4) The circuit should contain the fewest possible number of components consistent with the foregoing requirements in order to lend itself to miniaturization and implantation.

The circuit diagram of a transmitter which meets these requirements is shown in Fig. 1. The second stage is an amplifier-modulator-oscillator, essentially as developed by Thomas and Klein but with fewer components and a different type of transistor (*2*).

Sufficient circuit amplification is provided in the second stage; however, the input impedance of the second stage is about 25,000 ohms, which is considerably less than the required value. The first stage is needed to increase the input impedance. It is an emitter-follower which uses the direct-coupled input impedance of the second stage as its load (*3*).

A photograph of the transmitter and its battery is also shown in Fig. 1. Assembly was accomplished by mounting standard miniature components upon a substrate. Conventional soldering techniques were used. Before implantation, the transmitter was encapsulated with a polyethylene resin.

Measured characteristics of the transmitter are as follows: carrier frequency, 94 Mcy/sec; input impedance, 250,000 ohms; frequency response, 3 db down at 0.1 cy and 16 kcy/sec; deviation sensitivity, 8 mv (r.m.s.) for $\pm$100 kcy/sec; equivalent noise input, 5 μv (r.m.s.) with 20,000-ohm source resistance and 16-kcy/sec bandwidth; weight with battery (encapsulated), 7.3 g; volume (encapsulated), 5 cm^3; battery drain, 500 μa. Battery life is approximately 48 hours when the smallest commercially available battery is used (two Mallory cells, type RM-312T2, in series).

Two electrocorticogram tracings taken from a single pair of electrodes implanted in the cortex of a cat are also shown in Fig. 1. The upper trace is the signal which was broadcast to an FM receiver before it was recorded. The lower trace was recorded simultaneously with wire leads from the same pair of electrodes. An electroencephalograph was used as the recorder in both cases.

Satisfactory recordings of other brain potentials have been made with all leads and the transmitter implanted subcutaneously.

With the advent of more efficient transistors of smaller size, a transmitter of about one-third the size of the one described here has been fabricated. A system whereby the battery may be recharged by induction while remaining in the animal is being investigated. Also under investigation are methods of providing for several channels of information (*4*).

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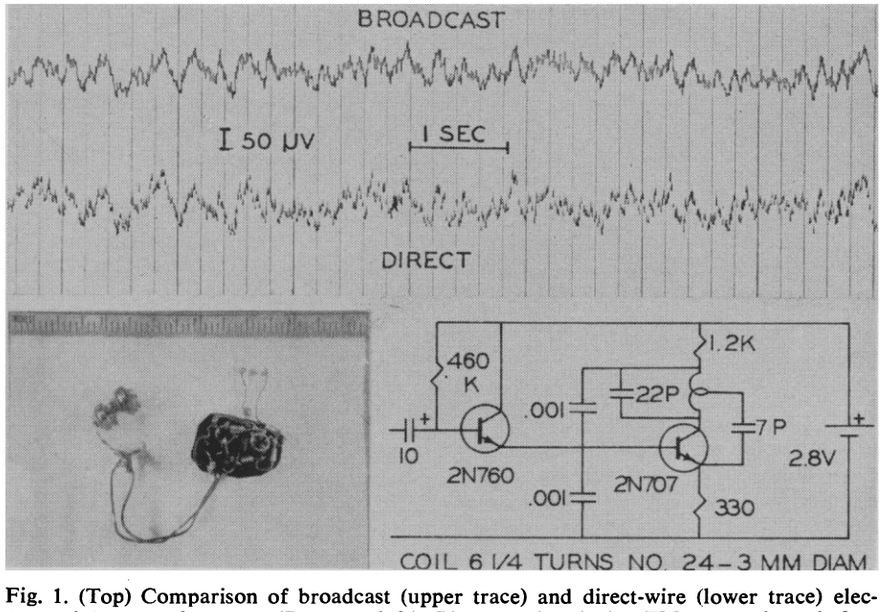

Fig. 1. (Top) Comparison of broadcast (upper trace) and direct-wire (lower trace) electrocorticogram of a cat. (Bottom, left) Photograph of the FM transmitter before encapsulation. (Bottom, right) Circuit diagram of the FM transmitter.

References and Notes

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Passage of Saccharides from Cerebrospinal Fluid to Blood

Abstract. Saccharides with a molecular weight ranging from 182 to 50,000, which enter the cerebrospinal fluid at extremely slow rates when administered intravenously, all pass readily at similar rates from cerebrospinal fluid to blood after injection into a lateral cerebral ventricle. The mechanism of transfer appears to be a filtration of cerebrospinal fluid across a sieve-like boundary possibly located at the arachnoid villi.

There is considerable evidence that drugs and other foreign organic compounds diffuse from plasma into cerebrospinal fluid at rates dependent on their lipid solubility. For example, organic acids and bases in general enter cerebrospinal fluid mainly in their undissociated form at rates roughly parallel to the lipid-water partition coefficients of these drug forms. Moreover lipid-insoluble organic ions such as quaternary ammonium compounds and sulfonic acids, as well as lipid-insoluble molecules such as sulfaguanidine and sucrose, penetrate into cerebrospinal fluid at very slow rates (*1*). In contrast, the transfer of drugs in the reverse direction—that is, from cerebrospinal fluid to plasma—does not appear to be highly dependent on lipid solubility. For example, Mayer *et al.* (*2*) have shown that, after intracisternal injection, compounds with low lipid solubilities leave the cerebrospinal fluid almost as rapidly as those with high lipid solubilities. Thus, drugs may pass from blood to cerebrospinal fluid by diffusion across a lipid-like boundary, but they appear to pass from cerebrospinal fluid to blood mainly in a different way.

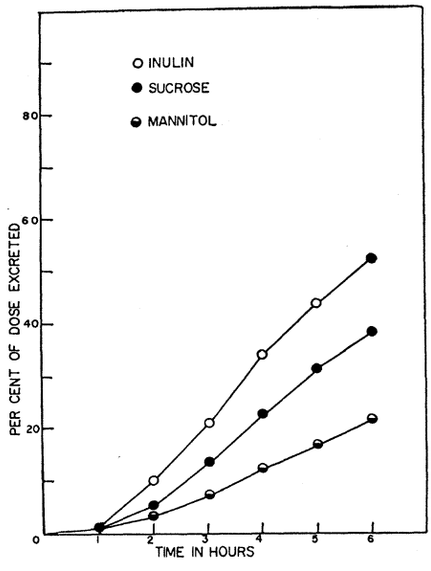

Fig. 1. Rates of appearance in urine of substances injected into a lateral cerebral ventricle of anesthetized rabbits. Each point represents the mean value for five animals. The standard errors for the points ranged from ± 1 to ± 3. The doses of the C^{14}-labeled substances in (mg/kg) were as follows: inulin, 0.15; sucrose, 0.20; mannitol, 0.05. The total radioactivity administered was 1 to 2 μc.

The investigation reported here is an attempt to describe the nature of the boundary across which substances pass from the cerebrospinal fluid into the blood stream. Lipid-insoluble foreign substances were investigated, since they would be unable to leave the cerebrospinal fluid by way of the lipid-like barrier between it and blood.

Five microliters of a solution of inulin-carboxyl-C^{14}, sucrose-C^{14}, or mannitol-1,6-C^{14} was injected into a lateral cerebral ventricle of male albino rabbits (2.1 to 2.3 kg) anesthetized with ether. Injections were made with the aid of a stereotaxic instrument which held the injection needle firmly in place throughout the experimental period, thereby preventing leakage of cerebrospinal fluid through the puncture. After the injection, the compounds moved rapidly toward the subarachnoid space, appearing in the cisterna magna within 5 minutes. Direct evidence that the compounds readily left the cerebrospinal fluid was provided by their detection in urine. The relative rates at which the compounds appeared in urine are shown in Fig. 1; 52 percent of the injected dose of inulin, 38 percent of the sucrose, and 23 percent of the mannitol were excreted in 6 hours.

To ascertain whether the appearance of the substances in urine was a measure of the rates of exit from the cerebrospinal fluid, the rates of urinary excretion of the substances were compared after a single intravenous injection in groups of three animals. Most of the inulin (92 to 95 percent) was excreted in 6 hours; sucrose was excreted to the extent of 82 to 94 percent, and mannitol, to the extent of only 76 to 82 percent. Little or no additional mannitol was recovered between the 6th and 7th hours after injection, suggesting that the compound may be metabolized or localized in the body. In any case, the incomplete recovery in urine of intravenously injected sucrose and mannitol suggests that these compounds had left the cerebrospinal fluid more rapidly than was apparent on the basis of their appearance in urine.

Evidence that sucrose, mannitol, and inulin leave the cerebrospinal fluid at similar rates was obtained on comparing the decline in concentration of the three saccharides in the fluid. The concentrations in cisternal cerebrospinal fluid 6 hours after intraventricular injection, expressed as a percentage of the dose in 1 ml of cerebrospinal fluid, were as follows: inulin, 10.1 (S.E., ± 0.6 in nine animals); sucrose, 10.2 (S.E., ± 1.0 in five animals); and mannitol, 8.1 (S.E., ± 0.4 in six animals). Preliminary experiments with dextran-carboxyl-C^{14} (molecular weight, 40,000 to 50,000) indicate that these large molecules pass from cerebrospinal fluid to blood at a rate almost the same as that of the other saccharides studied.

There is considerable evidence that cerebrospinal fluid flows from the cerebral ventricles toward the subarachnoid space and then filters across the arachnoid villi into the dural venous sinuses (*3*). This process of filtration or "bulk flow" into the blood stream would explain the essentially one-way transfer of lipid-insoluble molecules observed in the investigation reported here.

The results of this study suggest that drugs in general may pass from cerebrospinal fluid to plasma at similar rates by a nonspecific process of filtration across a porous boundary.

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