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BIOLOGICAL EFFECTS OF STATIONARY MAGNETIC FIELDS

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INTRODUCTION

An inherent sensitivity to the weak geomagnetic field ($\approx 50 \mu\text{T}$) has been demonstrated for a number of different organisms and animal species. It has been well documented experimentally that weak magnetic fields influence the migratory patterns of birds,¹⁻⁴ the kinetic movements of mollusks,⁵ the waggle dance of bees,⁶ the direction-finding of elasmobranch fishes,^{7,8} and the orientation and swimming direction of magnetic bacteria.^{9,10} The mechanisms underlying the magnetic sensitivity of elasmobranchs and magnetotactic bacteria have been described in the preceding chapter.¹¹ A precise mechanism underlying the magnetic sensitivity of other organisms has not been elucidated, although small deposits of magnetite crystals have been discovered in the cranium of pigeons,^{12,13} the tooth denticles of mollusks,^{14,15} and the abdominal region of bees.¹⁶ Magnetite has also been reported to be localized in various anatomical sites in dolphins,¹⁷ tuna,¹⁸ butterflies,¹⁹ turtles,²⁰ mice²¹ and humans.^{22,23} The possible role of magnetite in the geomagnetic direction-finding mechanism possessed by some of these species has not been established, nor is it clear that a sensitivity to the geomagnetic field direction exists for all of the mammalian species in which magnetite deposits have been reported to occur.^{24,25}

Although the directional cues derived from the weak geomagnetic field by certain species of animals have been demonstrated by careful experimentation, the possible effects of fields with intensities that are thousands of times as great as the earth's field on the physiology and behavior of higher organisms is by no means established at the present time. The existing literature on

the bioeffects of strong magnetic fields is frequently confusing, and there are numerous examples of contradictory reports from different laboratories. In an effort to provide a framework for the discussion of the current state of knowledge regarding magnetic field bioeffects, this chapter has been divided into two major sections. The first section presents a critical review of the magnetic field literature on the response of tissue and organ systems that involve ionic conduction processes, and are thereby potentially sensitive to electrodynamic interactions with high magnetic fields. The response of the cardiovascular, neural and visual systems to stationary magnetic fields will be discussed in this section. The second section of this chapter will provide a general summary and critique of the literature related to the biological effects of magnetic fields, and will conclude with a discussion of current research on the circadian physiology of animals exposed to large stationary magnetic fields.

PHYSIOLOGICAL SYSTEMS INVOLVING IONIC CONDUCTION PROCESSES

Cardiovascular System

The occurrence of magnetically-induced potentials associated with pulsatile blood flow into the aortic vessel have been demonstrated from electrocardiogram (ECG) measurements on rats,²⁶ rabbits,²⁷ dogs,²⁸ baboons²⁹ and monkeys³⁰⁻³² exposed to stationary magnetic fields. The primary change in the ECG recorded in the field is an alteration of the signal amplitude at the locus of the T-wave, as discussed in the preceding chapter.¹¹ Because the repolarization of ventricular heart muscle, which gives rise to the T-wave signal in the normal ECG, occurs at approximately the same time in the cardiac cycle as the pulsatile ejection of blood into the aortic vessel, it is reasonable to expect that the magnetically-induced flow potential and the T-wave should be superimposed.

From the theoretical discussion of this phenomenon given in the preceding chapter,¹¹ four predictions can be made regarding magnetically-induced blood flow potentials and the associated magnetohydrodynamic effects: (1) an induced flow potential should have a linear dependence on the applied magnetic field strength; (2) the magnitude of the potential should be a function of the orientation of the animal relative to the field direction; (3) the induced potentials observed in the ECG should increase with the size of the animal species under study; (4) the resultant magnetohydrodynamic effects should be small. In the following paragraphs, experimental data will be described that directly relate to these four predictions.

Linear relationship of induced flow potentials and magnetic field strength. Experimental tests of the linear relation between

the magnetically-induced aortic blood flow potential and the applied magnetic field strength have been carried out by recording the ECG of rats,²⁶ dogs,²⁸ baboons²⁹ and monkeys³² during exposure to graded field intensities. From the ECG records of rats exposed to stationary fields ranging from 0.1 to 2.1 T [see Fig. 1 in preceding chapter¹¹], a field-strength-dependent increase in T-wave amplitude was observed at field levels greater than 0.3 T. The T-wave signal increase was a linear function of the applied field up to 1.4 T. For dogs,²⁸ baboons²⁹ and monkeys,³² the threshold for detection of the T-wave amplitude change was 0.1 T, and the increase in signal strength was a linear function of the magnetic field up to 1.0 T. These data support the concept that the T-wave alteration is a consequence of the superposition of an induced aortic blood flow potential, which is theoretically predicted to have a strictly linear dependence on the magnetic field intensity.

The increase in T-wave amplitude observed in the rat ECG exhibits a steeper slope at field levels above 1.4 T.²⁶ A similar change in slope has been observed in the ECG of dogs²⁸ and monkeys³² at field levels exceeding 1.0 T. Gaffey and Tenforde²⁶ have proposed that this effect may result from the superposition of one or more additional blood flow potentials that have thresholds for detection at high field levels. They have suggested that magnetically-induced potentials associated with pulsatile blood flows into the pulmonary, carotid and subclavian arteries could appear at the T-wave locus in the ECG record. Because of the smaller diameters of these vessels, the associated blood flow potentials would be expected to be significantly smaller than the aortic flow potential. These magnetically-induced flow potentials may therefore be detectable in the external ECG only at field strengths exceeding 1.0 T in the rodents and small primates that have been studied to date.

Induced flow potentials and field orientation. From theoretical considerations, it is predicted that the magnitude and the sign of the induced flow potential should be a function of the angle between the direction of blood flow and the direction of the applied magnetic field. Consistent with this prediction, it has been shown for rabbits²⁷ and for rats²⁶ that the amplitude of the T-wave signal can be increased, decreased, or unchanged by the superimposed aortic blood flow potential depending upon the orientation of the animal relative to the applied magnetic field. It was also demonstrated that the maximum change in the T-wave amplitude occurs when the long axis of a rat, and hence its ascending aortic vessel, is oriented perpendicular to the field.²⁶ This observation is completely consistent with the theoretical prediction that the magnitude of the magnetically-induced aortic blood flow potential should achieve its maximum value when the flow vector and the magnetic field vector are orthogonal.

Dependence of induced blood flow potentials on animal size.

The theoretical calculations presented in the preceding chapter¹¹ suggest that the magnitude of induced aortic blood flow potentials should be significantly greater for large animal species in comparison with the rodent. From ECG measurements on animals exposed to a 1.0 T field with an orientation perpendicular to the body axis, the maximum aortic flow potentials recorded at the body surface were 75 μV for 0.25-kg rats,²⁶ 175 μV for 5-kg baboons,²⁹ 200 μV for 5-kg monkeys,³² and 390 μV for 9-kg dogs.²⁸ The greater magnetically-induced blood flow potential observed with the larger species of animal thus conforms to theoretical expectations. It should be noted that the aortic blood flow potentials measured in external ECG records of rats, baboons, monkeys and dogs were, respectively, 5, 18, 20 and 14 times less than the values predicted to occur within the ascending aortic vessels of these animals on the basis of blood flow rate and aortic vessel diameter. However, a significant reduction in the magnitude of the induced blood flow potential between its locus in the ascending aorta and the body surface would be expected to occur because of the high electrical resistance of the conductive pathway joining these locations.

Magnetohydrodynamic effects. The only direct experimental test of potential alterations in hemodynamic parameters as a consequence of magnetohydrodynamic interactions was made by recording the intraarterial blood pressures of monkeys during exposure to homogeneous, stationary magnetic fields ranging from 0.1 to 1.5 T. Within the ≈ 2 mm Hg accuracy with which the systolic and diastolic blood pressures could be recorded, no measurable alteration was observed in fields up to 1.5 T (Fig. 1). This observation is fully consistent with the theoretical prediction that minimal hemodynamic alterations should result from magnetohydrodynamic interactions with blood flow in fields less than 2 T.³²

In concluding this section on the cardiovascular system, it is worthwhile to review the existing data on the cardiac response to large magnetic fields in an effort to assess the potential stress effects resulting from electrodynamic and magnetohydrodynamic interactions with blood flow. The indices of cardiac performance that have been studied include blood pressure, heart rate and the bioelectric activity of heart muscle. As described above, there is no measurable alteration in the blood pressure of monkeys exposed to a 1.5 T stationary field. The heart rate and electrical properties of heart muscle have been determined from ECG measurements on rats exposed to stationary fields up to 2.1 T,²⁶ rabbits in a 1.0 T field,²⁷ dogs²⁸ and baboons²⁹ in fields up to 1.5 T, and monkeys exposed to fields up to 1.5 T by Tenforde et al.³² and to a 10.0 T field by Beischer.³¹ In none of these studies were significant changes in heart rate observed during acute magnetic field exposures. Similarly, the amplitudes of the P, Q, R and S waves of the ECG were not altered, indicating that the applied magnetic field

MONKEY ELECTROCARDIOGRAM AND BLOOD
PRESSURE

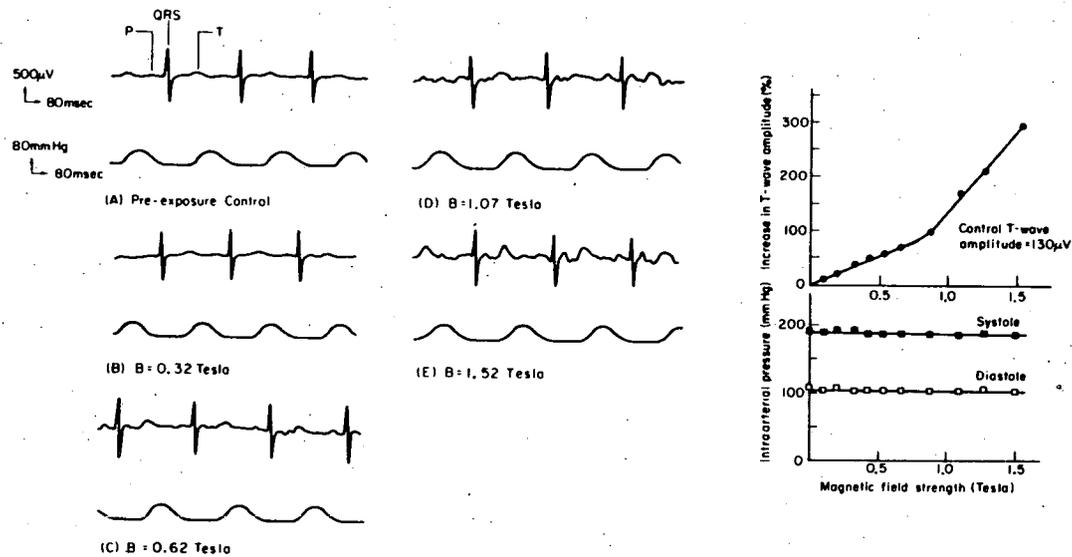


Fig. 1. Electrocardiogram and intraarterial blood pressure records are shown at the left for a *Macaca* monkey during exposure to stationary fields up to 1.5 Tesla. The graphs at the right are plots of the percentage increase in T-wave amplitude and the systolic and diastolic blood pressures as a function of magnetic field strength. The percentage increase in T-wave amplitude is defined as $100(T_m - T_c)/T_c$, where T_c and T_m are, respectively, magnitudes of the T-wave signal in the control state and during magnetic field exposure. [From T.S. Tenforde, C.T. Gaffey, B.R. Moyer and T.F. Budinger, *Bioelectromagnetics* 4:1 (1983). Reproduced with permission of the authors and publisher (Alan R. Liss, Inc.).]

had no effect on the depolarization characteristics of auricular and ventricular heart muscle. The data from these studies with various species of animals also indicate that no cardiac arrhythmias occur during acute exposures to the field levels indicated above.

The set of experimental observations summarized here therefore provide evidence that little or no cardiovascular stress should result from exposure to the highest stationary magnetic field levels (< 2 T) routinely encountered by man. This conclusion must be tempered, however, by the recognition that there are no data available in the literature relating to cardiovascular performance during protracted exposure to large stationary magnetic fields. Also, from the theoretical considerations discussed in the preceding chapter,¹¹ it would be anticipated that measurable hemodynamic perturbations could occur during exposure to stationary fields exceeding approximately 5 T.

Nervous System

On the basis of theoretical models described in the preceding chapter,¹¹ it would not be anticipated that stationary magnetic fields with intensities up to 2.0 T would produce measurable alterations in nerve bioelectric properties either through the Lorentz force exerted on moving ionic currents, or through inductive interactions between the applied field and the moving current loops associated with a propagating action potential. The existing experimental information on the behavior of isolated neurons and the central nervous system in large stationary magnetic fields will be given in the following paragraphs, with a view towards assessing the relevance of theoretical models to the actual behavior of nervous tissues in an applied magnetic field. For isolated neurons, several different bioelectric parameters, including the excitation threshold, the amplitude and conduction velocity of maximal action potentials, and the properties of the refractory period that follows nerve excitation, will be treated separately.

Excitation threshold of isolated neurons. The threshold for neural excitation has been examined for both intact frog sciatic nerves and single myelinated sciatic nerve fibers during exposure to a homogeneous, stationary magnetic field.^{33,34} In both studies, the field orientation was transverse to the nerve axis. No evidence was obtained in these experiments for an effect of a 1.0 T magnetic field on the minimum electrical stimulus strength required to evoke action potentials in either single fibers or intact sciatic nerves.

An important observation that has a direct bearing on other studies described below was made by Gaffey and Tenforde,³⁴ who determined the temperature coefficient of the frog sciatic nerve excitation threshold. In experiments with 29 intact nerve preparations, they found that the submaximal action potential elicited by a

threshold stimulus exhibited a 2.7 mV rise per 1.0 °C increase in the environmental temperature. This increase was 12.8% of the maximal action potential amplitude that could be evoked by suprathreshold stimuli. From this observation, it was concluded that considerable care must be taken to maintain the ambient temperature within 0.1 °C when examining the threshold for nerve bioelectric activity.

Action potential amplitude and conduction velocity in isolated neurons. Several groups of investigators have studied the properties of evoked action potentials in isolated nerve preparations during exposure to stationary magnetic fields oriented either parallel or perpendicular to the nerve axis. Schwartz³⁵ exposed the circumesophageal connective nerve of the lobster to stationary fields with a maximum strength of 1.2 T. The nerve preparation was maintained in an L-shaped chamber, and the field gradient along the sections of nerve oriented parallel and perpendicular to the field lines were 2 and 15 T/m, respectively. No effects of either the parallel or perpendicular fields applied for periods up to 30 min were observed on the nerve conduction velocity. Gaffey and Tenforde³⁴ conducted similar measurements on intact frog sciatic nerves exposed to either parallel or perpendicular 2.0 T stationary fields that were homogeneous to within 0.1% over the entire length of the nerve. With both field configurations, no effects were observed of a continuous 4-h exposure on either the amplitude or the conduction velocity of maximal evoked action potentials. Extending the duration of exposure to 17 h was also found to have no influence on the impulse conduction velocity.

Schwartz³⁶ has used the double sucrose gap technique to measure under voltage-clamp conditions the membrane potentials and transmembrane currents in lobster circumesophageal connective nerves exposed to a 1.2 T stationary field. Both parallel and perpendicular field orientations relative to the nerve axis were used in these experiments, and the field gradients were identical to those described above in the discussion of Schwartz's studies on nerve conduction velocity.³⁵ No effect of the parallel or perpendicular magnetic fields was observed on either the action potentials or the transmembrane currents during nerve excitation.

In contrast to the negative results of the studies described above, two other investigations have yielded apparent positive effects of stationary magnetic fields on nerve bioelectric activity.^{37,38} In studies with intact frog sciatic nerves, Reno³⁷ found that the application of a homogeneous 1.16-T field oriented parallel to the nerve axis led to a measurable increase in the impulse conduction velocity beginning after approximately 5 min of exposure. After 20 min in the field, the nerve conduction velocity reached a level that was 30% above the pre-exposure control value. Upon removal of the field, a progressive increase in conduction

velocity continued for an additional 20 min, and reached a maximum value that was 70% above the control level. The conduction velocity then began to decline towards the initial control value.

Two aspects of Reno's observations suggest that the apparent effect of an applied magnetic field may, in fact, have resulted from an elevation in the ambient temperature due to the heat dissipated from the coils of his electromagnet. First, the physical interaction of a stationary magnetic field with the ionic currents involved in impulse propagation would be expected to have an immediate effect on nerve bioelectric activity, rather than producing an effect that is manifest only after 5 min of exposure. Secondly, the physical influence of the field on conduction currents would not be expected to persist after termination of the exposure. On the other hand, the slow increase and subsequent decay of the magnetic field effect observed by Reno is fully consistent with the effect on nerve conduction velocity that would be expected from the heating and cooling trends that occur during and after the excitation of electromagnet coils to high power levels.

In another series of experiments that produced positive effects, Edelman et al.³⁸ reported that the application of 0.10-0.71 T stationary magnetic fields perpendicular to the frog sciatic nerve axis produced a gradual increase in the amplitude of evoked action potentials. This effect appeared 15-20 min after the field was applied, and the action potential amplitude reached levels as high as 80% above the pre-exposure control level after 1 h of exposure. When the field was removed, the action potential amplitude declined at a slower rate than it had risen during the field exposure. This apparent magnetic field effect thus had a time course that was qualitatively similar to the effect on nerve conduction velocity described by Reno.³⁷ As discussed above, the delayed emergence of a magnetic field effect on nerve bioelectric activity, and a persistence of the effect after termination of the exposure, would not be expected if the influence of the field resulted from a direct physical interaction with ionic conduction currents. However, the results reported by Edelman et al.,³⁸ like those of Reno,³⁷ are fully consistent with thermal effects associated with the dissipation of heat from electromagnet coils under conditions where no provision is made for rigorous temperature regulation within the magnet gap. It should also be noted that Edelman et al.³⁸ used electrical stimuli that produced submaximal action potentials with amplitudes of 7-10 mV. As discussed above, Gaffey and Tenforde³⁴ have demonstrated that such submaximal action potentials are extremely temperature sensitive.

Absolute and relative refractory periods of isolated neurons.
Following the passage of a maximal action potential, an isolated peripheral nerve enters an absolute refractory period of 1-2 ms duration during which a second impulse cannot be evoked. Subsequent

to the absolute refractory period, the nerve enters a relative refractory period during which action potentials of progressively increasing amplitude can be evoked by electrical stimulation. After a period of approximately 4-6 ms, the second action potential reaches the same maximal amplitude as the impulse elicited by the initial stimulus, thus denoting the end of the relative refractory period. The characteristics of both the absolute and relative refractory periods have been examined during the exposure of frog sciatic nerves to a homogeneous 2.0 T field.³⁴ Using both parallel and perpendicular configurations of the magnetic field relative to the nerve axis, no influence of the field was observed on the duration of either the absolute or the relative refractory periods. In addition, the amplitudes of impulses evoked during the relative refractory period were unaffected by the magnetic field exposure.

Central nervous system response to stationary magnetic fields.

Several reports have been made of profound changes in brain electrical activity during the exposure of experimental animals to stationary fields ranging from approximately 0.1-9.1 T. In a series of electroencephalogram (EEG) measurements on squirrel monkeys, Beischer and Knepton³⁹ observed that exposure to stationary magnetic fields produced a significant increase in the amplitude and frequency of brain electrical signals recorded with silver electrodes inserted below the scalp in the frontal, parietal, temporal, occipital and median cranial regions. Recordings of the EEG were made in homogeneous fields produced by a Bitter magnet with field strengths ranging from 1.47-9.13 T. EEG measurements were also made in the strong gradient fields at the periphery of the magnet gap. During exposures ranging from 3-45 min, it was found that the predominant EEG frequencies shifted from their pre-exposure range of 8-12 Hz to 14-50 Hz, independent of the field intensity or homogeneity. The amplitude of the signals also increased from the control level of 25-50 μ V to 50-400 μ V. These changes were uniformly observed in the different cranial regions that were simultaneously monitored, and there was no latency in the response upon application of the field. When the field was removed, both the amplitude and frequency spectrum of the EEG signals returned to their pre-exposure levels.

In analyzing the results of their experiments, Beischer and Knepton³⁹ considered several potential sources of artifacts, including ripple currents from the magnet power supply, animal movements associated with heart contractions and breathing, pick-up of stray 60-Hz fields by the EEG electrodes and leads, and skeletal muscle tremors. All of these factors except for muscle tremors could be excluded because their characteristic frequencies were outside of the frequency range observed for the predominant EEG signals in the presence of a stationary magnetic field. However, the characteristics of the EEG tracings obtained from monkeys in the magnetic field suggest that "myographic noise" from the movement of

skeletal muscles may have been superimposed on the brain electrical signals. It is also possible that environmental factors present only during excitation of the magnet coils, including mechanical vibrations, audible noise and an increased ambient temperature, could have led to an altered pattern of brain electrical activity.

In direct contrast to the above findings with monkeys, Kholodov has reported that the exposure of rabbits to relatively weak, 0.08-0.10 T stationary fields produces an EEG signature that is characteristic of a general inhibitory state in the central nervous system.⁴⁰⁻⁴² The major changes in the EEG during magnetic field exposure were the occurrence of slow waves and high-amplitude spindles that were observed in the electrical activity recorded from different regions of the brain. This phenomenon was not uniformly exhibited in all of the experimental tests conducted by Kholodov; in a series of 100 field exposures on 12 rabbits, he observed the occurrence of spindles in 30% of the tests, and an increase in the number of slow waves with frequencies less than 4 Hz in 19% of the tests.⁴¹ Both phenomena occurred with a latency of approximately 15 s after the field was turned on, and reached maximum levels after 45 s of exposure. The increased number of spindles and slow waves persisted during exposures to a 0.1 T field for 3 min, and decreased immediately after the field was turned off. However, 15-25 s after the exposure was terminated, a transient increase in the number of spindles and slow waves occurred with a duration of approximately 20-30 s.

Kholodov⁴¹ has presented evidence that EEG alterations observed in his experiments with rabbits were not artifacts resulting from the induced potentials that occur during the switching on and off of an electromagnet. This possibility was excluded on the basis of trials in which the magnet was energized and de-energized at varying rates, with no resulting change in the character of the observed EEG alterations. However, Kholodov has not discussed the possibility that other extraneous factors such as low-frequency mechanical vibrations and acoustic noise within the magnet gap, irregularities in the breathing rate or the rate of cardiac contraction, sporadic muscle tremors or episodic shivering of the experimental subjects could have led to spurious signals in the EEG record. Another factor that must be considered in evaluating these studies is the lack of data on the field strength dependence of the reported effects. Such information might lend insight into the existence of variables other than the magnetic field that could have produced abnormal features in the EEG recordings.

In summary, the majority of the experimental studies that have been conducted to date indicate that stationary magnetic fields up to 2 T have little or no influence on the bioelectric properties of isolated neurons. This finding conforms quite well to the theoretical predictions discussed in the preceding chapter.¹¹ The few

instances of reported effects of magnetic fields on the electrical activity of peripheral nerves may have resulted from an inadequate control of temperature within the magnet gap.

Studies on the response of the central nervous system to stationary magnetic fields with a wide range of intensities have produced conflicting results that are currently difficult to interpret. Both excitatory and inhibitory responses of the central nervous system to magnetic fields have been observed by different investigators, and the potential sources of artifacts in these experiments cannot be adequately analyzed from the information that is available. Valentinuzzi⁴³ has pointed out that a summation of magnetic field inductive effects could possibly occur in complex neural networks. This additive field effect might conceivably lead to alterations in the bioelectric activity of the brain that would not be seen in studies with individual neurons. However, the database that is available at the present time is clearly inadequate for making an unequivocal judgment as to the existence of magnetic field effects on the central nervous system. It should be noted, however, that extensive behavioral studies on rodents exposed for prolonged intervals to a 1.5 T stationary magnetic field have not revealed abnormalities that could be attributed to altered central nervous system characteristics.⁴⁴

Visual System

As discussed in the preceding chapter,¹¹ one of the most clearly established magnetic field effects in biological systems is the phenomenon of magnetophosphenes, in which a flickering light is produced in the visual field during exposure to oscillating magnetic fields with frequencies greater than 10 Hz and amplitudes exceeding 10 mT.⁴⁵⁻⁴⁸ The locus of the magnetic field effect has been shown to be the retina rather than the central nervous system visual pathway,⁴⁸ and electrophysiological recordings suggest that the site of action is in the photoreceptors as opposed to the neural elements of the retina.⁴⁹

Although the psychophysical phenomenon of phosphenes has not been reported by human observers during exposure to large stationary magnetic fields, there are two potential interaction mechanisms between these fields and elements of the retina that are involved in the visual response to photic stimulation. First, the photoreceptor outer segments are subject to orientation in a stationary magnetic field as the result of their large diamagnetic anisotropy.⁵⁰⁻⁵³ Second, the initial photoisomerization event elicited by photon absorption in the retinal photopigments is followed by a series of ionic fluxes that lead to excitation of the retinal neurons, and ultimately the visual cortex via a complex neural pathway. This component of the phototransduction process could be influenced by stationary magnetic fields as the result of ionic current distortion.

and/or inductive effects, as discussed in the preceding chapter.¹¹

In an effort to elucidate whether stationary magnetic fields perturb the photically elicited electrical activity of the retina, Raybourn⁵⁴ has recorded the external electroretinogram (ERG) of isolated turtle retinas during photic stimulation in the presence of magnetic fields of graded intensities. When the retinal preparations from light-adapted or dark-adapted eyes were studied, no changes in the ERG occurred in fields up to 1.0 T. However, the amplitude of the ERG b-wave, which results from electrical activity of nerve cells in the outer plexiform layer of the retina, was consistently suppressed in retinas prepared during the light-to-dark transition phase of the diurnal 12-hr-light/12-hr-dark cycle. During this transition phase, which extends for approximately 2 hr after the onset of darkness, the photoreceptor cells undergo rapid changes in both their physiological and metabolic activities.^{55, 56} As shown in Fig. 2, the magnetic field effect was observed with intensities as low as 2-3 mT, and was rapidly reversible following termination of the field exposure. This effect was observed in both the cone-dominant retinas of *Pseudemys scripta* turtles, and the mixed rod-cone retinas of *Chelydra serpentina* turtles, thus suggesting that it is independent of the photoreceptor cell type. The circadian dependence of the magnetic field sensitivity has been clearly demonstrated by experiments in which the light/dark cycle was phase shifted by several hours.⁵⁷ In addition, the b-wave response compression produced by magnetic field exposure was shown not to be identical to the response compression that results from adaptation to background illumination, insofar as there is no loss of visual sensitivity to graded photic stimuli in the presence of the magnetic field.

The mechanism underlying the magnetic field sensitivity of turtle retinas during one brief phase of the light/dark cycle has not been determined. The magnetic field strengths that produce a b-wave response compression are well below the levels that could exert orientational effects on photoreceptor disk membranes, and this fact suggests that charge translocation mechanisms in the retina may be involved in the magnetic field interaction. However, electrophysiological measurements of the early receptor potentials in the retinal ERG will be required in order to determine whether the locus of the magnetic field effect lies in the photoreceptors or in the neural elements of the retina. It will also be of considerable interest to investigate whether a similar magnetic field sensitivity occurs in the electrical response of mammalian retinas to photic stimulation.

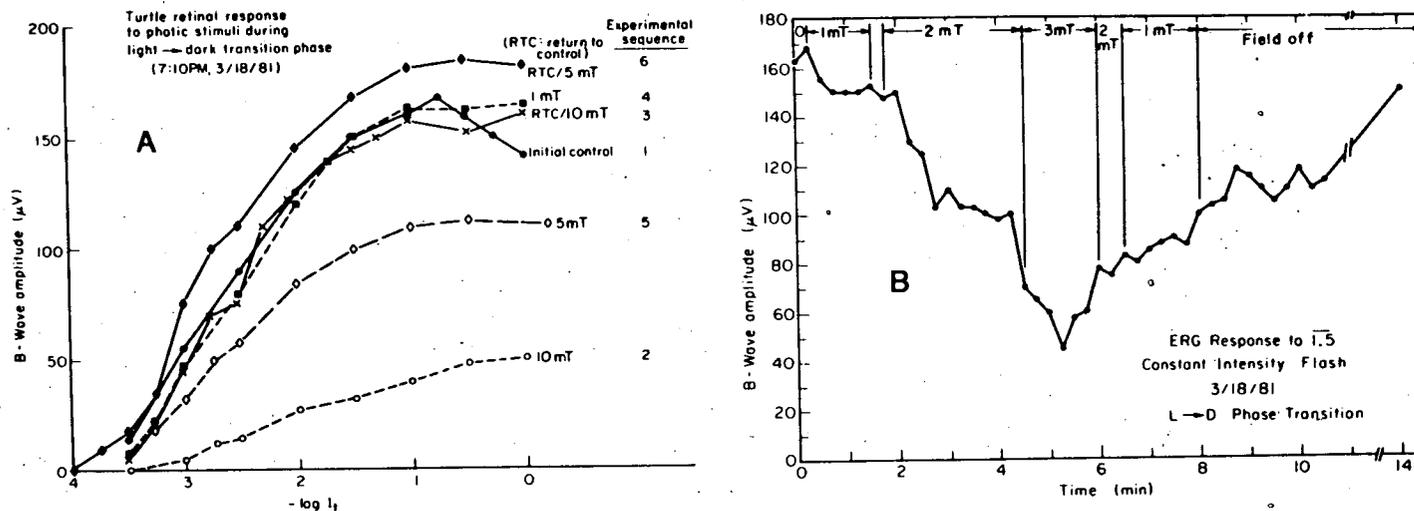


Fig. 2. (A) The b-wave amplitude in the electroretinogram of an *in vitro* turtle retinal preparation is shown as a function of magnetic field strength from 1 to 10 millitesla. I_t represents the intensity of the white light test flash used to evoke the b-wave, and is plotted logarithmically over four decades of light intensity. The b-wave response compression over to control intensity-response curves is evident in fields exceeding 5 millitesla. The response compression saturates at 10 millitesla (data not shown). (B) The electroretinogram b-wave response amplitudes elicited by a constant intensity light flash are shown as a function of time during short-term exposure to 1, 2 and 3 millitesla magnetic fields. The interval between test light flashes was 15 s. [From M.S. Raybourn, *Science* 220:715 (1983). Reproduced with permission of the author and publisher (American Association for the Advancement of Science).]

GENERAL SUMMARY OF MAGNETIC FIELD EFFECTS AT THE MOLECULAR, CELLULAR, ORGAN AND ANIMAL LEVELS

Several comprehensive reviews of magnetic field bioeffects have been published during the last decade,⁵⁸⁻⁶⁷ and an attempt will not be made here to analyze all of the existing magnetobiology literature on systems ranging in complexity from individual molecules to whole organisms. In surveying this body of literature, one pervasive theme that emerges is the existence of numerous examples of contradictory observations made in different laboratories. This fact obviously provides considerable difficulty in any attempt to synthesize the available information on magnetic field bioeffects into a coherent picture.

Molecular Interactions

As one example at the molecular level of a data set that is currently difficult to interpret, the results of studies on various enzyme systems subjected to magnetic field exposure *in vitro* are summarized in Table 1. A total of 15 reports have appeared in which the reaction rates of 17 different enzymes were studied during exposure to stationary magnetic fields over a broad range of field strengths, and with widely varying exposure times, reaction temperatures and pH levels, and conditions of field uniformity. Overall, 58% of the experimental tests showed no effect of the field exposure, while 33% and 8% of the tests showed increases and decreases, respectively, in the rate of enzyme reaction in the exposed samples relative to controls. As discussed below, in certain systems such as enzymes that involve radical intermediate stages as part of their reaction pathways, it might be anticipated that the reaction rate would be sensitive to the presence of a magnetic field. However, for several other enzyme systems there is no obvious physical mechanism that could explain the observed magnetic sensitivity at the field intensities that were used. It is interesting to note, for example, that Smith and Cook⁷⁹ found the activity of trypsin to increase by up to 23% during a 2-h exposure to a 0.8 T field, whereas Vajda⁸² and Nazarova et al.⁸¹ observed no change in enzyme activity during exposures of 2-8 h duration in a 1.4 T field. Also, Nazarova et al.⁸¹ found trypsin activity to be unaffected by a 2.5-h exposure to a 10.0 T field, and Rabinovitch et al.⁸⁰ observed no change in trypsin activity either during a 9-min exposure to a 22 T field, or following a 3:7-h pretreatment of the enzyme in a 20.8 T field.

Another aspect of the data presented in Table 1 that merits comment is the finding in two different laboratories of an increase in the reaction rate of the metalloenzyme catalase in response to magnetic field exposure.^{74,75} The action of this enzyme may involve a radical intermediate state which, as discussed in the preceding chapter,¹¹ might be anticipated to exhibit magnetic sensitivity.

TABLE 1. MAGNETIC FIELD EFFECTS ON ENZYME SYSTEMS

Enzyme (Ref. No.)	Maximum Field Strength (Tesla)	Effect of Exposure on Enzyme Activity
Acetylcholinesterase (68)	1.7	Increase
Alcohol dehydrogenase (69)	1.4	None
Aldolase (70)	17.0	None
Asparaginase (71)	1.7	Increase
β -galactosidase (72)	1.0	None
Carboxydismutase (73)	2.0	Increase
Catalase (74)	6.0	Increase
Catalase (75)	0.8	Increase
Cytochrome oxidase (76)	1.3	Increase
DNase (77)	0.3	Increase
Glutamic dehydrogenase (74)	7.8	Decrease
Histidase (71)	1.7	Decrease
Lactic dehydrogenase (69)	1.4	None
Peroxidase (70)	17.0	None
RNase (70)	17.0	None
RNase (78)	4.8	None
RNase (69)	1.4	None
RNase (77)	0.3	None
Succinate-cytochrome c reductase (78)	4.8	None
Trypsin (79)	0.8	Increase
Trypsin (80)	20.8	None
Trypsin (81)	10.0	None
Trypsin (82)	1.4	None
Tyrosinase (70)	17.0	None

Several other biologically important enzymes that may have radical intermediate steps in their reaction pathways include the cytochrome P-450 enzymes, which are involved in steroid hormone metabolism, and lipoxygenase and cyclo-oxygenase, both of which are involved in the synthesis of prostaglandins. Further studies on these enzyme systems would provide useful insight into whether enzymatic pathways that involve radical intermediate states exhibit sensitivity to stationary magnetic fields, with possible consequences for cellular and tissue functions.

Cellular Responses to Magnetic Fields

A number of studies conducted in the 1960's and earlier suggested that exposure to stationary magnetic fields may lead to physiological, morphological and growth abnormalities at the cellular level. Degenerative changes such as pycnosis,^{83,84} depressed respiratory rate,⁸⁵⁻⁸⁸ decreased DNA synthesis⁸⁹ and growth inhibition^{90,91} were noted for various types of normal and tumor cells. In contrast to these observations, a large number of more recent studies using magnetic field intensities and exposure times that were equal to or greater than those used in the earlier work have failed to produce effects on cell growth.⁹²⁻⁹⁹ It is also interesting to note that early reports^{100,101} of *in vivo* tumor growth inhibition by stationary magnetic fields have not been replicated in subsequent studies.^{102,103}

In 1976 it was reported by Malinin et al.¹⁰⁴ that exposure of human WI-38 fibroblasts and murine L-929 cells to a 0.5 T field for 4-8 h at 4 °K led to subsequent growth inhibition relative to controls when the cells were thawed and cultured at 37 °C. The exposed cultures also appeared to undergo morphological transformation and to lose sensitivity to contact inhibition of cell division in long-term cultures. These observations were later shown to be the result of using unconventional culture techniques in which control cells were subcultured at 5-6 d intervals, while cultures grown from exposed cells were only passaged at 28-45 d intervals. When Frazier et al.⁹⁸ used similar culture techniques, they were able to replicate in unexposed cultures of WI-38 and L-929 cells the morphological transformation that had been reported by Malinin et al.¹⁰⁴ to result from magnetic field exposure.

Although the preponderance of available experimental evidence indicates that stationary magnetic fields with intensities up to 2 T exert little influence on cell growth properties, there are potential mechanisms through which effects could occur under certain specialized conditions. (1) As discussed above, enzymatic pathways that contain radical intermediate stages may be sensitive to the presence of strong magnetic fields. (2) The suggestion has been made that cellular effects could result from the redistribution of

paramagnetic oxygen molecules in the presence of a strong magnetic field gradient.¹⁰⁵ The magnetomechanical movement of dissolved oxygen in an aqueous medium has been demonstrated experimentally,^{106,107} but there are as yet no clear tests of the potential biological consequences of this effect. (3) The lamellar phospholipids of cell membranes are diamagnetically anisotropic, and the proposal has been made that the orientational effect of an applied magnetic field exceeding approximately 0.1-1.0 T could significantly perturb membrane transport properties.¹⁰⁸ In support of this proposal, direct evidence has been obtained for magnetic field effects on the diffusional properties of liquid crystals.¹⁰⁹⁻¹¹¹ Using measured values for the anisotropic diamagnetic susceptibility of model phospholipid membranes,¹¹² it can be estimated from the theoretical formulae presented in the preceding chapter¹¹ that the magnetic interaction energy within a typical cell membrane will exceed the Boltzmann thermal energy, kT , in stationary fields greater than approximately 0.5 T. At sufficiently high magnetic field intensities, a perturbation of membrane properties might therefore be expected to occur, with possible consequences for other cellular functions. (4) The interesting proposal has been made that the sensitivity of cell membranes to magnetic field interactions may be greatest at phase transition temperatures.^{105,113} This proposal is based on the concept that perturbations introduced by relatively weak magnetic interactions should be amplified near a phase transition temperature at which membrane properties undergo abrupt changes. Some indirect support for this hypothesis was obtained from studies on thermally-induced developmental failure in flour beetles,¹¹³ in which higher temperatures were required to elicit developmental wing abnormalities in the presence of a strong magnetic field.

Although none of the magnetic field interaction mechanisms described above has been shown to directly influence the structural, functional or growth properties of living cells, further experimental studies are needed to test their potential biological relevance. In this context, investigations with magnetic fields that significantly exceed 1 T would be extremely useful for establishing the threshold field levels above which perturbations may occur in cellular functions and growth properties.

Genetics, Reproduction and Development

Developing organisms frequently exhibit a strong response to noxious factors within their environment. This observation, which has been well documented for toxic chemicals and ionizing radiation, has also stimulated a relatively large number of studies on the potential effects of stationary magnetic fields on the genetics, reproduction and development of various organisms. Investigations on a variety of nonmammalian test systems have led to several reports of mutagenic and developmental effects resulting from

exposure to both uniform and nonuniform magnetic fields. Effects observed with strong magnetic field gradients have included alterations in the sex ratio and development of Drosophila pupae,^{84, 114, 116} abnormal development of sea urchin, frog and salamander eggs,^{117, 120} and inhibition of limb regeneration in crabs.¹²¹ Uniform magnetic fields have been reported to alter the development of chicken embryos,¹²² guppies¹²³ and trout eggs.¹²⁴ It is interesting to note that Perakis¹¹⁷ found no effect of a uniform 3.3 T field on the development of sea urchin eggs, and Ueno et al.¹²⁰ observed no effect of a 1.0 T uniform field on the development of frog embryos. The absence of an effect of uniform magnetic fields on frog egg development is also supported by the experimental observations of Iwasaki et al.¹²⁵ and Mild et al.¹²⁶ In contrast, developmental abnormalities were observed in both sea urchin eggs and frog embryos exposed to high magnetic field gradients.^{117, 120} Ueno et al.¹²⁰ suggested that the developmental effects of nonuniform fields may result from a redistribution of dissolved oxygen or from the orientation of mitochondrial cytochromes in large magnetic fields with gradients exceeding 10^4 T/m.

In studies on mammalian systems, it has been reported that uniform and nonuniform fields up to 0.94 T inhibit weight gain in young mice and produce weight loss in older animals.¹²⁷ The rate and number of live births and the average birth weight have also been reported to decrease following prenatal and postnatal exposure of mice to an 80 mT uniform field.¹²⁸ In contrast to these reports, studies on young mice exposed for up to 15 d to a nearly uniform field with a maximum strength of 1.44 T revealed no effect on growth rate.¹⁰² The intrauterine exposure of mice and rats to either a 1.0 T uniform field or a 2.5 T/m gradient field has also been found to have no influence on fetal or postnatal development.^{129, 130}

Several studies have been carried out to determine whether genetic defects can be detected in Drosophila and rodents subsequent to magnetic field exposure. No increase in mutation frequency was observed by Kale and Baum¹³¹ among the progeny of Drosophila males exposed as eggs, larvae, pupae and adults to 1.3-3.7 T uniform magnetic fields. Similar results have been obtained by Mittler¹³² and Diebolt,¹³³ who exposed Drosophila males to 1.0-1.1 T fields. Baum et al.¹³⁴ have also found that exposure of the plant Tradescantia to uniform fields up to 3.7 T led to no increase relative to controls in three mutagenic indices, namely, pollen abortion, micronuclei formation, and pink stamen hair production. Dominant lethal assays have been conducted by Mahlum et al.¹³⁵ with male mice exposed to either a uniform 1.0 T field or a 2.5 T/m gradient field for 28 d prior to mating. The occurrence of dominant lethal mutations in the offspring of the exposed males was judged from early fetal resorptions and litter size, and no effect of exposure to either the uniform or nonuniform magnetic field was observed. Recent studies have also demonstrated that the exposure

of cultured Chinese hamster ovary cells to a 0.35 T uniform field does not lead to alterations in DNA synthesis or chromosome structure,¹³⁶ and the structure and biological activity of bacteriophage DNA have been found to be unaffected by exposure to a 2 T uniform field.¹³⁷

In general, the majority of available evidence suggests that exposure to stationary magnetic fields has little or no direct influence on the genetic characteristics of many different types of organisms. However, the possible occurrence of developmental abnormalities in response to magnetic field exposure must presently be regarded as an unresolved issue, especially in nonmammalian systems.

Organ and Tissue Effects

Possibly the most difficult set of experimental observations to interpret at the present time are the numerous reports that have appeared throughout the world's literature on the effects of stationary magnetic fields on diverse organ and tissue functions and structure. Examples of mammalian tissue and organ alterations that have been observed following magnetic field exposure include changes in (1) blood and bone marrow cellular composition,¹³⁸⁻¹⁴⁰ (2) serum chemistry,^{141,142} (3) microcirculation,¹⁴³ (4) thrombocyte coagulation,¹⁴⁴ (5) electrolyte balance in blood, urine and various tissues,¹⁴⁵⁻¹⁴⁷ (6) functional and structural properties of various organs and tissues,^{85,86,148-154} (7) immune response,^{155,156} and (8) endocrine regulation.¹⁵⁷⁻¹⁵⁹ With the exception of one study on endocrine changes,¹⁵⁹ all of the reported alterations in tissue and organ properties were observed at stationary magnetic field levels below 1 T. These observations are therefore difficult to reconcile with the growing body of evidence that the development, growth and homeostatic regulation of mammals is not significantly affected by prolonged exposure to fields of this magnitude.

Several aspects of the research on tissue and organ effects deserve mention. First, many of the experimental reports have been based on studies with small numbers of exposed and control subjects, and often no attempt was made by the investigators to replicate their experimental results. Second, the magnetic field exposure conditions have generally not been well documented, and many of the reported tissue and organ effects of magnetic fields are typical of those which occur in response to stresses imposed by other factors such as adaptation to new caging conditions, poor temperature regulation, high ambient sound levels, cage overcrowding, concurrent infections of the subjects, and so forth. Third, there have been few attempts to verify the findings of tissue and organ effects through independent replications in other laboratories. In the few cases where such attempts have been made, the original results have not been successfully replicated. For example, the early

reports¹³⁸⁻¹⁴⁰ of hematopoietic alterations have not been confirmed in other studies.^{102, 160-162} Similarly, earlier reports^{155, 156} that magnetic fields alter the immune status of exposed subjects have not been confirmed in recent experiments designed to test humoral and cell-mediated immunity in mice exposed for 6 d to a 1.5 T stationary magnetic field.¹⁶³ In view of these considerations, the possible existence of deleterious effects of stationary magnetic fields on tissue and organ functions must be considered at present to be an unresolved issue, towards which more extensive research efforts need to be directed.

Physiological Regulation and Circadian Rhythms

In assessing the response of living organisms to stationary magnetic fields, an important aspect to be considered is the maintenance of normal homeostatic regulation. One of the central issues in this assessment is whether exposure to magnetic fields produces an alteration in the normal circadian rhythmicity of major physiological and behavioral variables. Several of the investigations cited above indicate that the exposure of mammals to stationary magnetic fields may lead to hormonal alterations and to other tissue effects that could potentially perturb physiological regulation, and thereby lead to an alteration in the normal circadian waveform. Although there is relatively little information available on this subject, several reports in the literature suggest that weak electric and magnetic fields may influence circadian regulation. Wever^{164, 165} has reported that the exposure of human subjects to a 10 Hz, 2.5 V/m square-wave electric field in air produces a significant reduction of the free-running circadian period in body temperature and sleep/wakefulness cycles. Brown and Skow¹⁶⁶ observed a modulation of the normal 24-h circadian activity period in hamsters when a weak magnetic field with a maximum intensity of 26 μ T was applied in 26-h cycles. The nocturnal sensitivity of mice to morphine was found by Kavaliers et al.¹⁶⁷ to be diminished when the subjects were exposed to a rotating magnetic field with an intensity ranging from 150 μ T to 9.0 mT. A cancellation of the earth's magnetic field by Helmholtz coils was found by Bliss and Hepner¹⁶⁸ to alter the circadian activity pattern of birds when the normal light/dark cycle had been removed. Semm et al.¹⁶⁹⁻¹⁷¹ recently reported that the electrical activity of rodent and avian pineal cells can be altered by artificial changes in the strength and direction of the local geomagnetic field, and Welker et al.¹⁷² have observed that the circadian waveform in pineal melatonin content and serotonin-N-acetyltransferase activity were also modified by changes in the ambient magnetic field. Finally, the observations by Raybourn⁵⁴ described in an earlier section of this chapter indicate that circadian variations may exist in the sensitivity of turtle retinal cells to magnetic fields with intensities exceeding 2-3 mT.

As a result of the various reports of alterations in tissue properties and circadian variables in organisms exposed to magnetic fields, a program was undertaken in the author's laboratory in 1979 to measure the circadian oscillations in several physiological and behavioral variables of rodents exposed for prolonged periods to a 1.5 T stationary magnetic field. These studies were designed to provide continuous measurements of core body temperature, heart rate, respiration, body mass, locomotor activity, food intake and excreta. For this purpose, a variety of exposure chambers and transducer techniques were developed to achieve the noninvasive monitoring of physiological and behavioral variables during continuous periods of 2-3 months duration.¹⁷³ As an example of the type of circadian data obtained in these experiments, Fig. 3 shows 5 serial days of body temperature data recorded from a mouse implanted abdominally with an FM radiotelemeter. Data on the various physiological and activity parameters listed above have been analyzed by computer using a nonlinear regression technique¹⁷⁴ that provides best-fit values for the amplitude, acrophase and period of the circadian waveform. In each experiment, baseline measurements of circadian parameters were made during an initial field-off condition. The rodents were then subjected to a homogeneous 1.5 T field under three different exposure regimens: (1) continuous exposure for 5 days; (2) intermittent exposure with an 8-h "on"/16-h "off" cycle for 10 consecutive days; (3) serial exposures to the field under the 5-day continuous and 10-day intermittent schedules. In addition, the sensitivity of circadian oscillations to an applied magnetic field was tested both in rodents that were entrained to a 24-h light/dark cycle, and in animals placed in a free-running circadian state by the maintenance of continuous dim illumination. The results of a large number of experiments conducted up to the present time have provided no evidence that the circadian regulation of physiological or behavioral variables is influenced by a 1.5 T stationary magnetic field under any of the exposure conditions described above.¹⁷⁵⁻¹⁷⁷ Post-experiment evaluations of blood cell composition, serum chemistry, organ weights and tissue histology have also given no indication of deleterious effects resulting from exposure to the 1.5 T field. In contrast to many earlier reports from other laboratories, the results of these studies thus indicate that physiological regulation and tissue properties are not significantly perturbed in rodents as the result of prolonged exposure to a high-intensity stationary magnetic field.

CONCLUDING REMARKS

It is evident from the discussion of magnetic field bioeffects given in this chapter that there are numerous unexplained observations and unresolved questions that remain to be answered through careful biological, biochemical and biophysical research. In some instances, experimental observations have been directly linked to

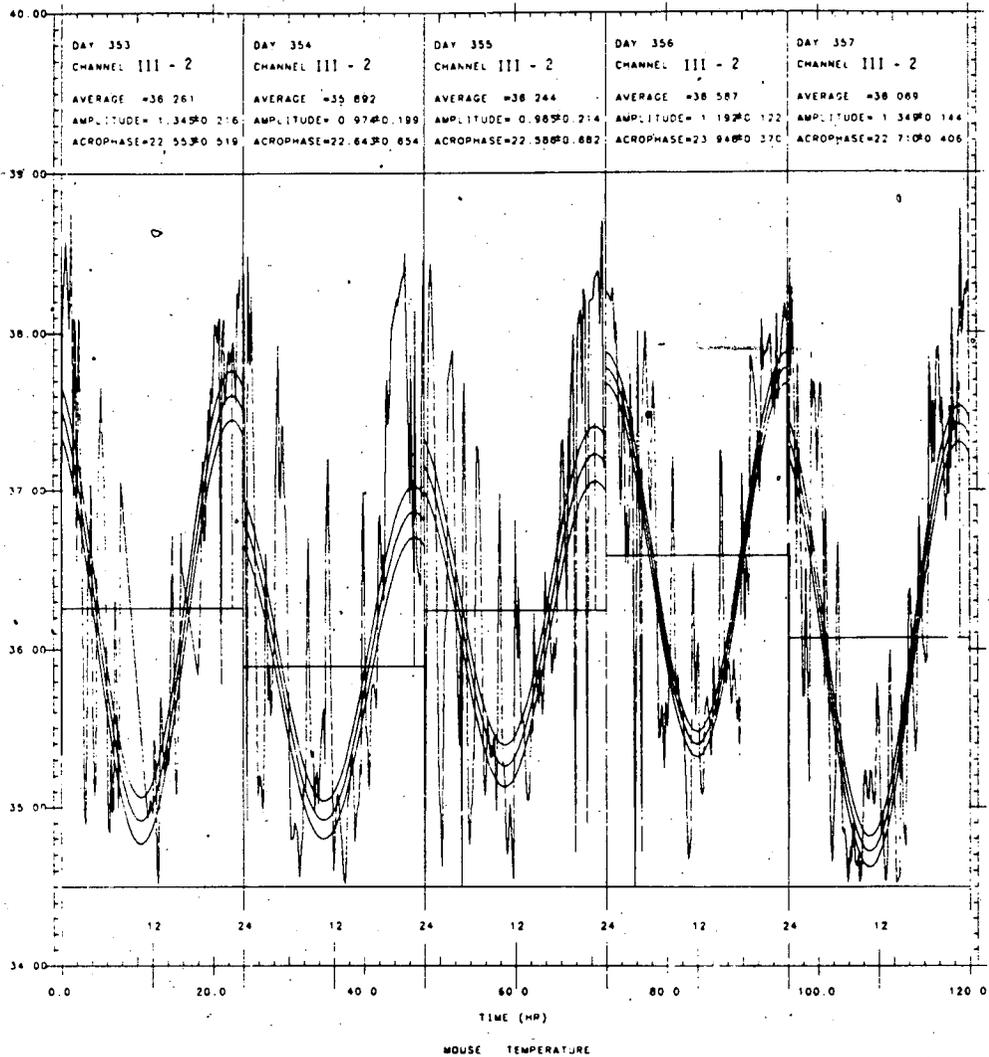


Fig. 3. Five serial days of deep-body temperature data measured by telemetry in an adult female LAF-1 mouse. The circadian rhythm of this animal was entrained with a 24-h period by using a 12-h light/12-h dark schedule of cage illumination. The middle smooth curve in each panel represents a computer fit of the circadian waveform to a cosine function, and the upper and lower fitted curves are the 95% confidence intervals. The average daily body temperature, the amplitude of the circadian waveform, and the hour at which the temperature reached a daily maximum (the acrophase) are given in the captions at the top of the figure. [Unpublished data from the author's laboratory.]

well-defined interaction mechanisms, an example being the magnetic induction of electrical potentials in the central circulatory system. However, in a great majority of the reports which indicate that magnetic field exposure leads to alterations at the molecular, cellular, organ and whole-animal levels, there are no clear physical interaction mechanisms that can be invoked to explain the observed phenomena. For this reason it is the author's opinion that future research on magnetic field bioeffects must place an increased emphasis on mechanistic studies at all levels of biological organization ranging from individual molecules to the intact organism. Studies of this nature will be essential if we are ultimately to gain the necessary information for drawing firm conclusions on the biological effects of stationary magnetic fields.

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