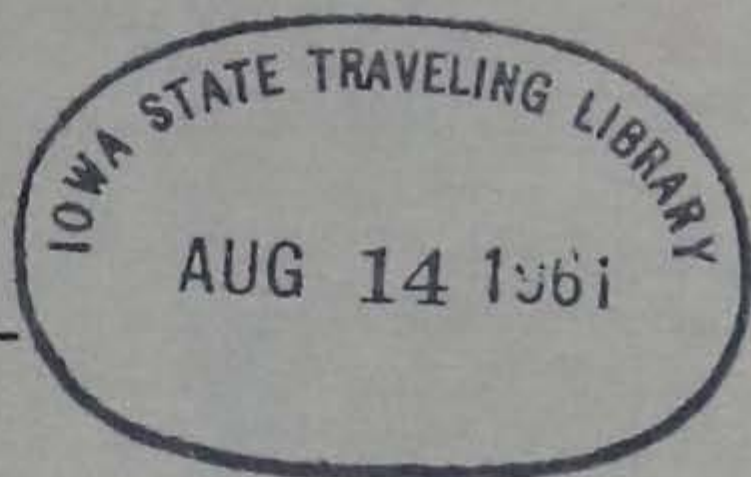


State University of Iowa Studies
in Natural History



Radio Telemetry of Electrocardiogram
and Body Temperatures from
Surgically Implanted Transmitters

WARREN O. ESSLER

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G. W. MARTIN, *Editor*

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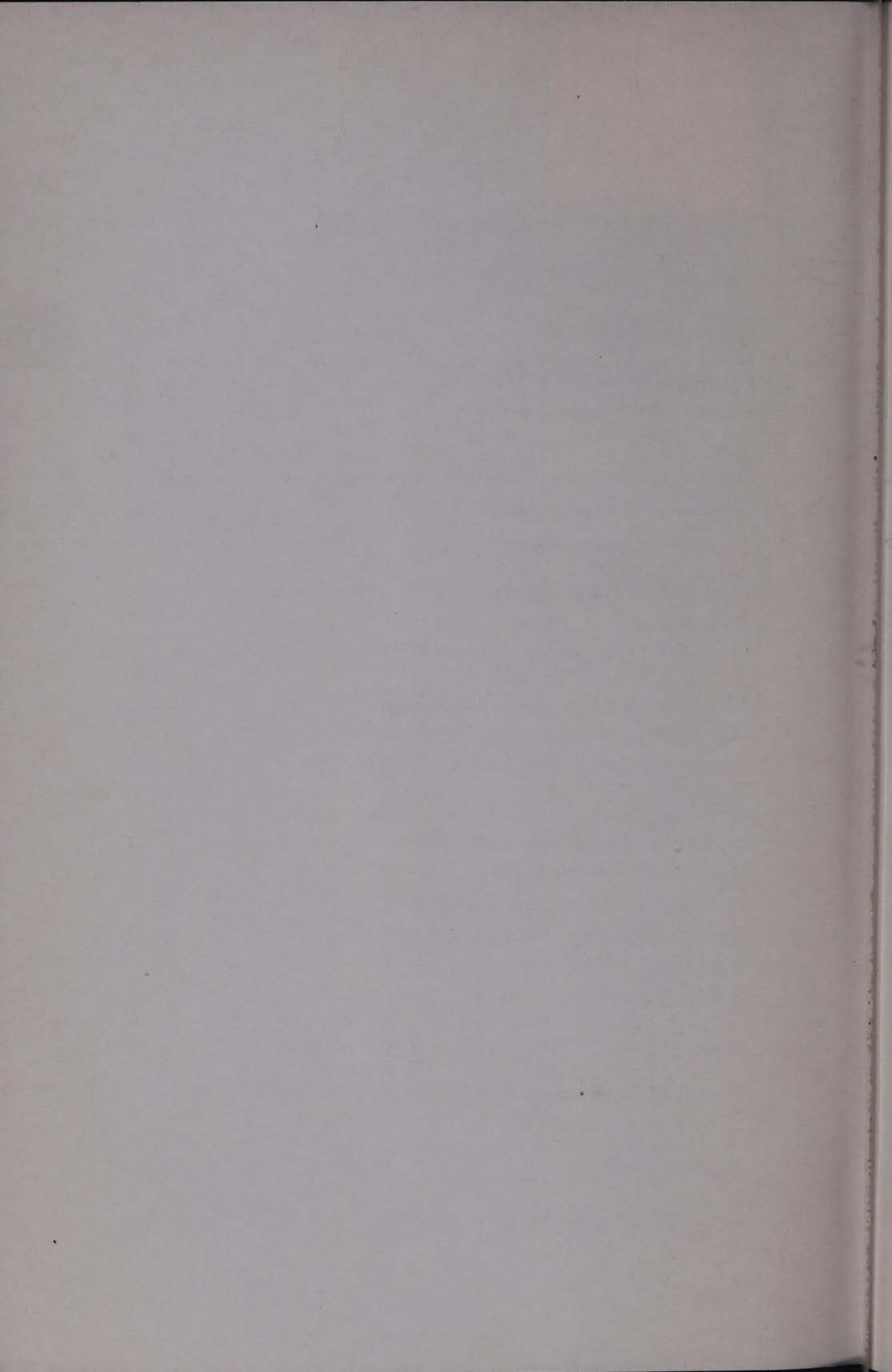
unb. The writer is greatly indebted to the following: Professors L. A. Ware and H. M. Hines, whose cooperation and encouragement made this interdisciplinary study possible; Professor G. E. Folk, Jr., for his very personal day-to-day guidance, assistance, and encouragement; Harold W. Shipton for his many conferences and constructive criticisms; the many other members of the State University of Iowa staff who assisted in this investigation; Professor W. H. Gamble of the Electrical Engineering Department of South Dakota State College, whose early encouragement and support initiated the academic effort; the National Science Foundation and the National Institutes of Health for the Predoctoral Fellowships which made the academic work possible; the National Institutes of Health (Institutional Grant 2G-225); and his family for their continued encouragement, especially his wife, Gloria, for her cheerful acceptance of abnormal family responsibilities.

This report is a condensed version of a dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, in the Departments of Electrical Engineering and Physiology, in the Graduate College of the State University of Iowa, in August, 1960.

Warren O. Essler, formerly Associate Professor of Electrical Engineering, South Dakota State College, Brookings, is now Professor and Chairman, Department of Electrical Engineering, College of Technology, University of Vermont, Burlington.

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INTRODUCTION AND STATEMENT OF PROBLEM

The use of electronic instrumentation has, in recent years, spread rapidly to nearly all areas of scientific investigation, but the development of electronic instrumentation for the biological sciences has not been as rapid as in other areas. The major advantage of electronic devices lies in their ability to transport quickly and to operate efficiently upon information; this information can then be made available to the scientist in an easily interpreted form.

Measuring biological phenomena in living animals presents problems that are markedly different from the problems found in the electrical laboratory where conditions can be rigidly controlled. One important example of a problem existing in many biological experiments is the perturbation of data resulting from the state of excitement or fear of the animal. These responses are influenced by such nebulous factors as the awareness of the animal that it is the focal point of attention or that an observer is near, or even that a slight change in its environment is imminent. Undoubtedly, this effect results from the animal's inherent dependence upon his immediate environment. The responses, many of which are not directly observable, may be in the form of biochemical and other substrate changes within the tissues, as well as more easily measured changes such as heart rate, blood pressure, and body temperature.

As the phylogenetic scale is ascended, the animal's responses to his environment become more varied and more complex because of a more highly developed nervous system. Unfortunately, among the higher forms direct observation of biologic phenomena may frequently result in mutual interaction between the investigator and the experimental animal. The use of radio telemetry, which allows the observer to set himself aside and record indirectly the events at a distant point, removes the possible interference effects of this interaction. The penalty that must be paid for this privilege, however, is more complex and elaborate instrumentation.

To date, no telemetry system has been devised in which the transmitter has the combined characteristics of small size, long life, and great range. Each of these characteristics opposes the others, dictating that any resulting design must, therefore, be a compromise. Any given transmitter, then, must be designed for a particular purpose and its use limited to a narrow range of experimental conditions. For example, to measure the heart rate of a football player during the game, it would be desirable to use a small, easily concealed transmitter having a range

of at least 100 yards and a battery life of approximately one hour. However, nearly opposite characteristics would be necessary to measure the temperature of an undisturbed laboratory animal during hibernation. In this case, it would be desirable to use a transmitter suitable for implantation with a range of 10 to 20 feet and an exceedingly long battery life of possibly six months. The size, shape, and electrical circuits for the transmitters of these two examples would be very different.

The specific problem of this research was to design recording telemetry systems, economically feasible for small research projects, for the determination of normal variations in heart rate and core temperature of laboratory animals, and to verify the applicability of the system in a short series of experiments.

REVIEW OF LITERATURE

Today radio telemetry equipment is commercially available for many applications involving standard measurements. Most of the equipment is not suitable for measurement of physiological phenomena. Several investigators have studied the possibility of measuring temperature, pH, heart rate, etc., in living animals. These investigations have resulted in the design of special equipment for specific types of experiments. Their reports have indicated that the recording of physiological phenomena by radio telemetry is economically feasible within certain limitations.

The first of these reports concerned a "swallowable intestinal transmitter" which was successfully used by Ardenne and Sprung¹ in 1958 for the diagnosis of disturbances in the intestinal tract of man. They indicated that the unit could be used for the measurement of pressure, pH value, or temperature, depending upon the technical form of the construction. The units operated at a frequency of 1.5 megacycles and were frequency-modulated. A frequency shift of 5 kilocycles was obtained by the influence of pressure on the inductance of an oscillatory circuit. The battery, a nickel-cadmium cell, provided an operational life of thirteen hours. The receiving system utilized the heterodyne method of measuring frequency.

MacKay and Jacobson² reported that the hydrogen ion in the intestinal tract was measured by radio telemetry in June, 1957. They used a mechanical-chemical transducer utilizing the mechanical expansion of a copolymer to change the position of a ferrite core of an inductance. The unit operated at a frequency of 400 kilocycles. The radio signal was received by a loop antenna connected to a standard receiver. The tuning of the receiver was indicative of the hydrogen ion con-

centration in the vicinity of the transmitter. In subsequent work MacKay and Jacobson³ measured simultaneously two physiological variables with one unit. Through the use of a blocking oscillator as a transmitter, pressure was transmitted as the base frequency, and temperature was indicated by the pulse repetition rate due to the blocking action of the oscillator. The latter measurement was somewhat dependent upon pressure. The life of the batteries in the transmitter was approximately four days.

A report on the first unit to become available commercially appeared in 1957. Farrar, Zworykin, and Baum⁴ successfully developed a pressure-sensitive telemetering capsule for the study of gastrointestinal motility. They used an inductance with a cup core in the tuned circuit. The inductance was also the element which was mutually coupled to the receiver. The external field of this type of core is very small. As a result, the mutual coupling of the inductance and loop antenna of the receiver was also very small, which undoubtedly reduced the range of the system. The size and shape of the inductor indicates that the unit operated in the kilocycle frequency range. This unit apparently had no advantages over the previous unit. It, however, was the first successful unit developed in the United States and was subsequently produced commercially by the Airborne Instruments Laboratory. The commercial unit has an operating battery life of seventy-two hours and apparently requires the use of a specially designed companion receiver.

In 1958 M. M. Marchal and M. T. Marchal⁵ reported that they had constructed in 1955 a radio pill, or capsule, suitable for swallowing. This unit apparently is protected by French and foreign patents. The passive unit contained a quartz tuned circuit which was activated from an external pulsed power generator of the same frequency. Apparently the ringing of the quartz crystal was indicative of the condition of the transmitter. The transmitter measured digestion time of various foods. For example, a piece of protein was placed between the contacts of a shorting strap, which rendered the unit inoperative when the contacts were open. The unit was then ingested and when the protein was digested the contacts closed, making the unit operative and the ringing of the tuned circuit detectable in a receiver. Marchal and Marchal claim that the unit, by simple modification, could be used for the measurement of internal temperature, pH, and pressure. They claim their unit is very small and can be fixed in the stomach, jejunum, ileum, or the colon by means of a magnet.

The first reported use of a transmitter surgically implanted in an animal was in January of 1959 by LeMunyan⁶ and others. Their unit was used to locate released animals for ecological studies. The unit constructed weighed 122.5 grams and had a volume of approximately 42

cubic centimeters. A crystal oscillator whose frequency was in the 190 to 550 kilocycle range was used to drive a pulsed power amplifier. With this arrangement the range was eighteen yards and the battery life was 161 days. The unit contained twenty-one components including two batteries. The components formed their own framework and were potted in foamed polystyrene and then coated with Castiplast No. 11. The total cost of the unit was approximately \$25. Several experiments were conducted, and it was found that a successful implantation could be made in the peritoneal cavity.

The successful measurement of incubating penguin egg temperature was reported in March of 1959.⁷ The units used by Eklund and Charlton possessed many of the characteristics required of an implantable transmitter. The unit was constructed so that it could be placed within the shell of a penguin egg. A false egg containing the transmitter was placed in the nest and a loop antenna was constructed about six feet above the nest. The transmitter included a transistor oscillator which operated at a low frequency, a temperature-sensitive element, three mercury-cell batteries whose life was about 100 hours, and a multi-turn single-plane loop antenna. The unit operated successfully in the measurement of the temperature of incubating Adelie Penguin eggs.

The use of the first subdermal telemeter for indicating heart function was reported by Kaeburn⁸ in November, 1959. A low-frequency transmitter, approximately 2.5 inches long, was implanted in a male beagle hound. It was suggested that a dog or a monkey equipped with a similar unit be sent into space for physiological data.

A simple telemetering system for signaling high pressures in the rumen of a cow was recorded by Payne⁹ in February, 1960. This unit operating in the frequency range of 75 to 150 kilocycles was powered by a 9-volt battery. The transmitter, a Hartley transistor oscillator, was strong enough to provide a substantially interference-free signal from a 150-square-yard field. Included in the unit was a microswitch which applied power to the oscillator whenever the pressure exceeded a predetermined value. With continuous operation the battery life was approximately twelve days. The unit was approximately one inch in diameter and six inches long. The receiving antenna consisted of a single-turn loop surrounding the field.

In February of 1960, Busser¹⁰ proposed an implantable temperature telemeter, for laboratory animals, which would have an infinite power supply life. He suggested that the energy to operate the implanted unit could be supplied by magnetic induction from an external power source.

Haynes and Witchey¹¹ reported a successful passive transmitter system in March of 1960. Their unit utilized a tuned circuit energized by

magnetic coupling to an external power generator. The system was similar to the one devised by Marchal and Marchal. The external power source was pulsed, causing the resonant circuit to ring. The frequency of the resonant circuit indicated the pressure within the intestinal tract. This unit, along with the associated receiving equipment, is fully developed and is at present being field tested. The range of the system is probably very limited due to the reduction in energy transferred in both directions.

TABLE I

SUMMARY OF TELEMETRY SYSTEMS FOR PHYSIOLOGICAL PARAMETERS

INVESTIGATOR AND DATE REPORTED	FREQ. (MC.)	SIZE (CM. ³)	RANGE (FT.)	LIFE (DAYS)	MEASUREMENT
<i>Subdermal telemeters:</i>					
Ardenne <i>et al.</i> (1958)	1.5	2.04		0.5	Pressure
MacKay <i>et al.</i> (1957)	.04	2.0	3	4	Pressure, pH and temp.
Farrar <i>et al.</i> (1957)	low	2.3	3	3	Pressure
Marchal <i>et al.</i> (1958)	low			inf.	Pressure
LeMunyan <i>et al.</i> (1959)	0.4	42	54	161	Location of animals
Eklund <i>et al.</i> (1959)	low	25	6	4	Temperature
Kaeburn (1960)	low	27			Heart
Payne (1960)	0.1	73	36	12	Pressure
Haynes <i>et al.</i> (1960)	0.4	2.9		inf.	Pressure
<i>External telemeters:</i>					
Basay <i>et al.</i> (1958)	28	720	450		Respiration
Rozenblat <i>et al.</i> (1958)	40		1500		EKG
Beenken <i>et al.</i> (1958)	104		500	5	Multi.
Botsch <i>et al.</i> (1959)	1680	3738	3 mi.		Multi.

Up to the present time the measurement of physiological phenomena by radio telemetry has been limited. Table I is a summary of all work cited above. In addition, for the purpose of comparison, Table I includes several pack type, or external, telemetry units.

Three opposing and apparently inherent factors hamper the design of subdermal transmitters. These factors are space or volume, life of power source, and range of transmission. In no case has there been

designed a relatively small sized unit with a moderate range having an operational battery life greater than a few days. Apparently extension of telemetry methods to physiological phenomena other than pressure and pH will accompany further work in this area.

METHODS AND INSTRUMENTATION

Introduction

Instruments for the measurement of temperature and heart-produced electrical potentials by radio telemetry were designed and constructed. These designs were influenced by the three opposing factors of physical size, operational battery life, and range of transmission. An effort was made to extend the operational battery life to many times that obtained by other workers.

Frequency of Operation

The transmitters, which operated in the 200 to 500 kilocycle frequency band, were selected because of the characteristics of electromagnetic waves and the radio interference likely to be present.

Losses per unit volume of tissue increase with the frequency of electromagnetic wave. A customary measure of energy loss within a given material is the depth of penetration, or the depth at which the electromagnetic wave is attenuated to $1/e$, or approximately 37 per cent. It is estimated that the depth of penetration at 100 kilocycles is nearly one meter as opposed to two centimeters at 100 megacycles. A very low frequency would be selected if the depth of penetration were the only criterion.

Other factors were also considered in the final choice of frequency. Component size is of importance in that capacitors and inductors used at low frequencies are generally larger than those used at high frequencies. Another factor of importance is the interference anticipated in various low-frequency bands. The frequencies above 500 kilocycles are allotted to broadcast, amateur, and various other private and governmental facilities, all of which are very active. The 200 to 500 kilocycle band is used primarily for navigational aids and is very quiet.

As a result of considering tissue losses, component size, and interference, the 200 to 500 kilocycle band was selected.

Electromagnetic Field Considerations

The transmitting range is dependent upon the power of the transmitter, the sensitivity of the receiver, the geometric configurations of the transmitting and receiving antennas, and upon the electrical interference in the vicinity. The power of the transmitter is controlled by its design and is limited by the size and battery requirements. The

sensitivity of the receiver used was 10 microvolts for avc threshold. The nature and magnitude of the interference depends upon the location or site of the installation.

Several geometric configurations of antennas were examined in order to determine the best arrangement. Because of the long wavelength and very small transmitting power the receiving antenna will never be outside the so-called induction field. Therefore, the problem of transmission is not one of radiated power but one of mutual coupling between two loosely coupled coils. It can be shown that for maximum received signal the receiving antenna should encircle the area to be used. The plane of the receiving antenna should be the same as that of the transmitting antenna for maximum received signal. Of course, this condition cannot be assured if the animal carrying the transmitter is free to move. Therefore, to be always assured that a signal can be received, the receiving antenna configuration should consist of three mutually perpendicular antennas, any one of which may be connected to the receiver.

Temperature Instrumentation

Generally the approach to the telemetry of temperature requires the selection of a suitable temperature transducer and associated amplifier which is compatible with a given multichannel telemetry system. Designs of multichannel systems are optimized with due considerations of all types of information which may be telemetered. The requirement of transmitting temperature information from a subdermally located transmitter placed stringent requirements upon the transmitter characteristics and suggested that an integrated transmitter and temperature transducer be used. Thus the focal point of the system was the transmitter. After the nature of the transmitter was decided, the remaining parts of the system were planned.

In this research a preliminary investigation was conducted to discover possible circuit configurations for the temperature transmitter. Early in the investigation it was found that the frequency of a sinusoidal transistor oscillator was dependent upon temperature because of the characteristics of the transistor. Furthermore, it was found that the input power requirement could be lower than 10 microwatts when the circuit components were properly selected. Theoretically a transmitter using pulse type modulation having a very short duty cycle could possess these same desirable characteristics, but the results of the preliminary investigations were not promising. Simple amplitude modulation was not considered because it would require the use of d.c. amplifying techniques, which are subject to drift over extended periods of time, and because variations in field strength as the animal moved would

ultimately be interpreted as temperature variations. Therefore, the decision was made early to use a sinusoidal transistor oscillator whose frequency was a function of temperature in the region of the transmitter.

A transistor oscillator was used in which the transistor was operated with the collector current slightly greater than I_{co} . A search was made for a transistor whose upper frequency limit allowed its use as an oscillator in the 200 to 500 kilocycle frequency region and whose amplifying properties were useful with a total input current of 2 to 15 micro-

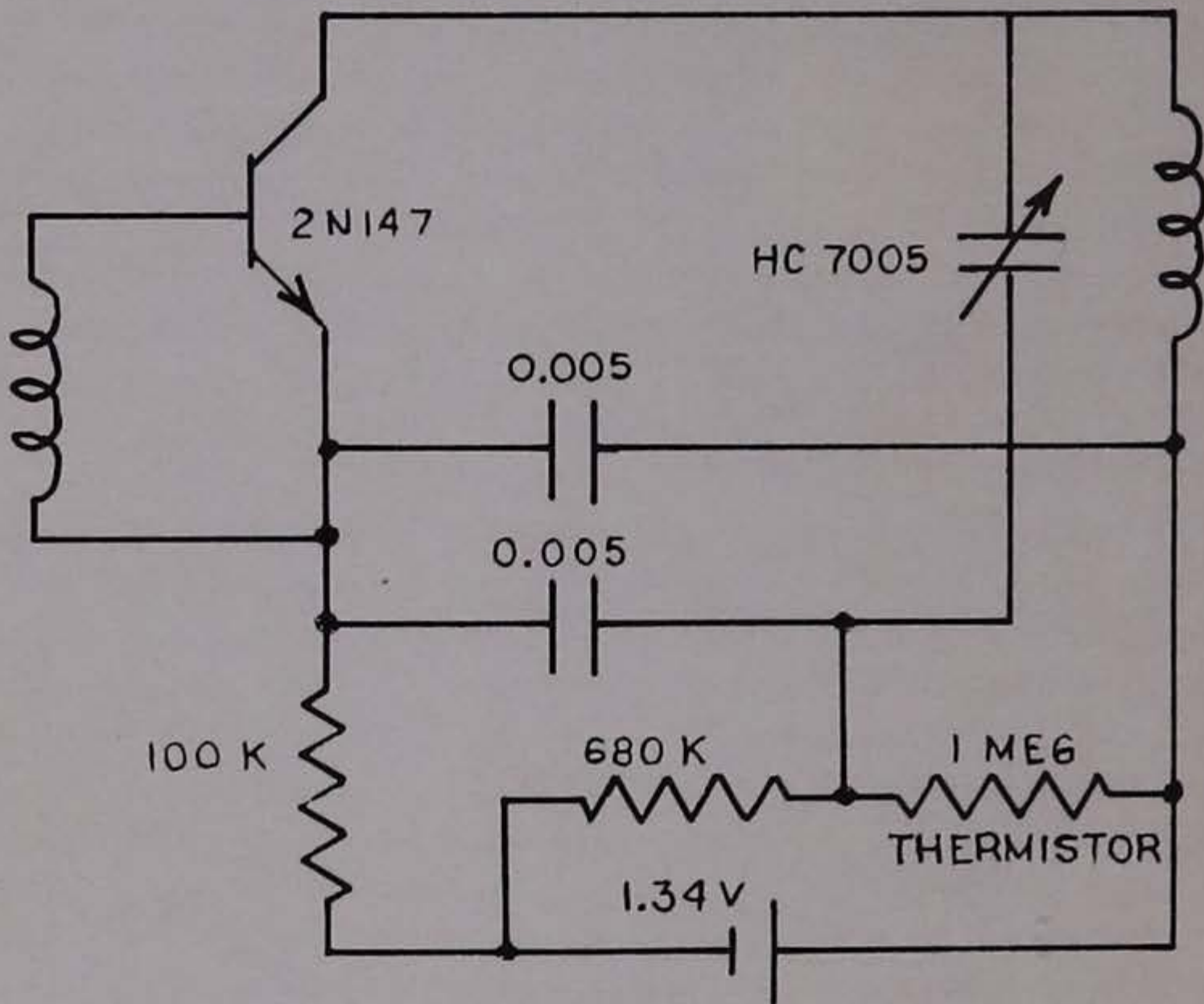


FIG. 1—A temperature transmitter using a 2N147 transistor.

amperes. The selection of the transistor type was on a trial and error basis, inasmuch as standard transistor specifications and curve sheets do not provide the necessary information. Several transistors were found to function adequately under these conditions. A standard circuit was used which inductively couples the collector circuit to the base circuit in a common emitter configuration. Oscillators whose total input power, including the power dissipated in a series-dropping resistor, was one microwatt were operated in breadboard fashion. Transmitters with such a low input power, though desirable from the standpoint of battery life, were not suitable because the oscillator stability was marginal and because the range was insufficient.

The temperature dependence of the oscillator is the result of several

factors acting simultaneously. The transistor itself is temperature sensitive due to the facts that I_{co} is a function of temperature and that the depletion layer at any back-biased interface in the transistor is a function of temperature. In general for every 10 degree centigrade change in temperature, I_{co} increases 2.9 times for germanium. In the circuit used, the variation of I_{co} varies the voltage drop across the series resistor, thus varying the effective supply voltage to the oscillator. Therefore, an increase of I_{co} as temperature increases causes the effective supply voltage to decrease. The capacity due to the presence of the depletion layer is a function of both the temperature of that layer and

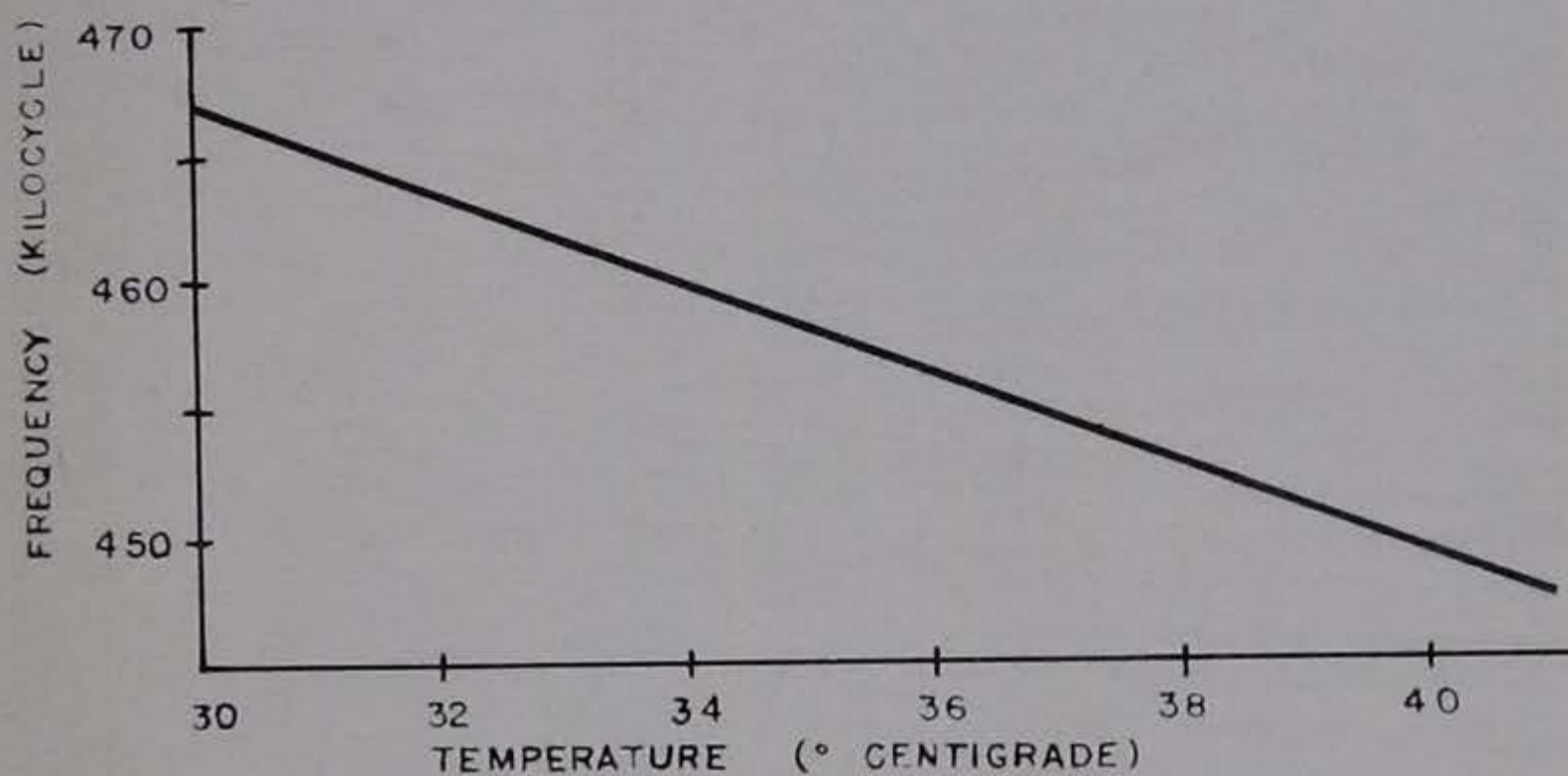


FIG. 2—Temperature calibration curve for the transmitter in Figure 1.

the voltage causing the layer to be formed. This capacity is reflected from the base circuit through the inductive coupling to the collector circuit and influences the resonant frequency of the tuned circuit. In addition to the effect of depletion layer capacity in the transistor, a diode capacitor utilizing the same depletion layer phenomenon was used as the component capacitor of the resonant circuit. Inasmuch as the diode's capacity is also a function of temperature and voltage it increases the temperature coefficient of the circuit.

Several temperature transmitters were designed using a variety of transistors and circuit elements. Figure 1 is the circuit of a transmitter which has a linear temperature-versus-frequency characteristic throughout the physiological temperature range of 30 to 40 degrees centigrade. The temperature dependence of this circuit (Fig. 2) is a function of the temperature characteristic of the thermister half-bridge in addition to the inherent temperature characteristics of the transistor and crystal diode.

The mechanical arrangement of the component parts of the temperature transmitter is shown in Figure 3. The outer shell, or case, is of machined nylon. The temperature-sensitive elements protruding from

one end are covered with the tip from a finger of a surgical glove. Seals between the latex finger tip and the nylon case are made by wrapping and tying with nylon suture. This method of sealing the unit has been found adequate in the experiments conducted. The seal against moisture may be further assured by dipping the unit in Tygon K-83, thereby providing a continuous plastic coating. No toxic reactions were noted when the unit was implanted in the dog.

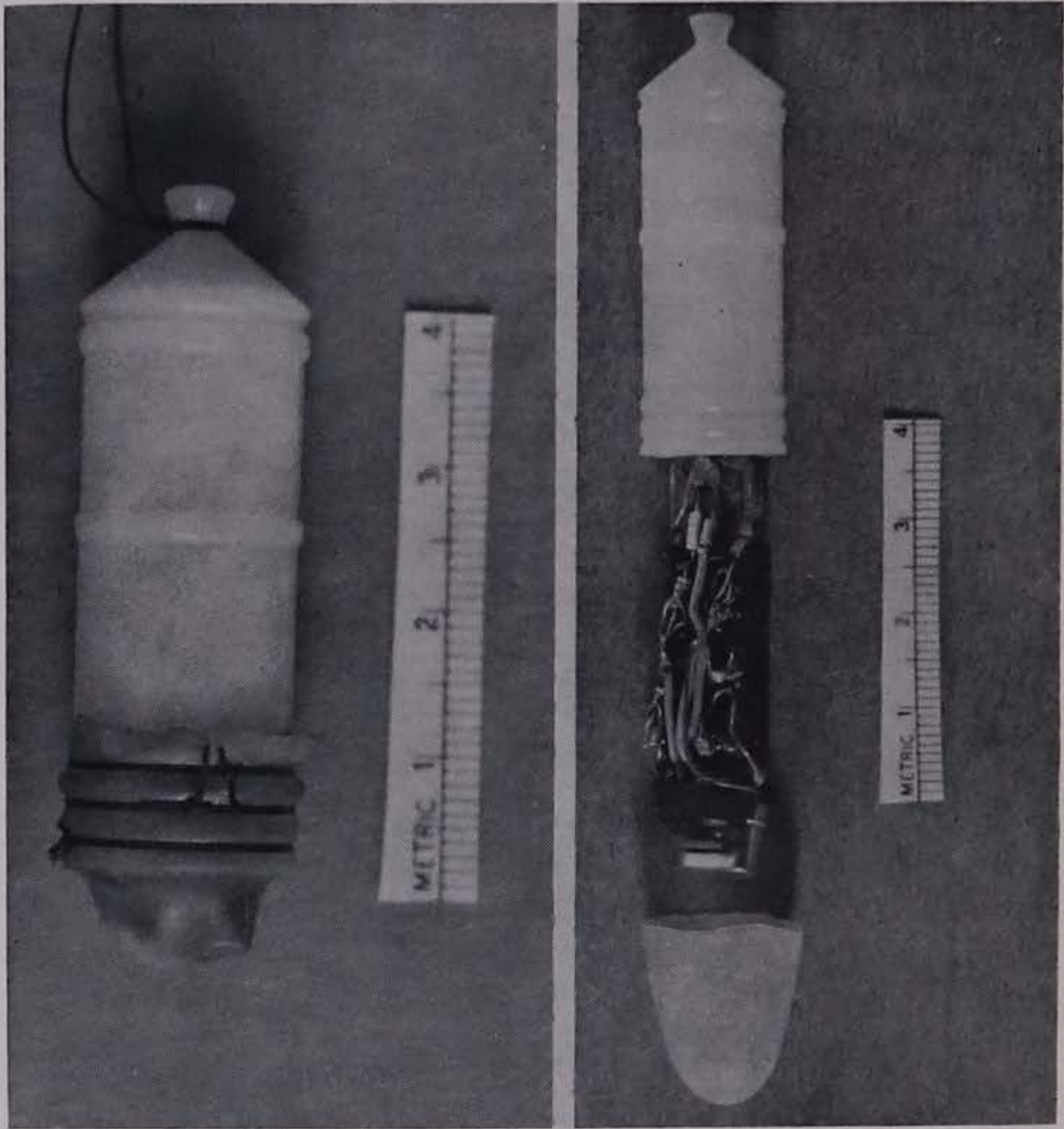


FIG. 3—Temperature transmitter using the 2N147 transistor, showing its component parts.

A mercury-cell battery was selected to power the unit because of the excellent discharge characteristics and because the by-products or gases produced are non-toxic and are all absorbed within the cell. The life of the 75-milliampere-hour cell exceeds 200 days.

The transmitting distance, or range, is such that a laboratory animal is free to move anywhere within a square room with an area of 100 square feet. The strength of the received signal is dependent upon the orientation of the temperature transmitter relative to the receiving

antenna. The larger the area of the room, the more precise the alignment must be. Only rarely did an animal orient itself so that the signal strength was too low to be received when a single-plane antenna with an internal area of six square feet was used.

The telemetry receiving system used with the temperature transmitter must, in reality, be a frequency-measuring system. Heterodyne and frequency-counting methods were used because of the availability of equipment and the degree of accuracy obtainable (Fig. 4).

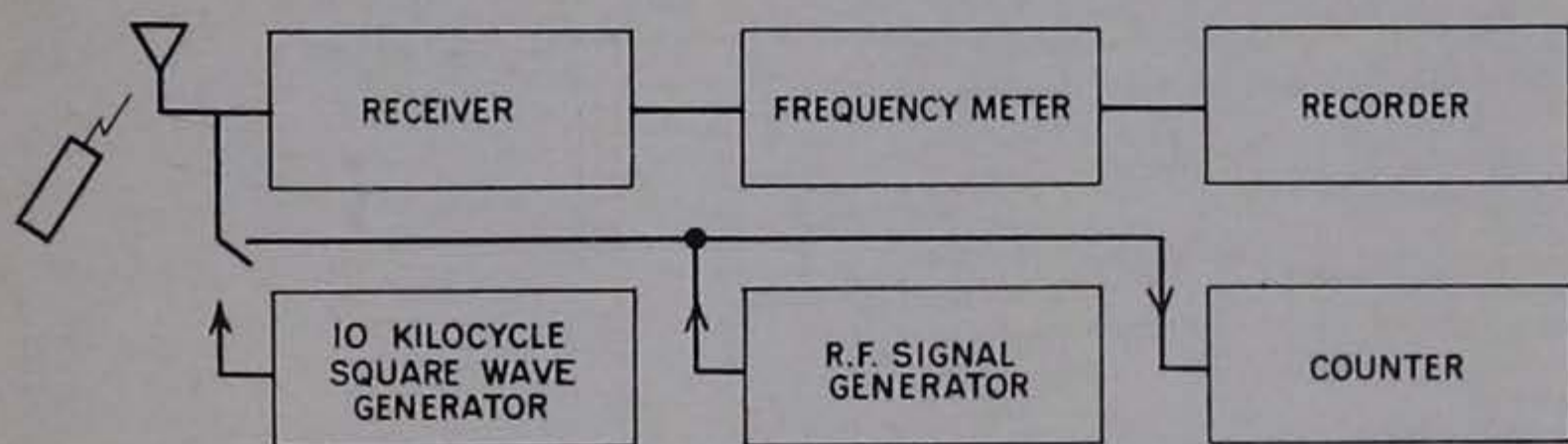


FIG. 4—Heterodyne and frequency-counting systems for temperature.

The heterodyne method is one that has been used for many years to measure frequency accurately. In using this method a signal of a known frequency near the frequency of the unknown signal (in this case the frequency of the temperature transmitter) is injected at the input, or antenna, terminals of a receiver along with the signal of unknown frequency obtained from the antenna. The two signals are then amplified together throughout the radio-frequency and intermediate-frequency sections of the receiver. Due to nonlinearities in various stages of the receiver the difference frequency is produced. The difference frequency is then measured and its value added to or subtracted from the known frequency, yielding the value of the unknown frequency. If the unknown frequency is below that of the known frequency, the difference frequency is subtracted from the known. If it is above, it is added to the known. The sense can be detected if the known frequency is shifted and the direction of change of the difference frequency noted. If it is desired to automatically record the frequency, the difference frequency is measured with a frequency meter and the output of the frequency meter is recorded. When the frequency is recorded, some knowledge of the unknown frequency must exist in order that the ambiguity indicated may be resolved. In the physiological experiments conducted, periodic hand readings were obtained using the frequency-counting method. Figure 5 is a photograph of the record from a post-surgical temperature experiment. Note the passage of the difference frequency through zero wherever a vertical line appears on the record. Following each passage of the difference frequency through zero, a hand reading was made in order to resolve the ambiguity.

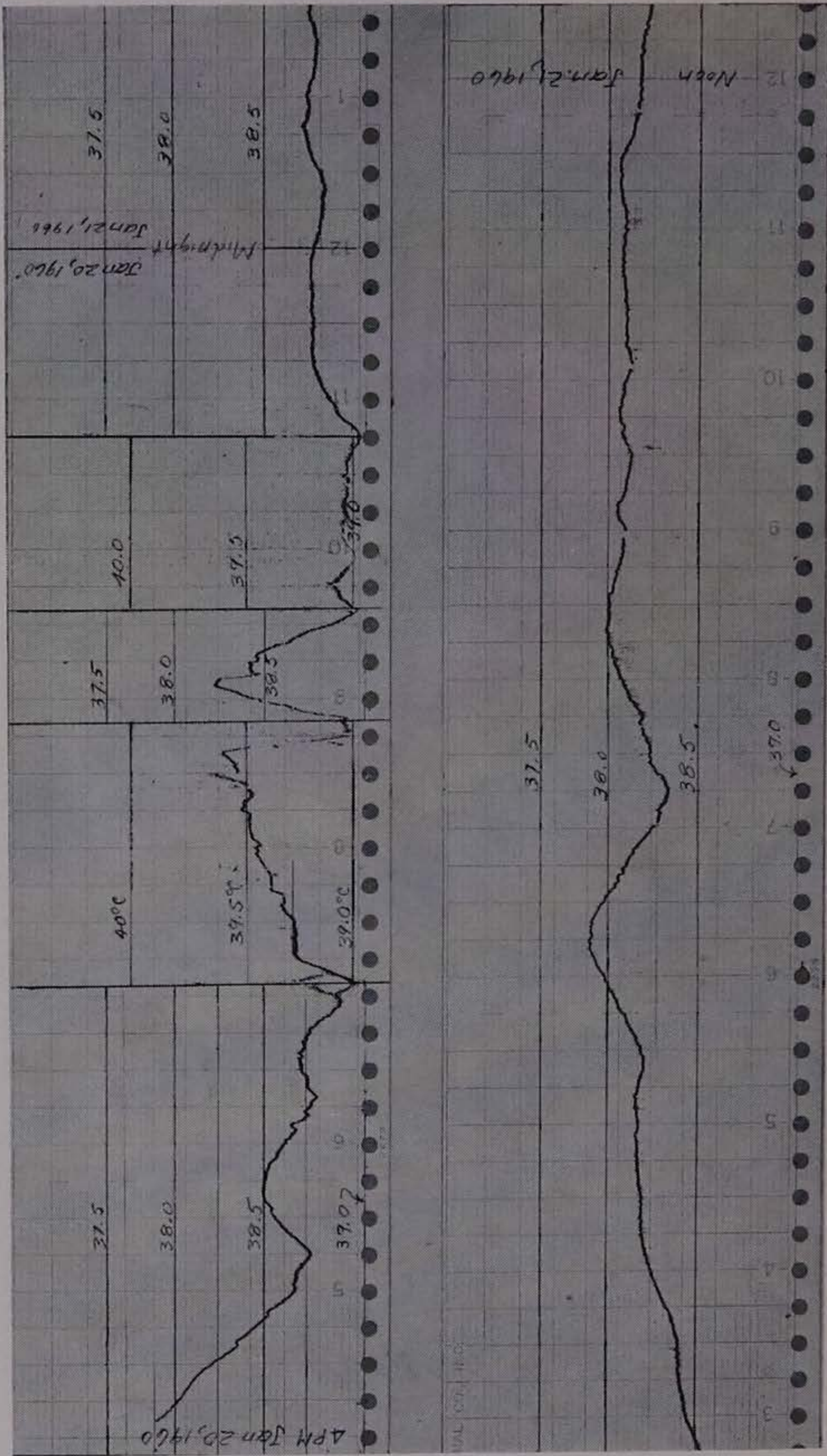


FIG. 5—Original temperature graph of post-surgical temperature experiment.

The frequency-counting method of determining frequency was used to obtain the calibration curves of the temperature transmitters as well as to periodically check frequency during the experiments. When the frequency of a signal is measured by this method, a signal from a variable oscillator is injected in the antenna terminals of the receiver along with the signal of the temperature transmitter. A difference frequency is produced as was discussed above. The variable-frequency oscillator is then adjusted so that the difference frequency is zero. Under this condition the frequency of the variable oscillator is exactly that of the temperature transmitter. A frequency counter then is used to determine the frequency of the variable oscillator. The accuracy of this scheme is probably the finest of the methods examined but, unfortunately, it does not lend itself to continuous automatic recording. Therefore, it was used only for the purposes of calibration and for periodic checks.

Heart Rate Instrumentation

The problems encountered in heart rate monitoring by telemetry methods are very similar to those of temperature monitoring. Thus, the procedure was generally the same as that used with the temperature unit. First the transmitter with its integrated amplifier was designed.

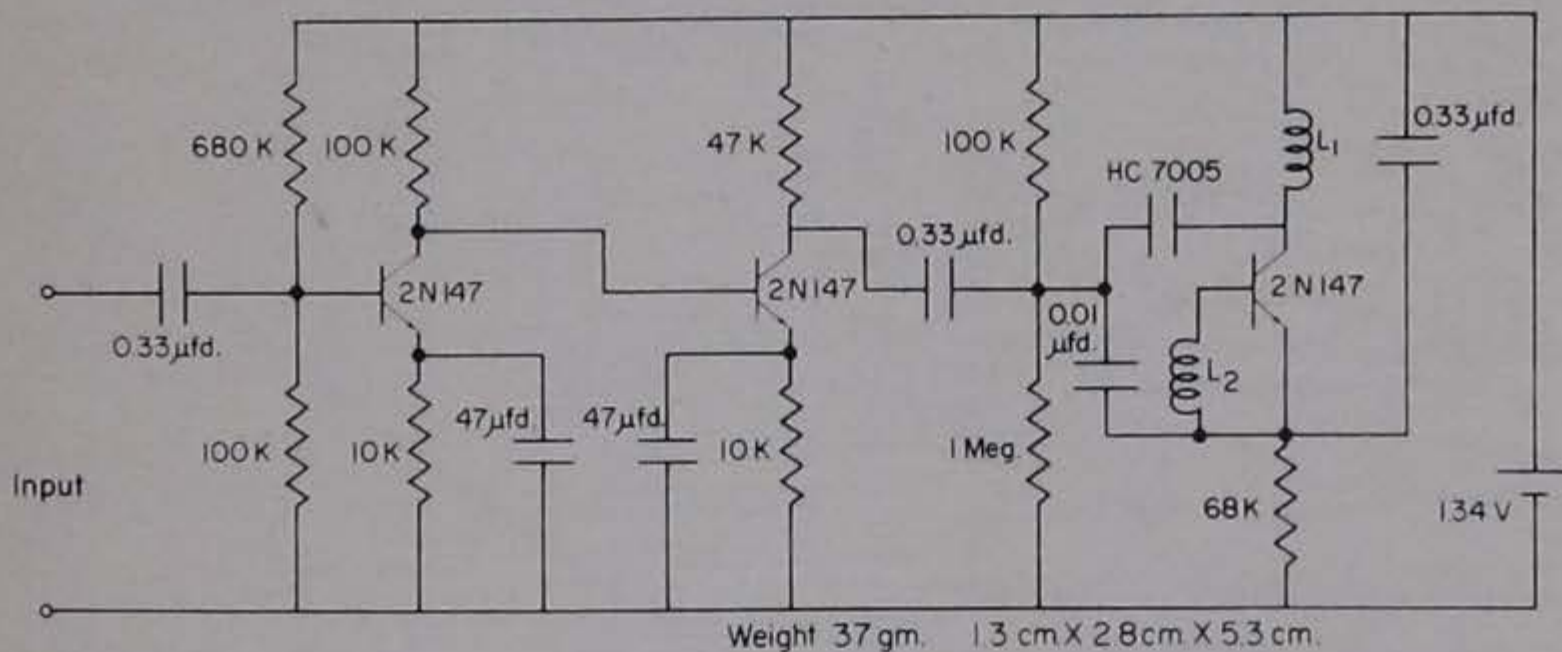


FIG. 6—EKG transmitter circuit.

Then a suitable receiving system, and companion equipment, was assembled to recover the information. The nature of the transmitter developed and of the associated system is such that the output information is in the form of a graph containing the characteristics of an electrocardiogram obtained using an electrocardiograph. Therefore, the transmitter is called an EKG transmitter.

The EKG transmitter consists of an amplifier and an oscillator (Fig. 6). Figure 7 is a photograph of the completed unit. Potentials in the tissue such as the potentials produced by the heart during its cycle are

amplified and used to frequency-modulate the oscillator. The amplifier consists of two cascaded transistor stages. The output of the last amplifier stage is applied to a diode capacitor which is the component capacitor of the tuned circuit of the oscillator. The capacity of the diode

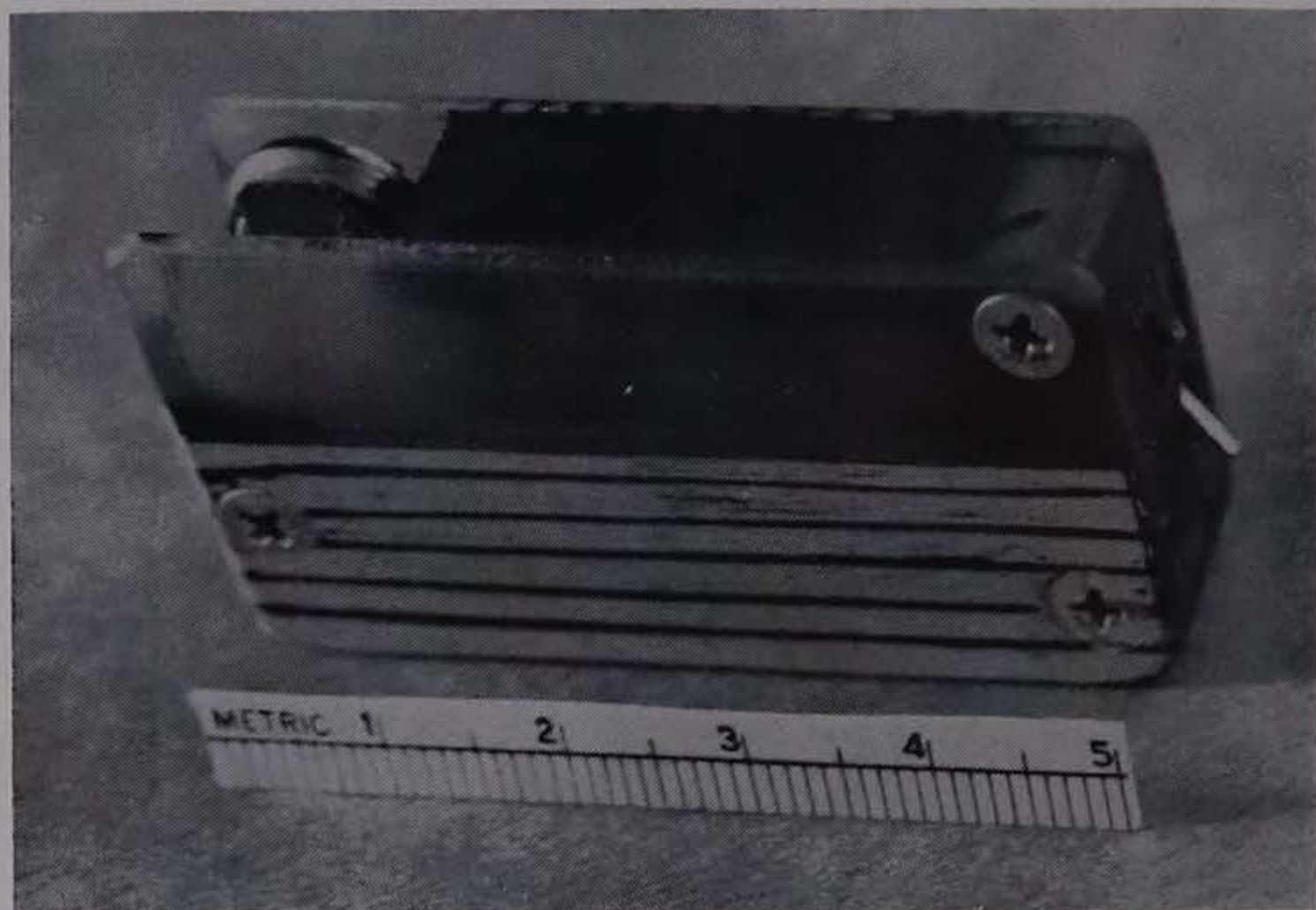


FIG. 7—Complete EKG transmitter.

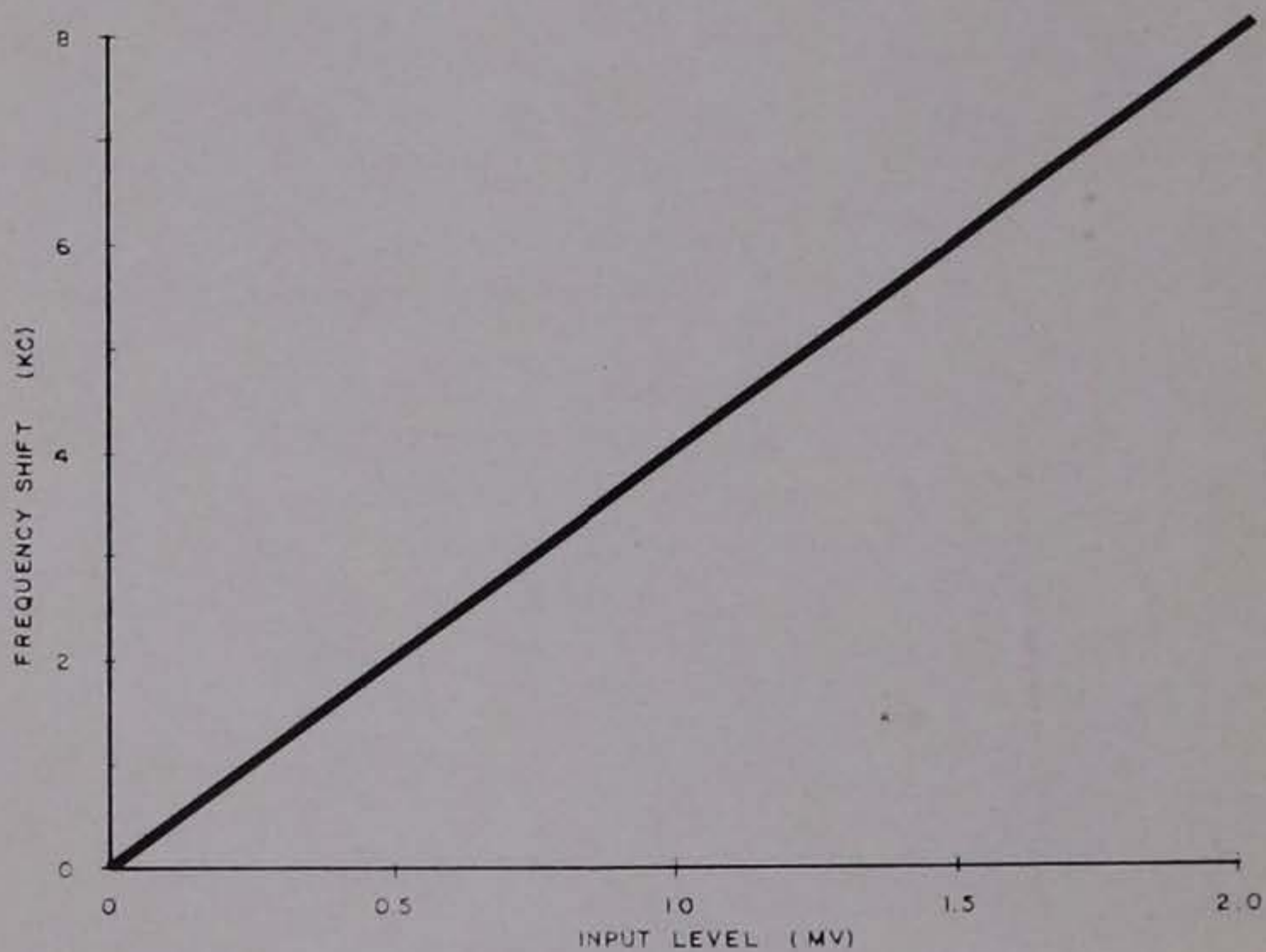


FIG. 8—Transfer characteristics of the EKG transmitter.

capacitor is a function of the voltage across it when it is back-biased.

The characteristics of the EKG unit were optimized for use in obtaining heart rates. The input impedance was measured by inserting a resistor in series with the electrodes and an audio oscillator. By this method an 87,000-ohm resistor halved the resulting frequency change of the oscillator with a constant-amplitude input signal. No phase shift of the signal occurred when the input frequency was 10 cycles per second. The transfer characteristics of the EKG transmitter are shown in Figure 8. The frequency response of the entire telemetry system is shown in Figure 9. The unit requires approximately 50 microamperes of current and has an operational battery life of greater than thirty-seven days from a 75-milliampere-hour battery.

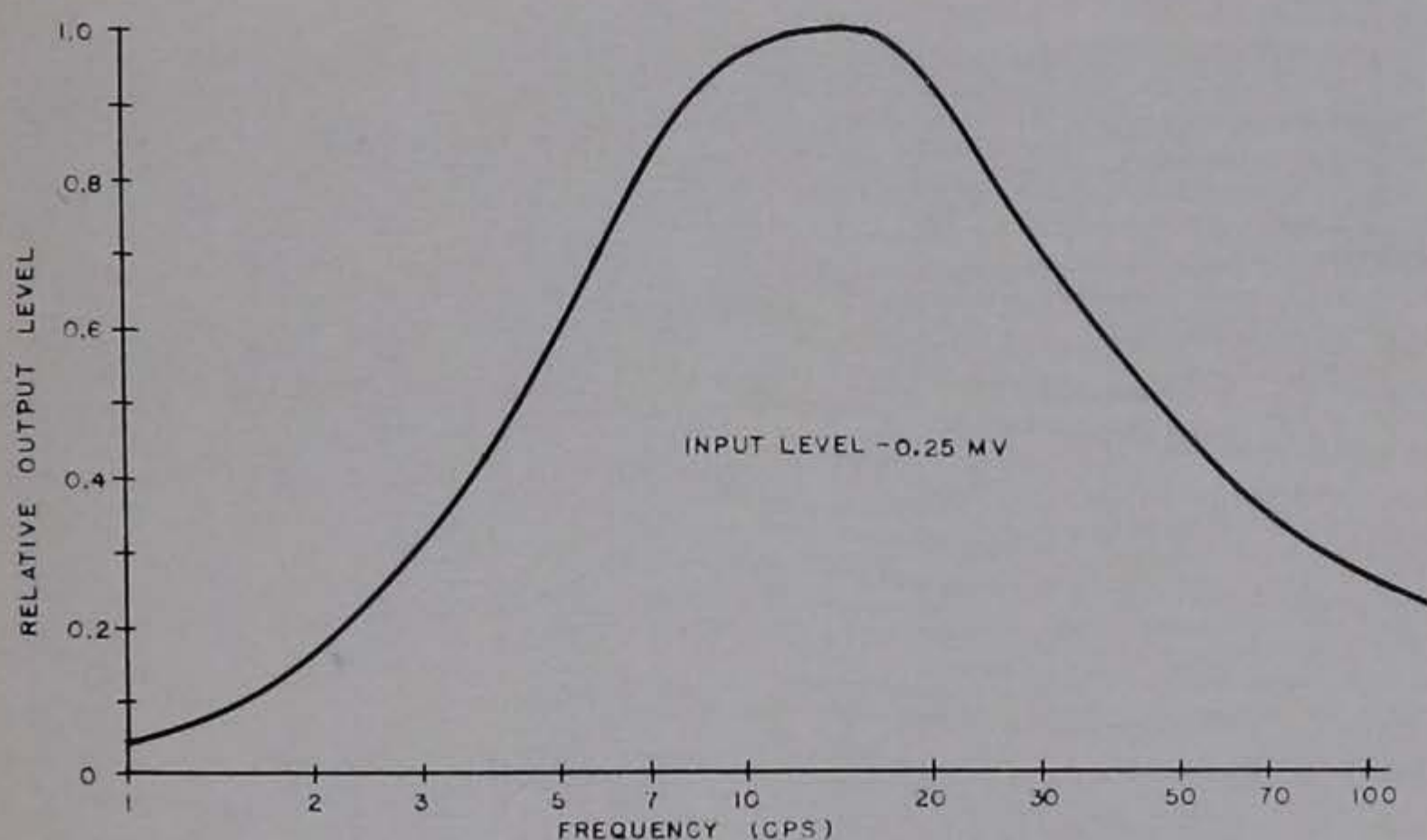


FIG. 9—Frequency response of the telemetry system developed in this research.

The telemetry system for heart rate is shown in the block diagram in Figure 10. A standard communications receiver suitable for receiving amplitude-modulated signals is used. The received signal is heterodyned against the beat-frequency oscillator within the receiver, producing an audible tone in the audio output of the receiver. This audible tone shifts in pitch in accordance with the potentials of the heart. A frequency meter connected to the audio output of the receiver produces an output voltage which, after filtering by a coupling unit, is suitable for recording with any standard electrocardiograph. Figure 11 is a photograph of electrocardiograms obtained from a variety of mammals. The heart rate can also be obtained by counting the number of pitch shifts per minute in the audio tone.

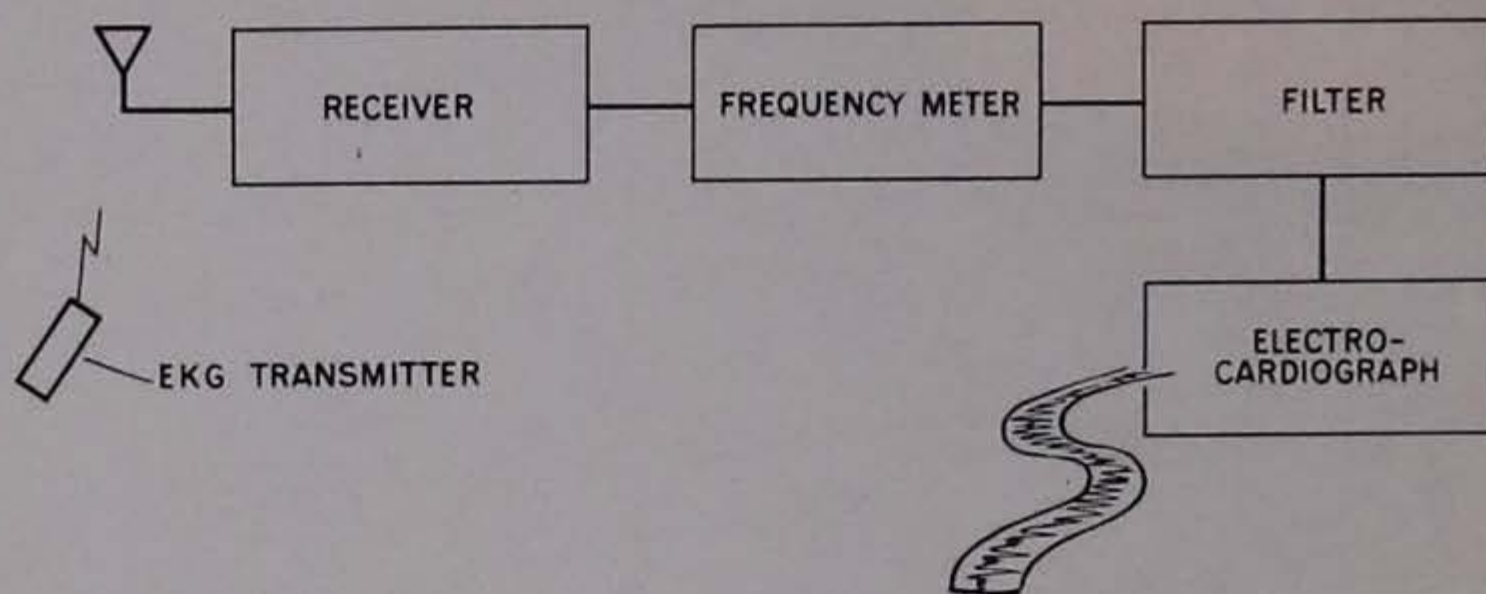


FIG. 10—Block diagram of the EKG telemetry system.

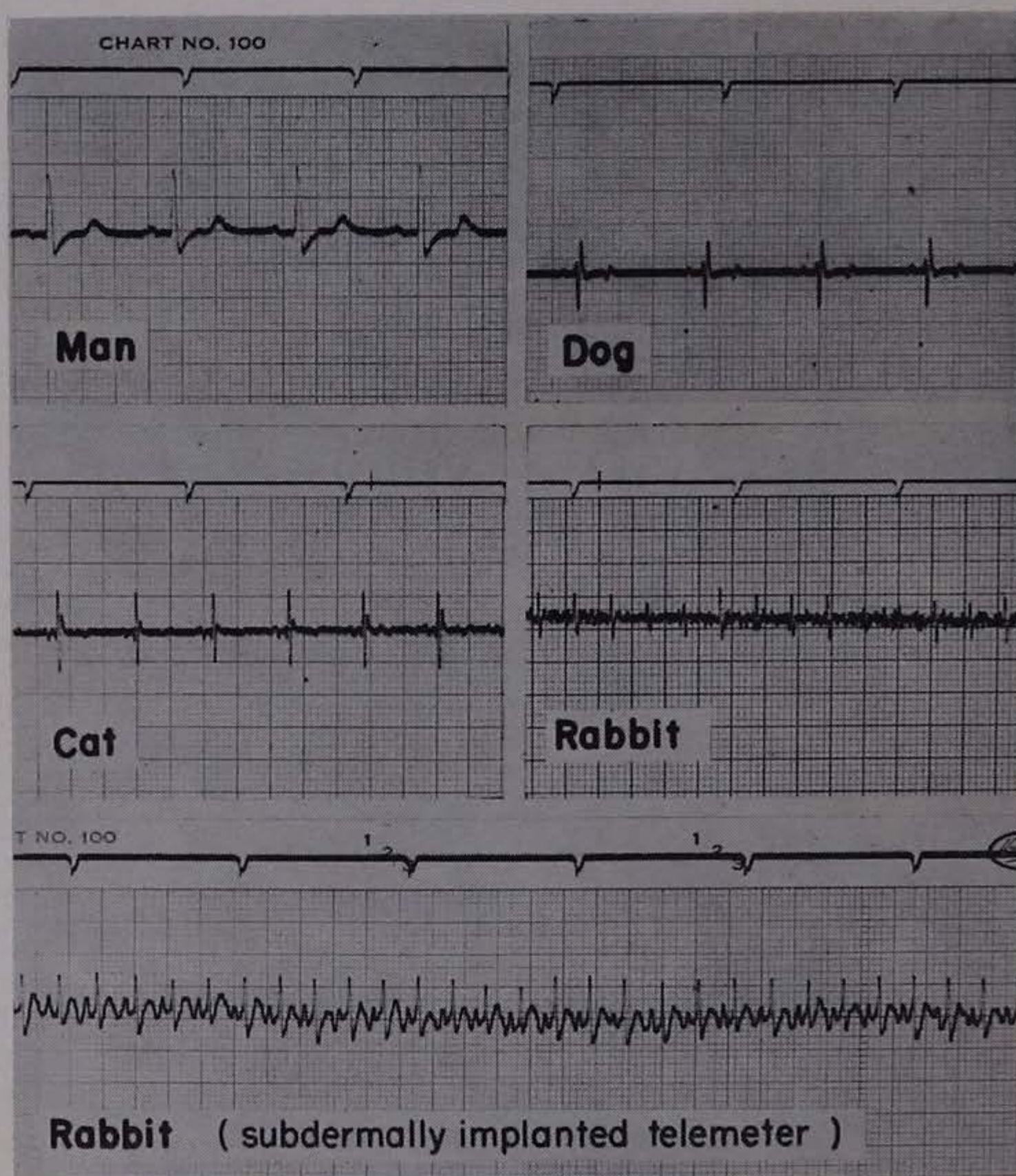


FIG. 11—Electrocardiograms obtained from four mammals by radio telemetry.

APPLICATIONS OF TEMPERATURE AND EKG
TELEMETRY SYSTEMS

Introduction

The telemetry systems devised during this research were tested in a short series of experiments involving species comparison of 24-hour heart rates, post-surgical recovery, and simultaneous heart rate and temperature measurements. In the first experiments, each lasting for three days, heart rates were recorded from several common laboratory animals. Then a 22-hour post-surgical temperature experiment was conducted which showed the effect of abdominal surgical procedures on core temperature. Finally, an experiment was conducted to demonstrate that simultaneous heart rate and body temperature rhythms could be measured for several consecutive days. A test was also made to determine the suitability of the EKG transmitter as a subdermally implanted telemeter.

Twenty-Four-Hour Heart Rate Periodicity in Dog, Cat, and Rabbit

In a series of short experiments with several animals isolated in an insulated room, various forms of 24-hour rhythms were found. Three animals, a dog, a cat, and a rabbit—all trained for several months to wear a harness, were used in three-day experiments. Tantalum subdermal electrodes were implanted weeks in advance near one scapula and the first lumbar vertebra. In each case the EKG transmitter was

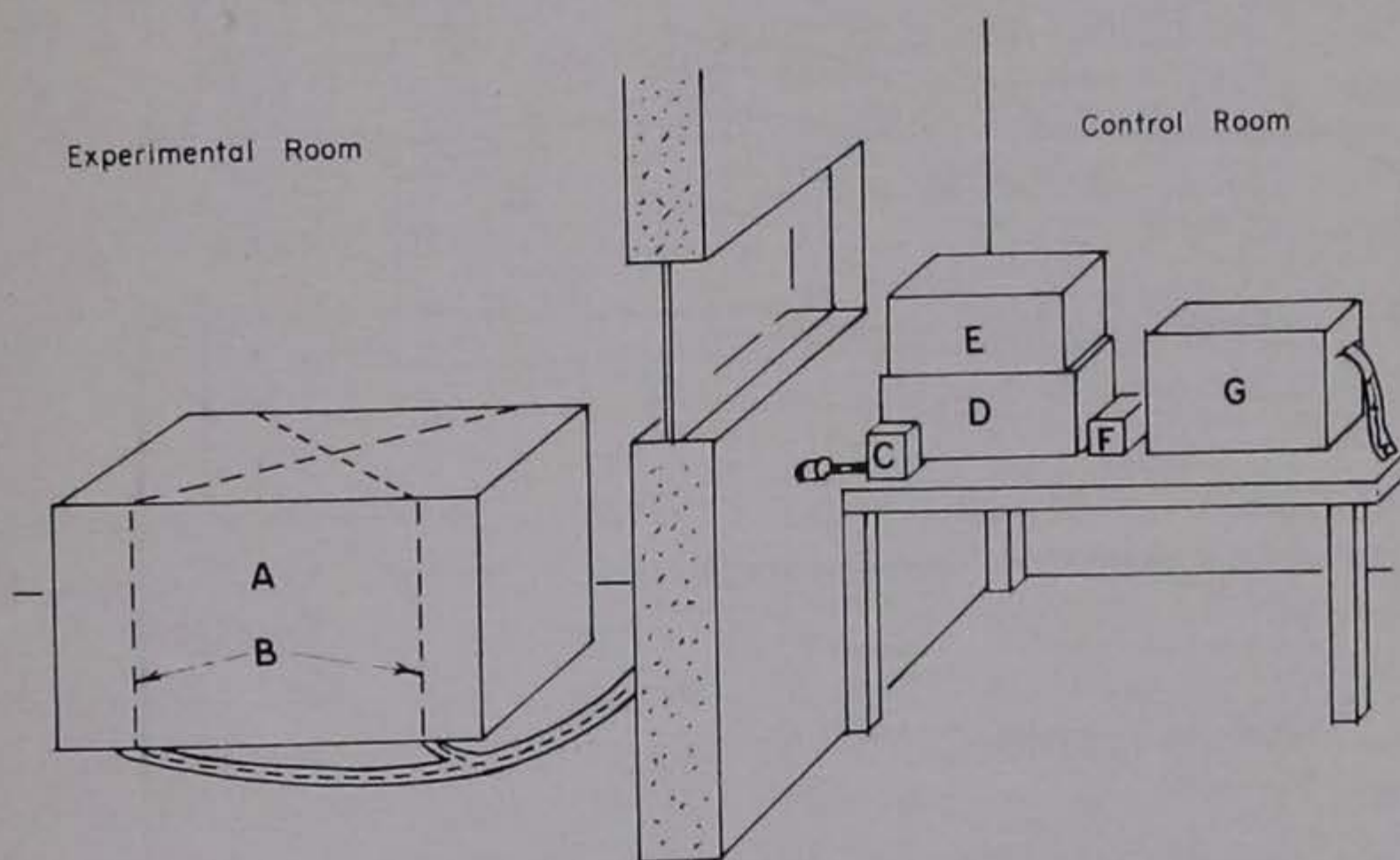


FIG. 12—Physical arrangement of equipment. Note that antenna leads could be 20-30 ft. long. Greater separation could be attained using amplifiers. A = experimental cage; B = antennas; C = antenna switch; D = receiver; E = frequency meter; F = filter; G = electrocardiograph.

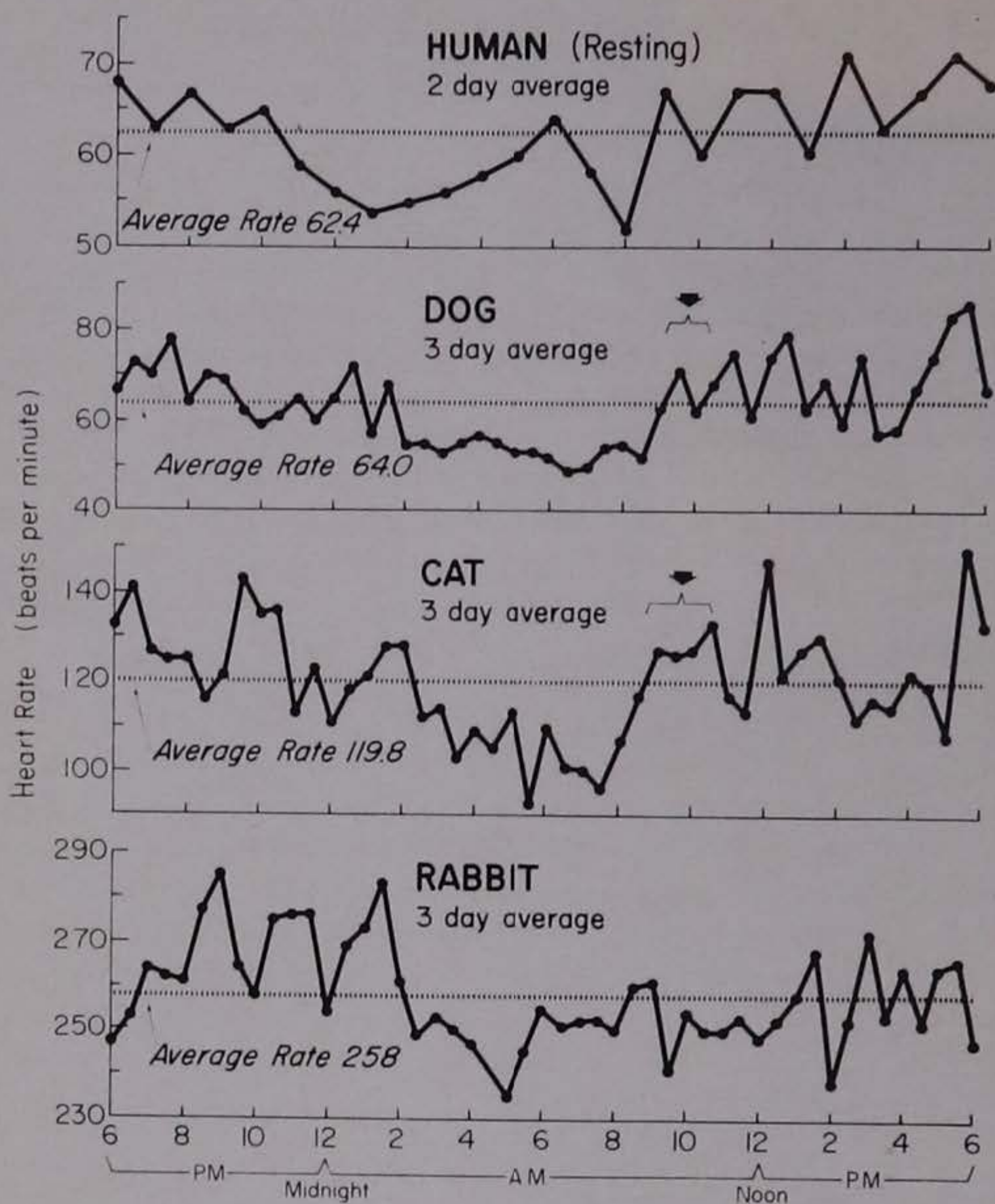


FIG. 13—Average heart rate of a dog, a cat, and a rabbit—compared with man—showing 24-hour periodicity. During the period marked with an arrow, fresh food and water was given to the animal each day.

mounted in a comfortable position on the animal and then connected to the electrodes. The animals were then placed in cages constructed of non-conducting material similar in size to their laboratory cages. Three mutually perpendicular loop antennas were placed around the cages. After a training period of several days in a semi-soundproof room (Fig. 12), heart rates of the animals were measured every thirty minutes for the subsequent 72 hours (see Appendix).

The data was first reduced by averaging, and then further analyzed to obtain a Fourier series. The three-day averaged heart rates for the dog, the cat, and the rabbit showed periods of fast heart rate which

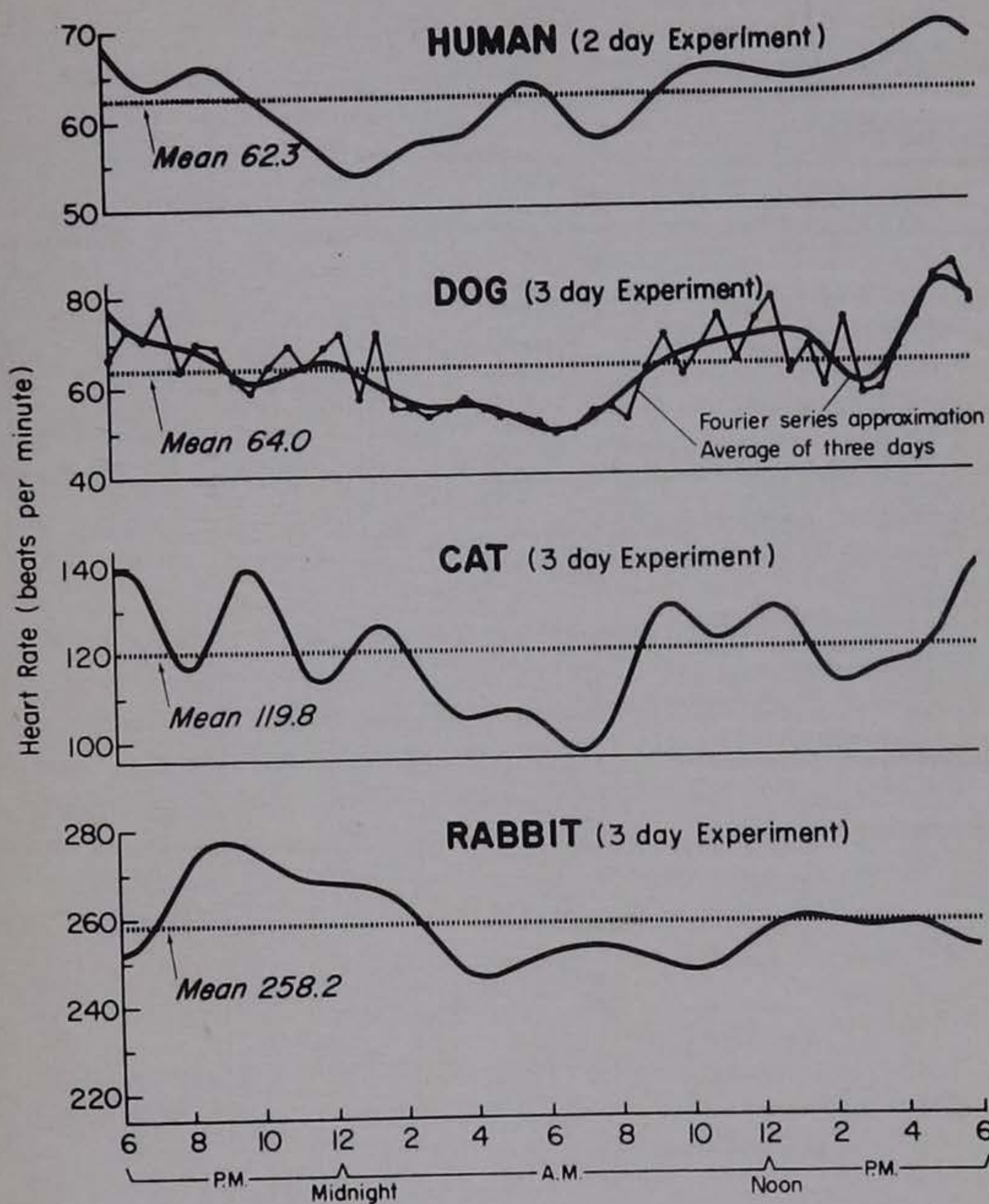


FIG. 14—Fourier series approximations of the data appearing in Figure 13.

coincide with normal periods of activity and conversely showed periods of low heart rate at times of normal resting (Fig. 13). These are compared in the figure with a two-day averaged heart rate for man which was obtained by Dr. G. E. Folk in an earlier experiment. Note that the period of maximum heart rate progresses from 2:00 P.M. for a human to 4:00 P.M. for a dog, to 6:00 P.M. for the cat, to 10:00 P.M. for the rabbit. The data was further reduced for the purposes of curve-smoothing (Fig. 14) and to obtain a quantitative expression in the form of a Fourier series (Table II). The major Fourier coefficients in order of their importance are the 24-hour, the 8-hour, the 6-hour, and the 12-hour

TABLE II

NUMERICAL VALUES OF THE NORMALIZED COEFFICIENTS AND PHASE ANGLES
FOR THE CURVES SHOWN IN FIGURE 14

Where $F(t) = K [1 + C_1 \sin(2t + \theta_1) + C_2 \sin(4t + \theta_2) + \dots + C_n \sin(2nt + \theta_n)]$,
in Which the Reference is 6:00 P.M. and t Is Time in Days

n	HUMAN K = 62.34		DOG K = 64.02		CAT K = 119.8		RABBIT K = 258.2	
	C_n	θ_n	C_n	θ_n	C_n	θ_n	C_n	θ_n
1	0.079	2.253	0.134	1.472	0.077	1.532	0.037	0.497
2	0.031	1.188	0.029	1.600	0.053	5.474	0.021	4.785
3	0.019	5.835	0.069	0.528	0.050	1.193	0.014	3.790
4	0.029	2.935	0.045	0.855	0.015	2.830	0.011	4.795
5	0.013	4.34	0.003	5.886	0.020	2.083	0.011	2.699
6	0.015	1.893	0.017	1.769	0.043	2.033	0.006	1.869
7	0.009	3.828	0.010	1.45	0.036	0.150	0.002	2.907
8	0.011	2.151	0.004	1.56	0.022	0.443	0.001	2.801

for the dog; the 24-hour, the 12-hour, the 8-hour, and the 4-hour for the cat; the 24-hour, the 12-hour, the 8-hour, and the 6-hour for the rabbit; and the 24-hour, the 12-hour, and the 6-hour for man.

During these experiments it was noted that throughout periods of deep sleep the heart rate of the animals displayed a marked degree of arrhythmia. A certain amount of arrhythmia occurred at all times, of course, but during sleep it was periodic and very radical. This effect was probably due to respiration. Arrhythmia in the cat heart rate was selected for illustration (Fig. 15).

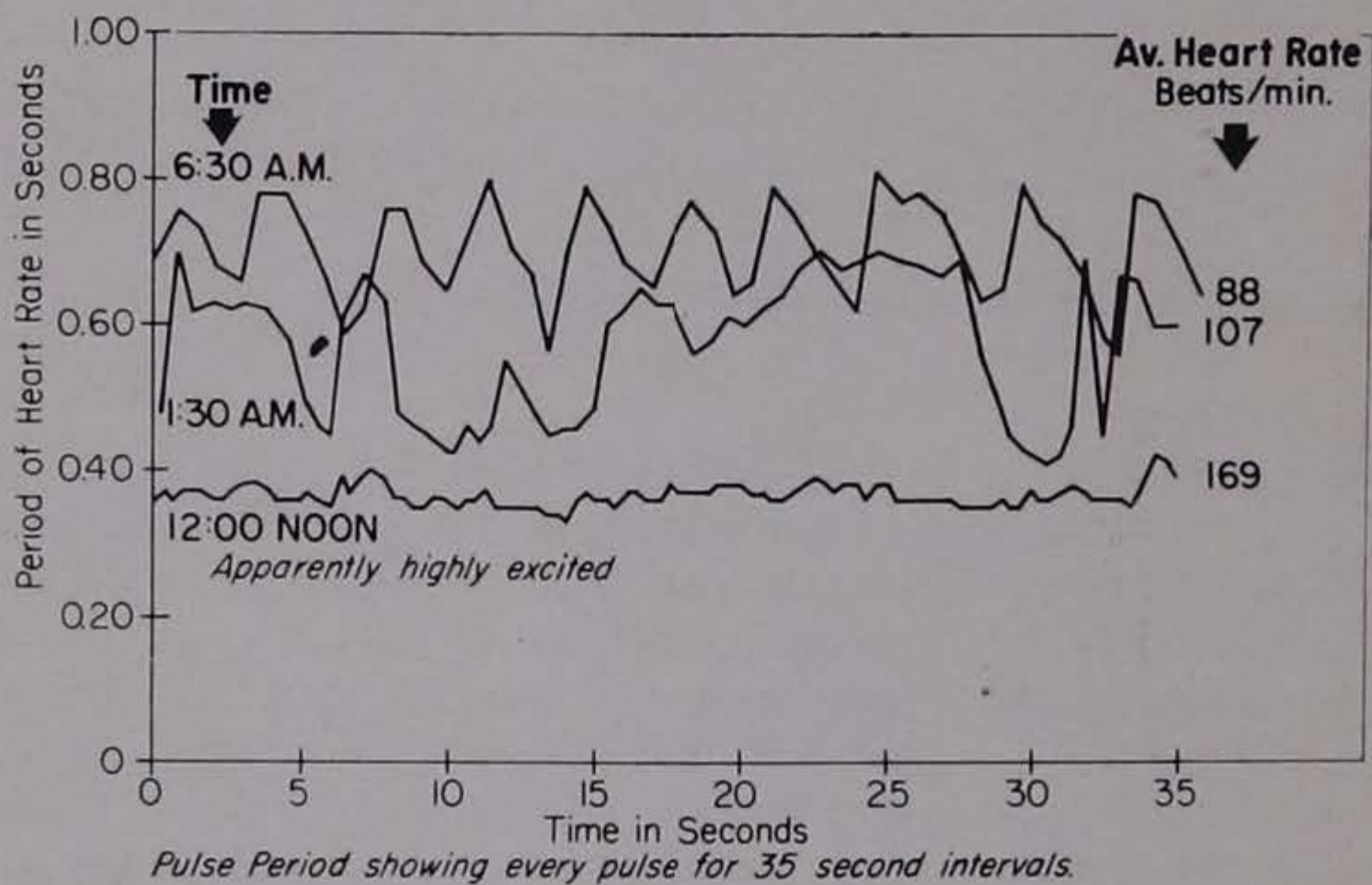


FIG. 15—Arrhythmia in the heart rate of the cat at three different times during a 24-hour period.

A second observation was that the lowest heart rates recorded for the dog and the cat (see Appendix) are considerably lower than those given in a standard biological handbook.¹² For the dog (weight: 10.5 kg.) the heart rates ranged from 41 to 114 beats per minute (b.p.m.), in contrast to the handbook range of 100 to 130 b.p.m. For the cat the heart rates ranged from 82 to 177 b.p.m., in contrast to the handbook range of 110 to 140 b.p.m. The low heart rates are attributed to the fact that the animals of this experiment attained a true resting condition.

Post-Surgical Temperature Experiment

In this experiment a temperature transmitter was surgically implanted next to the abdominal cavity of a dog, and the local internal temperature in the vicinity of the transmitter was recorded over the subsequent 24-hour period.

The temperature transmitter was placed retroperitoneally 1.6 cm. to the left of the linea alba about 5 cm. caudal to the xiphoid process. It was fastened with sutures that passed through the ventral abdominal muscles and skin and tied externally. The temperature-sensing transistor was facing in a dorsal direction in close proximity to the ventral-posterior aspect of the stomach. The sequence of events were as follows:

- Day 1. 2:00 P.M.—Nembutal administered, 35 mg/kg.
Female dog, weight 11 kg.
Transmitter was surgically implanted.
4:30 to 5:30 P.M.—Regurgitation.
5:30 P.M.—Uncoordinated swimming movements.
8:15 P.M.—Animal drank cold tap water.
The animal was left unattended throughout the night.
- Day 2. 2:00 P.M.—Experiment concluded and transmitter recovered.

The animal refused food. On several occasions the animal drank cool water. Because there was no chewing or scratching of the wound, the surgery evidently did not unduly upset the animal.

The original temperature record, which was obtained throughout the entire recovery period, is shown in an earlier section (Fig. 12). Temperature responses to drinking and regurgitation are clearly shown in Figure 16, which was prepared from the data in the original record.

Simultaneous Heart Rate and Temperature Experiment

In this experiment temperature and heart rate of a dog were measured and an interdependence of these two variables was found.

The techniques of measuring these variables required the use of two transmitters. The dog wore a harness which contained the EKG trans-

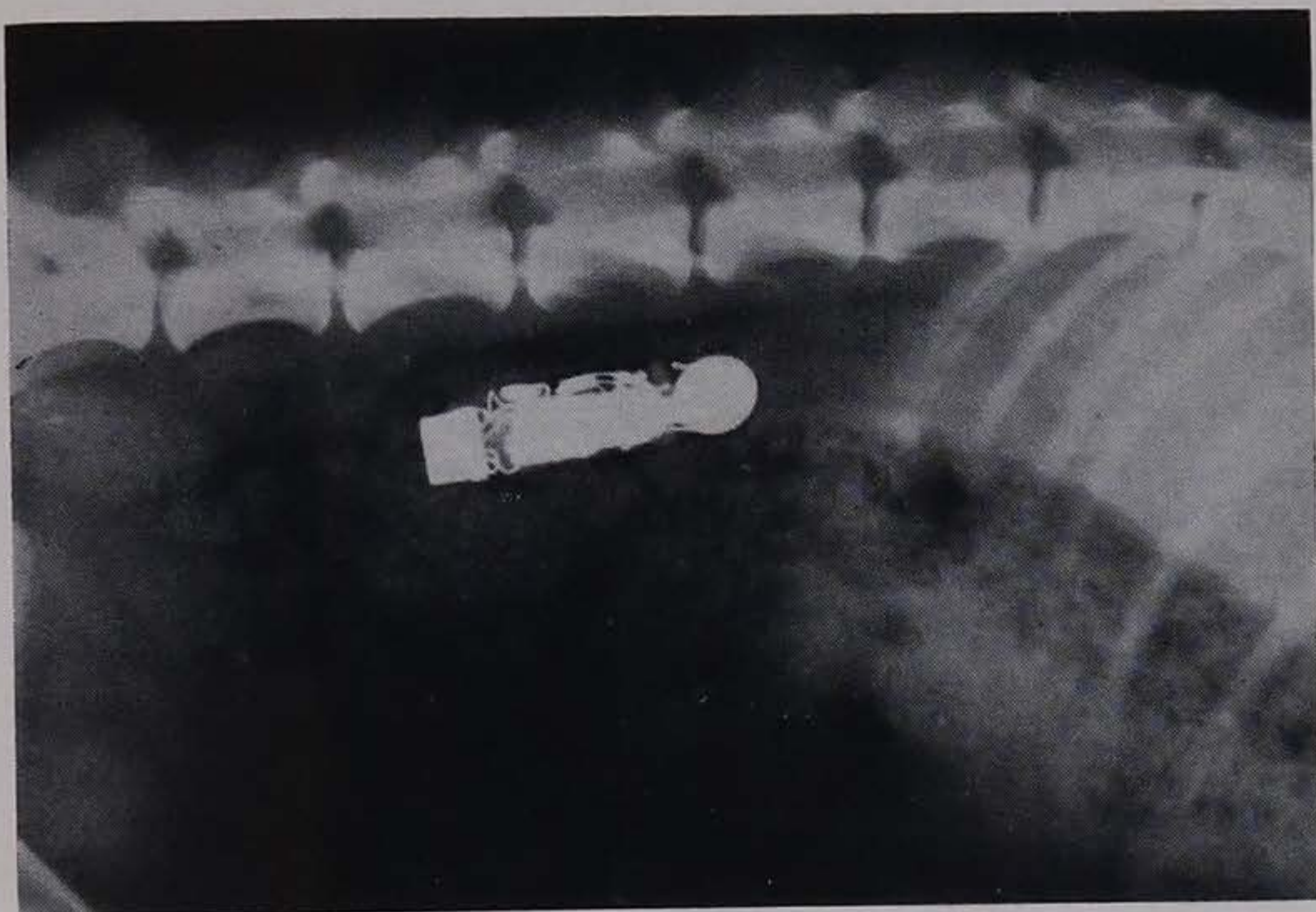


FIG. 18—Right to left lateral roentgenogram showing the position of the temperature transmitter.

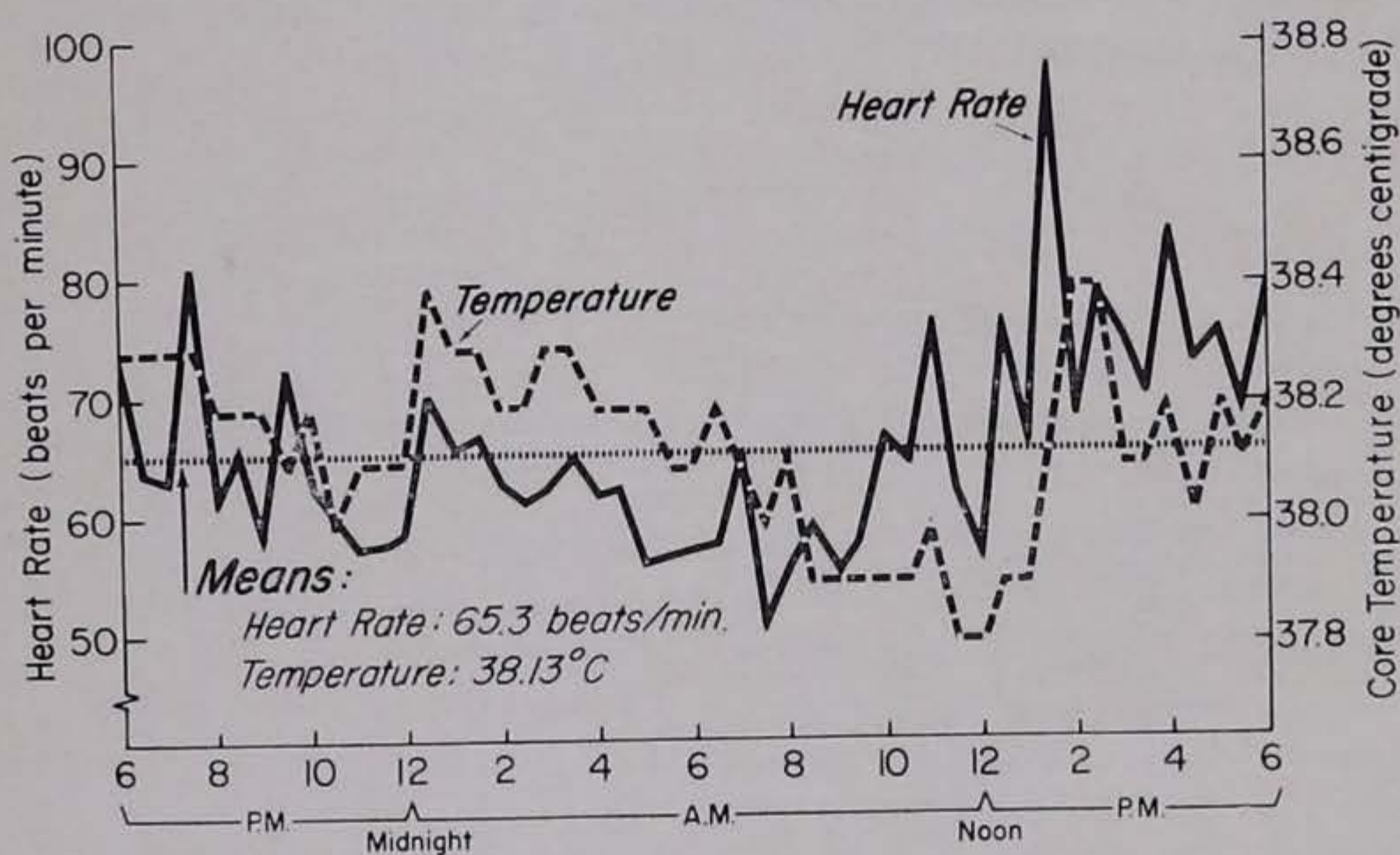


FIG. 19—Correlated heart rate and temperature of a dog for a 24-hour period as obtained from the original data.

semi-soundproof room. Sufficient food and water were supplied to last throughout the experiment. With these precautions it was hoped that normal biological rhythms in temperature and heart rate would be observed.

TABLE III

NUMERICAL VALUES OF NORMALIZED COEFFICIENTS AND PHASE ANGLES
FOR CURVES SHOWN IN FIGURE 20

Where $F(t) = K [1 + C_1 \sin(2t + \theta_1) + C_2 \sin(2t + \theta_2) + \dots + C_n \sin(2nt + \theta_n)]$,
in Which the Reference is 6:00 P.M. and t Is the Time in Days

n	HEART RATE $K = 65.34$		TEMPERATURE $K = 38.13$	
	C_n	θ_n	C_n	θ_n
1	0.113	2.047	0.0034	0.408
2	0.068	3.394	0.0028	2.542
3	0.007	0.310	0.0026	5.092
4	0.020	5.567	0.0019	5.97
5	0.0154	5.118	0.0014	6.14
6	0.171	2.272	0.0011	1.106
7	0.031	2.900	0.0016	2.178
8	0.043	5.347	0.0004	4.972

The original data was first graphed (Fig. 19) to show its trends. It was then analyzed by the Fourier method to smooth the curve and to obtain a qualitative mathematical expression describing the phenomena. The major Fourier coefficients (Table III), in order of their importance, are the 24-hour, the 12-hour, and the 6-hour for both heart rate and temperature. The graphs obtained using the Fourier series approximation (Fig. 20) show very clearly a simultaneous correlation between heart rate and temperature.

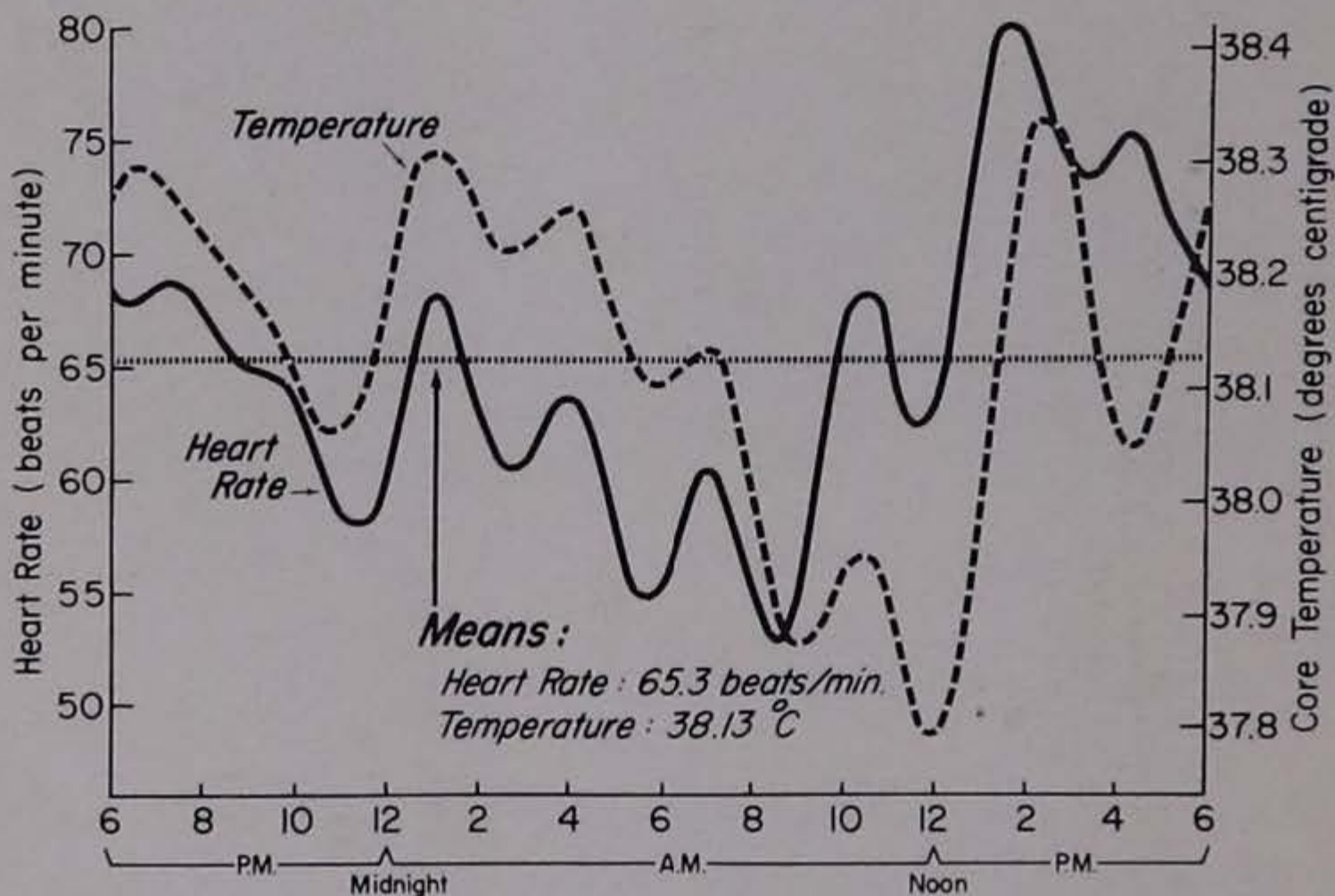


FIG. 20—Correlated heart rate and temperature of a dog for a 24-hour period (Fourier series approximation of data in Figure 19).

Operational Life Test of the EKG Transmitter

The EKG transmitter developed in this research was implanted in a rabbit in order to determine its suitability as a subdermally implanted telemeter. The test consisted of implanting the transmitter, and then daily checking of the animal's heart rate.

The EKG transmitter was prepared by fixing stainless steel electrodes to the input terminals of the transmitter and then hermetically sealing the unit. Stainless steel wires 0.015 inches in diameter were used for the electrodes and were formed in the manner shown in Figure 21. A new battery was soldered in place and then the unit was sealed with four coats of plastic paint (Tygon, clear K-83) by dipping. After sealing, the unit was ready for implantation.

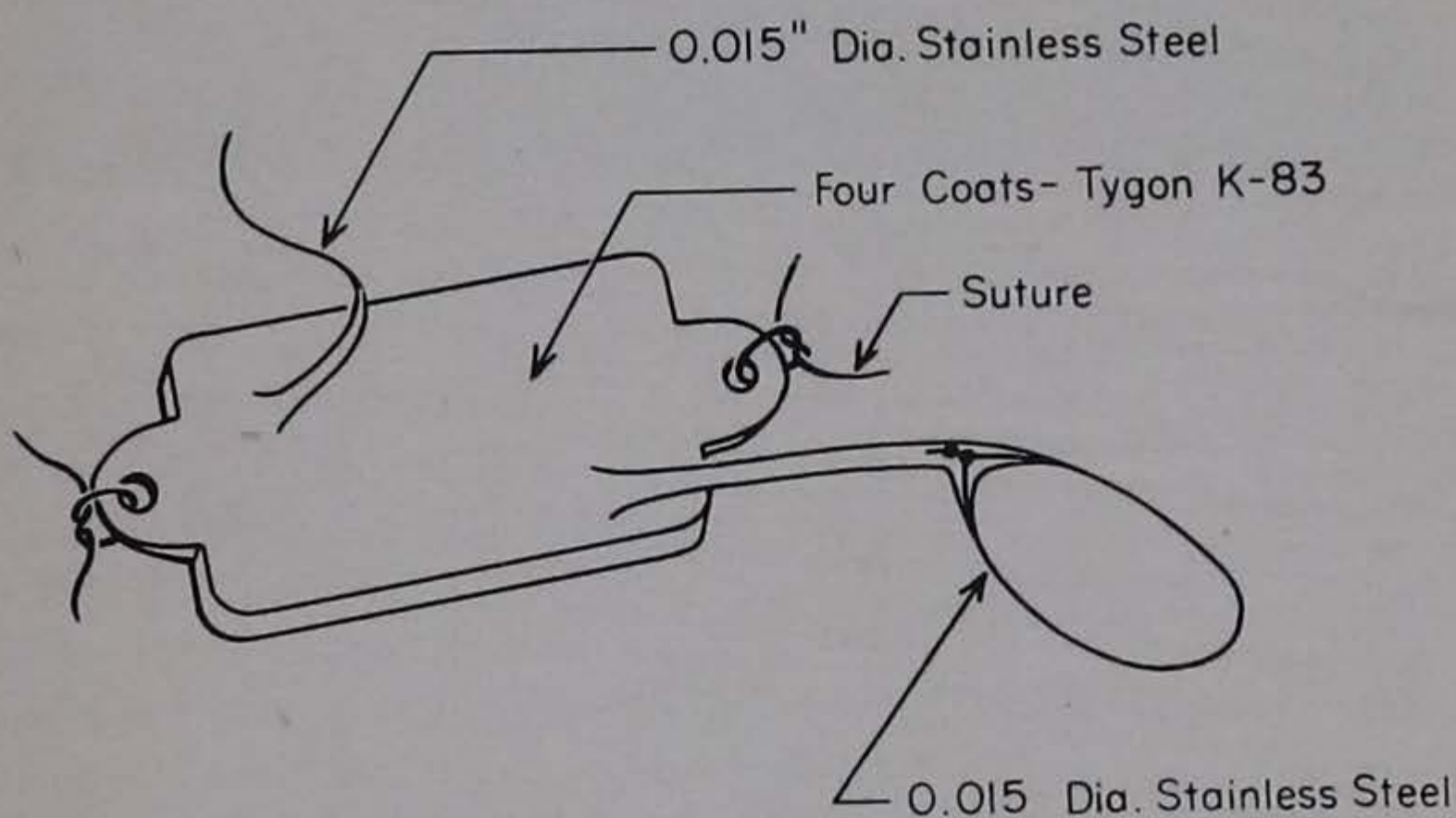


FIG. 21—EKG transmitter prepared for implantation.

The EKG transmitter was implanted in the abdominal cavity of a rabbit. The rabbit was anesthetized with ether and a midline incision was made. The transmitter was placed so that the indifferent electrode was in the lower right part of the abdominal cavity; the other electrode was in the upper left part of the abdominal cavity. The upper electrode probably rested on or near the diaphragm near the apex of the heart. The EKG transmitter lay flat on the ventral abdominal wall and was, therefore, supported by the abdominal musculature (Fig. 22).

Following surgery an electrocardiograph record was taken each day using the telemetry system. It was estimated that the operational life of the unit would be 30-40 days from the time of energizing the unit with the battery. A six-day delay was encountered before the unit was implanted. The actual operational life after implantation was found to be 31 days.



FIG. 22—Dorso-ventral roentgenogram showing the position of the EKG transmitter in the rabbit.

DISCUSSION

Subdermal Temperature Transmitter

Although many persons have conceived the use of radio telemetry as a means of measuring subdermal temperatures, only one such effort has been reported in the literature.³ MacKay attempted to measure temperature as well as pressure with the same unit. He found that the temperature-indicating parameter of the transmitted signal also showed a response to pressure. This necessitated the use of calibrating charts or weighting factors for the correction of temperature measurements. Evidently, due to this disadvantage plus a very limited operational life (four days), MacKay's unit has found little application, for no experimental data is found in the literature.

The unit used by Eklund⁷ was designed specifically to measure the temperature of large bird eggs during incubation. This unit had many of the characteristics which are desirable for a subdermal unit in that the size was small, the energy source was self-contained, and frequently transmission through the setting hen was necessary. The designers evidently compromised in favor of range, since the battery life was short and the size (25 cm.³) was relatively large.

The temperature transmitter developed in the present research has several superior characteristics which allow it to be continuously used

over long periods of time. The calculated battery life, based on the manufacturer's specifications of energy storage, indicates a useful life exceeding 200 days. The long operational life was achieved through a design compromise which restricted the range of transmission to a few meters. The actual range depends upon the sensitivity of the receiving equipment and upon the magnitude of noise level that can be tolerated. Since the unit is intended to be surgically implanted in tissue, the size requirements were not as stringent as for a "swallowable" telemeter. Units of the size and weight of the temperature transmitter can be implanted in animals as small as a rabbit. Therefore, the temperature transmitter designed during this study is apparently the first implantable unit of its kind. Furthermore, the operational life of this unit far exceeds that of the previously developed temperature transmitter.

Subdermal EKG Transmitter

Only one subdermal telemeter for measuring heart phenomena has been reported and the available information on it is very limited.⁸ The present unit (described under "Methods and Instrumentation"), although intended for measuring heart rate, transmits the wave form of the potentials developed by the heart and may be called an EKG transmitter. The frequency characteristics were adjusted to discriminate against skeletal muscle potential response and to enhance heart potential response. The EKG transmitter was found to have an operational battery life of thirty-seven days. This should be an adequate duration to permit the completion of most physiological experiments.

Twenty-Four-Hour Heart Rate Rhythms

Many physiological rhythms have been found and attempts have been made to describe them quantitatively. Some physiological rhythms, although known to exist, are very elusive because the available measuring techniques used tend to disturb the measurements. Therefore, as one of the illustrative experiments of this study, 24-hour heart rate rhythms of three animals were measured by means of radio telemetry. Although the durations of the experiments (three days) were very short, some significant data was obtained. As was expected, the period of restfulness was different for each animal. Furthermore, the lowest heart rates for dog and cat were much lower (50 per cent, 25 per cent) than those listed in a biological handbook.¹² In retrospect such slow heart rates would be expected after comparing the techniques of measuring heart rate in the conventional manner to measuring heart rate by radio telemetry. Unexpected gross variations in heart rate were also observed and were most prominent in deep sleep with dog and cat. During deep sleep the arrhythmia was very cyclic in nature. It is

suggested that this phenomenon is due to respiration through its influence on ventricle filling via intrathoracic pressure. If this is the case, then the respiration rate measured by noting the frequency of the cyclic arrhythmia is also approximately 25 to 35 per cent lower for dog and cat than that given in biological handbooks (dog, experimental—9 breaths per minute, handbook—11 breaths per minute; cat, experimental—18 breaths per minute, handbook—26 breaths per minute).

Fourier analysis was the method used to analyze the 24-hour periodicity experiments. The fact that there are a great many different mathematical approaches being used actively today creates a problem in determining the best approach for any given problem. Methods of analysis vary from the complex statistical piecewise curve-fitting and -smoothing approach of Sollberger,¹³ and the "periodograms" of Halberg,¹⁴ to a qualitative recognition of trends. A Fourier series defines a rhythmic or periodic phenomenon in its steady state form. The difference between a Fourier series approximation and the actual phenomenon can be made arbitrarily small and thus the degree of accuracy possible is no problem. Such a Fourier series represents a periodic phenomenon as a quantitative mathematical expression from which a graph may be drawn or which may be used in mathematical manipulation. In addition to having these qualities, the Fourier series representation is very useful for curve-smoothing. By not using the high-frequency terms one removes the sharp variations of the curve that effectively smooths the curve being studied. This method of curve-smoothing does not distort the time axis as do some other methods such as the moving-average method. As with any curve-smoothing operation, however, there is a loss of information. If the information lost is that due primarily to random perturbations, then it is welcome. If, on the other hand, it is a loss of information concerning the phenomenon, then it is undesirable.

The source of the question of how to handle the experimental data obtained stems from some of the major problems of the area itself. Are the rhythms thus far noted intrinsic or extrinsic or both? Are they merely synchronized by external factors? Do they exist as a self-perpetuating phenomenon or are they a result of activity dictated by external environment? Another appropriate question is: Just what is the external environment? Does it include just temperature, light, and pressure variations or does it include cosmic ray density and electromagnetic field changes? Each of these questions could be a target for an entire investigation. The nature of the particular investigation dictates the mathematical analysis. It has not been within the scope of this study to endeavor to find answers to these questions, but the awareness of them was important in formulating many of the basic design characteristics of the radio telemeters constructed.

Simultaneous Heart Rate and Temperature

The 24-hour simultaneous heart rate and temperature experiment illustrated not only rhythmic characteristics but also a correlation between two variables. The data obtained shows clearly a 24-hour variation.

Post-Surgical Temperature

The data obtained in the post-surgical temperature experiment probably is not unique, for it could have been obtained by more conventional methods, but the experiment does illustrate the method of measuring temperature by radio telemetry. The experiment also showed the effect of localized temperature variations that can occur near the stomach as a result of regurgitation and ingestion of cool water.

Other Applications

The experiments discussed above are but a few of the applications of the telemeters designed in this research. The following is a partial list of other applications:

1. Data to describe the relationship between basal body temperature and size (of large excitable animals) can only be determined by radio telemetry.
2. Daily physiological rhythms of normal human subjects over extended periods (days) also must be determined by radio telemetry.
3. Field investigations of physiological functions of mammals in an extreme environment (such as bears and hibernating woodchucks) appear to be dependent upon the application of radio telemetry.

The use of radio telemeters discussed in this section opens up new areas of research previously considered impossible. Through their use the investigator can set himself and his equipment outside of the environment of the experimental animal and, for the particular environmental conditions selected, observe indirectly true temperatures and heart rates, which include the hitherto elusive basal and resting values.

SUMMARY

This investigation included the development of systems for measuring body temperatures and heart rates for long periods of time (several months) by means of subdermally implanted radio telemeters. Pilot experiments showing several applications of the methods to physiological research were conducted. Data concerning 24-hour rhythms in heart rates and body temperatures and their interrelation were gathered and analyzed.

APPENDIX A

ORIGINAL DATA FROM TWENTY-FOUR-HOUR HEART RATE PERIODICITY
EXPERIMENT (CAT)

Time	CAT HEART RATE		
	Day 1	Day 2	Day 3
6:00 P.M.	177.0	112.8	110.4
:30	145.8	162.0	116.4
7:00	136.8	123.6	120.6
:30	147.0	112.2	117.6
8:00	148.8	121.8	106.8
:30	130.2	114.0	105.6
9:00	123.0	117.0	123.6
:30	149.4	169.2	112.8
10:00	126.0	111.6	168.6
:30	117.9°	172.2	120.6
11:00	117.9°	115.8	106.8
:30	109.8	113.4	147.6
12:00 Midnight	103.8	130.8	100.2
:30 A.M.	117.0	123.0	114.0
1:00	124.2	126.0	112.8
:30	114.0	116.4	154.2
2:00	128.4	119.4	136.2
:30	114.0	109.8	112.8
3:00	118.2	112.2	112.2
:30	96.0	103.8	109.2
4:00	103.8	103.2	121.8
:30	100.2	117.6	98.4
5:00	99.6	121.2	118.2
:30	102.6	87.6	89.4
6:00	108.6	106.2	116.4
:30	123.0	85.8	94.8
7:00	93.0	97.8	109.2
:30	83.4	109.8	96.6
8:00	81.6	118.5°	123.0
:30	112.8	118.5°	121.2
9:00	129.6°	118.5°	133.8
:30	146.4	127.2	104.4
10:00	126.0	129.3°	127.2
:30	132.0	131.4	136.8
11:00	114.6	117.6	119.4
:30	105.0	114.0	122.4°
12:00 Noon	144.0	172.2	125.4
:30 P.M.	123.6	111.6	127.8
1:00	131.4	113.4	138.6
:30	109.8	111.0	110.4
2:00	113.4	115.2	131.4
:30	105.0	103.2	130.2
3:00	121.2	115.2	111.6
:30	117.0°	114.0	112.2
4:00	112.8	139.8	115.5°
:30	112.8	127.2°	118.8
5:00	112.8	114.6	97.8
:30	113.4	129.6	207.6

°Averaged value

APPENDIX B

ORIGINAL DATA FROM TWENTY-FOUR-HOUR HEART RATE PERIODICITY
EXPERIMENT (DOG)

<i>Time</i>	<i>DOG HEART RATE</i>		
	<i>Day 1</i>	<i>Day 2</i>	<i>Day 3</i>
1:00 P.M.	51.2	60.5	76.6
:30	54.7	72.6	79.4
2:00	55.2	57.3	66.6
:30	73.0	64.8	84.2
3:00	49.0	57.6	65.4
:30	64.1°	55.8	57.0
4:00	79.2	60.9	62.2
:30	69.0	71.4	83.3°
5:00	66.0	81.0	104.4
:30	92.0	71.7	95.0
6:00	66.6	66.2	69.8
:30	72.0	71.3°	76.6
7:00	74.0	76.4	62.2
:30	67.7	98.1	70.0
8:00	74.0	56.7	63.4
:30	53.5	97.2	59.8
9:00	65.3	81.3	63.0
:30	58.5	67.8	60.6
10:00	60.9	59.4	57.4
:30	60.3	63.9	60.2
11:00	70.8	66.3	60.2
:30	62.7	60.3	58.4
12:00 Midnight	77.4	57.0	60.6
:30 A.M.	65.8°	55.5	95.8
1:00	54.3	58.5	60.2
:30	53.5°	64.0	88.2
2:00	52.8	54.2	60.2
:30	51.6	53.8°	60.4
3:00	50.4	53.4	57.8
:30	54.3°	55.2°	57.1°
4:00	58.2	57.0	56.4
:30	58.0	52.8°	55.0°
5:00	57.9	48.6	53.6
:30	56.2°	48.4°	55.4°
6:00	54.6	48.3	55.4°
:30	47.7°	46.8°	55.4°
7:00	47.7°	45.4	57.2
:30	47.7°	48.9°	65.8°
8:00	40.8	52.4	74.4
:30	54.3	48.4	54.4
9:00	87.0	50.4	54.0
:30	67.2	90.0	57.8
10:00	75.5	54.8	57.6
:30	101.2	57.4	45.6
11:00	114.0	64.2	49.4
:30	80.5	61.2	41.4
12:00 Noon	89.6	70.6	63.6
:30 P.M.	82.8	106.4	47.8

° Averaged value

APPENDIX C

ORIGINAL DATA FROM TWENTY-FOUR-HOUR HEART RATE PERIODICITY
EXPERIMENT (RABBIT)

Time	RABBIT HEART RATE		
	Day 1	Day 2	Day 3
1:00 P.M.	249	250	276
:30	245	302	257
2:00	226	250	240
:30	250	270	236
3:00	273	282	263
:30	252	255	253
4:00	263	270	260
:30	264	260	229
5:00	297	255	240
:30	317	242	241
6:00	264	257	222
:30	250	254°	257
7:00	296	252	246
:30	287°	270	231
8:00	278	250	257
:30	267	267	298
9:00	303	286	267
:30	262	283	249
10:00	281	250	243
:30	278	259	290
11:00	282	300	248
:30	262	270	298
12:00 Midnight	279	239	246
:30 A.M.	264°	283	262
1:00	250	258	313
:30	260°	305	286
2:00	270	252	262
:30	258°	248°	241
3:00	247	245	269
:30	254	241°	257°
4:00	261	237	245
:30	240°	236°	248°
5:00	219	236	252
:30	240°	242°	255°
6:00	262	248	255°
:30	255°	245°	255°
7:00	255°	243	258
:30	255°	251°	250°
8:00	248	260	242
:30	248	298	234
9:00	272	238	274
:30	253	233	238
10:00	280	240	244
:30	264	250	236
11:00	252	268	232
:30	303	226	226
12:00 Noon	249	251	246
:30 P.M.	249	218	290

°Averaged Value

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