MAGNETIC FIELDS IN BIOLOGY

Life scientists find many interesting interactions between magnetic fields and biological systems. Ranging from the pure research on magnetotropism to medical applications in the operating room, biomagnetism promises exciting developments.

ALEXANDER KOLIN

SUPERSTITION AND QUACKERY dominated experimentation and speculation on interaction of magnetic fields with living systems for well over a thousand years. More critical inquiry is of relatively recent origin. There is still controversy about a variety of findings, but sound observations and applications of magnetic interactions to biology and medicine are beginning to emerge. Thus, for instance, constant magnetic fields have been shown to affect plant growth and animal development, alternating magnetic fields have been used to stimulate nerves and to evoke visual sensations, and activity of nerves and muscles has been shown to be accompanied by transient magnetic fields. Most advanced is the development of magnetic methods of measurement. These methods include electromagnetic determination of blood flow and magnetic resonance spectrometry of biological molecules.

A MAGNETIC EFFECT ON PLANT GROWTH

As our first example we shall consider an ingenious idea of employing magnetic interactions to answer a fundamental question in plant physiology. That question was not answered but instead a new biophysical phenomenon, *magnetotropism*, was discovered.

Gravity determines which way roots and shoots of all higher plants will grow. If we examine a young plant that developed normally, we find a downward growing root and a straight upward shoot. If we rotate the plant by 90 deg, as shown schematically in figure 1a, the root will start curving downward and the shoot upward, as shown in figure 1b. Curvature is brought about by an increased growth rate on the underside of the shoot and the upper side of the root. Growth rate is regulated by growth hormones, and some graviperception mechanism initiates the geotropic response illustrated in figure 1.

A variety of mechanisms was suggested. The theory that looked most plausible to plant physiologist L. J. Audus of the University of London involved specialized cells, which were assumed to perceive gravity through certain rapidly sedimenting starch grains containing protoplasmic particles, the amyloplasts. No proof was discovered of a causative connection between the sedimentation of amyloplasts in gravitational or centrifugal fields and induction of curvature in roots and shoots of plants. Audus's idea for a test of this hypothesis concerning geotropism was *to use a different kind of force to displace the amyloplasts* to see if such a displacement would produce the stem and root curvatures observed in geotropism.

Idea for a physical test

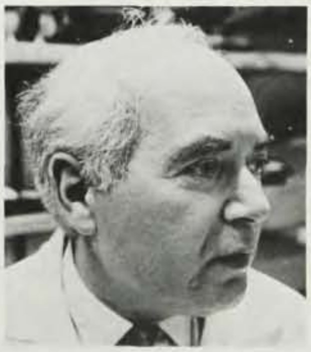
He chose the force **F** exerted upon a particle of volume V and magnetic susceptibility K_1 embedded in a medium of susceptibility K_2 in a nonuniform magnetic field **H**

$$\mathbf{F} = V(K_1 - K_2) \text{ grad } (\mathrm{H}^2) \quad (1)$$

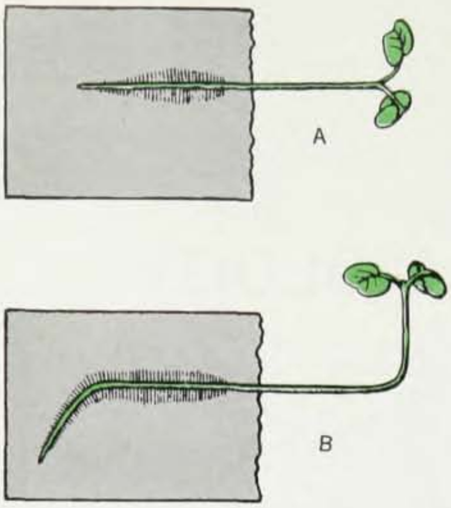
Neither the overall susceptibility of amyloplasts K_1 nor that of the intracellular fluid K_2 had been measured. So Audus had to make reasonable estimates of these values, with Pascal's magnetochemical equation that expresses the molecular susceptibility K_M of a compound in terms of the atomic susceptibilities K_A

$$K_M = \Sigma n_A K_A + \lambda \quad (2)$$

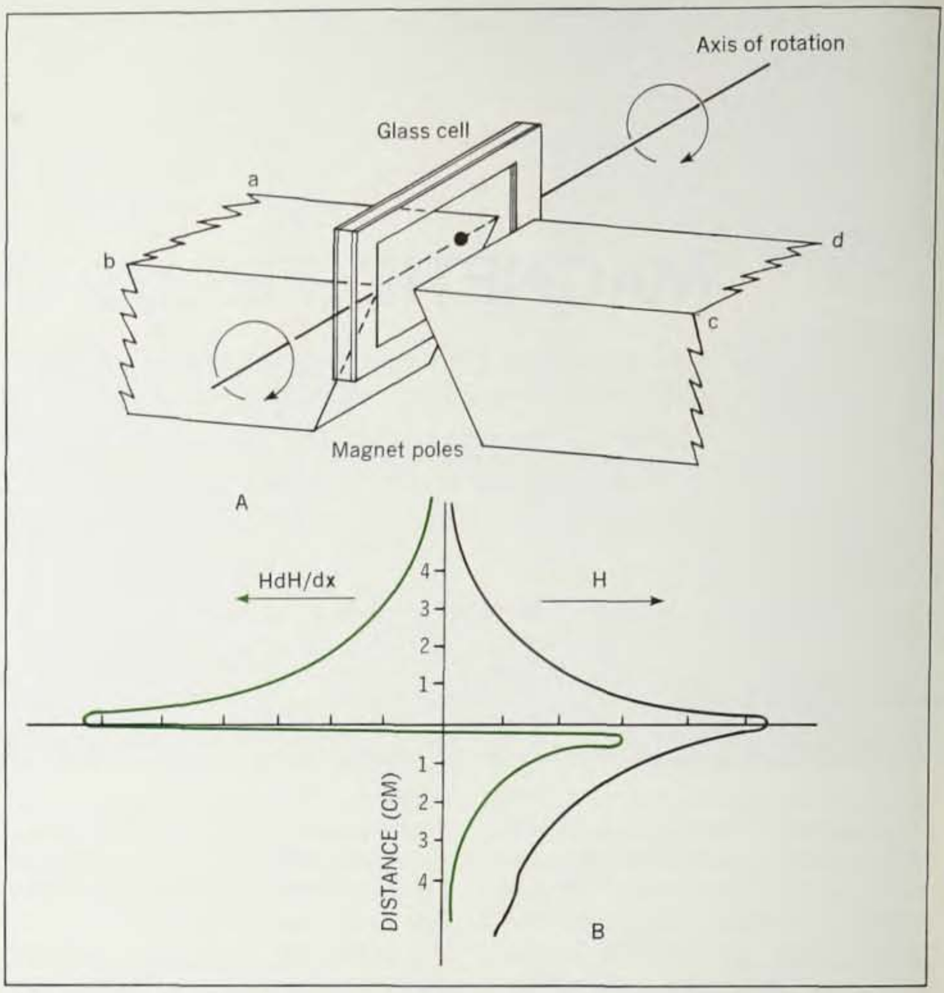
Here n_A is the number of atoms of susceptibility K_A in the molecule and λ is Pascal's constitutive correction constant, which is determined by the interatomic bonds in the molecule. Both susceptibilities turned out to be negative with $|K_1| > |K_2|$, and the starch grains were thus expected to move as diamagnetic objects would in a vacuum, that is, down the magnetic



Alexander Kolin was born in Odessa, Russia and came to the US after receiving his doctorate in physics from the German University of Prague in 1934. He is professor of biophysics at UCLA where he has been since 1956. Kolin was awarded the John Scott medal in 1965 for invention of the electromagnetic flow meter, and the Albert F. Sperry medal in 1967.



GEOTROPIC CURVATURE of root and hypocotyl of a mustard plant. At A the plant is in a horizontal position and at B as it looked one day later. From B. S. Meyer and D. B. Anderson, Van Nostrand, New York (1939). —FIG. 1



MAGNETOTROPISM. In A the germinating seedling is in the glass cell between the magnet pole pieces. The axis of rotation is horizontal. Distribution of the intensity of magnetic field H and of the parameter H dH/dx along the axis midway between the poles perpendicular to plane abcd is shown in B. —FIG. 2

field gradient. The calculated force on the particles turned out to be less than one percent of the force responsible for gravitational sedimentation. It appeared necessary to eliminate the force of gravity in the experiments to avoid masking the anticipated diamagnetic effect.

These considerations led Audus to design the experimental apparatus shown in figure 2. The entire apparatus (including the magnet) rotates slowly (1 revolution in 100 seconds) about a horizontal axis passing transversely through the maximal-field region between the sharp edges of the poles of a permanent magnet. This rotation exposes the young plant, initially parallel to the axis of rotation, to an alternating (rotating) gravitational field, thus eliminating the curvature caused by geotropism. We expect the seedling, as it germinates unaffected by gravity, to curve in accordance with effects induced by the nonuniform magnetic field in its growth-regulating mechanism. The maximal field intensity (in the plane *abcd* of figure 2) was approximately 4000 gauss and the field gradient more than 5000 gauss/cm.

The heterogeneous magnetic field induced curvature of roots as well as of shoots in these experiments. Figure 3 illustrates the results Audus obtained with cress roots (left column of photographs) and oat coleoptiles (right column). At $t = 0$ the root and the coleoptile near the bottom of the top frame are parallel and close to the white line at the bottom that indicates the location of the plane *abcd* of figure 2. As time goes on we see that both plant organs curve away from the plane of maximal field strength.

Failure and consolation

This success was a disappointment. If a magnetic analog to geotropism had been achieved the roots and shoots would have curved in opposite directions! They did not. Furthermore, microscopic examination revealed that the amyloplasts, whose sedimentation was assumed to be responsible for geotropic responses, and which Audus intended to displace by magnetic forces, showed no evidence of displacement within the cells. Thus his attempt to shed light on geotropism failed, but there was consolation in the discovery of a biomagnetic effect.

ANIMAL DEVELOPMENT

Insects are particularly suitable for detecting physically induced inheritable variations. For instance, the fruit fly *drosophila melanogaster* has been for many years the favorite experimental animal of geneticists studying genetic mutations induced by x rays. Insects also proved helpful for studies of effects of magnetic fields on animal development. We shall consider two examples: effects of homogeneous magnetic fields,[2,3] and effects of heterogeneous fields.[4,5]

Homogeneous magnetic fields

A typical insect goes through several stages of metamorphosis in the course of its development from the fertilized egg. The egg develops first into a mobile larva. The larva is transformed into a pupa that, though outwardly quiescent, is teeming with internal activity resulting in the emergence of an adult form (imago) that shows little resemblance to the preceding forms.

N. M. Amer and C. A. Tobias chose the flour beetle *tribolium confusum* for study. The pupa of this insect exhibits a critical dependence upon temperature. If the temperature is too high, the pupa fails to molt (develop into the adult form). At 40°C they all fail to molt. At 38°C molting failure is 26%; however, 5% of the insects that develop into an adult show wing anomalies. The dependence of molting failure and wing anomalies on the incubation temperature[3] is illustrated in figure 4. Note the sharp rise in the incidence of molting failure near 40°C.

Amer and Tobias made the interesting discovery that exposure of the flour-beetle pupa at a given temperature to a uniform magnetic field during its development reduces the frequency of molting failure. Exposure to a magnetic field has thus an effect equivalent to reduction in temperature. For example, for pupae developing in air at 39.5°C, maintenance of a magnetic field of 6.2 kilogauss produces the same depression of molting-failure incidence as a temperature drop of 1.5°C. The effect of a uniform magnetic field on molting failure is illustrated in figure 5. The frequency of molting failure decreases with increasing magnetic-field intensity until 8 kilogauss and rises beyond this point.

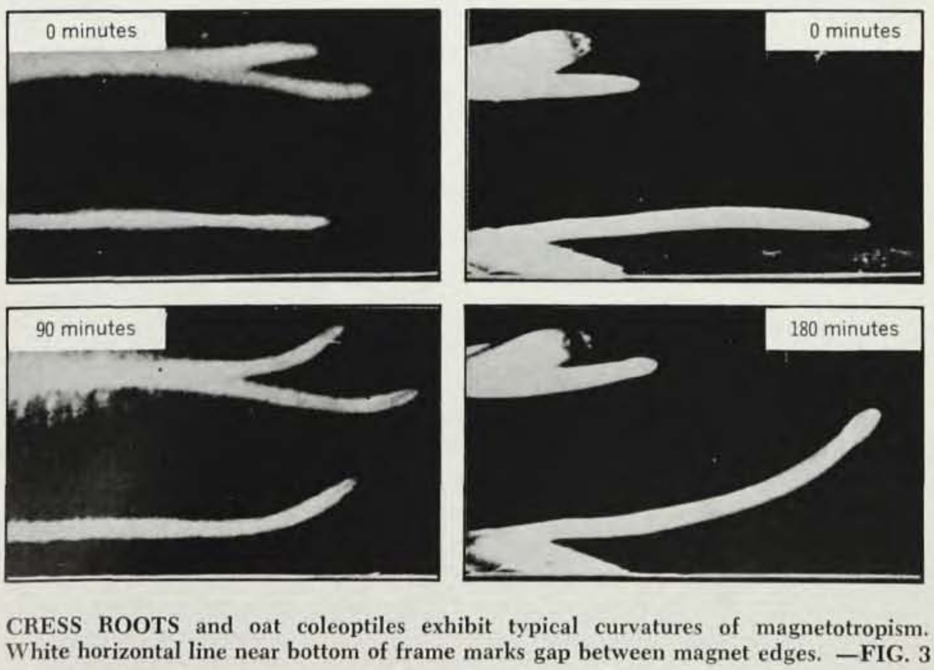
To explain their observations, Amer and Tobias wrote,[2] tentatively: ". . . The data are explained with the following working hypothesis: in the course of developmental transformations at some time paramagnetic molecules (eg, free radicals) become essential for the process: interactions of such molecules determine whether or not eclosion (emergence) and wing development is normal. The presence of magnetic fields alters the probability of radicals for interaction; in first approximation one might assume that the number of degrees of freedom of thermal motion are altered and changes occur in molecular magnetic coupling . . . ." A great deal of work remains to be done before a well established theory can be offered for these interesting phenomena and other effects described by Amer.

Nonhomogeneous magnetic fields

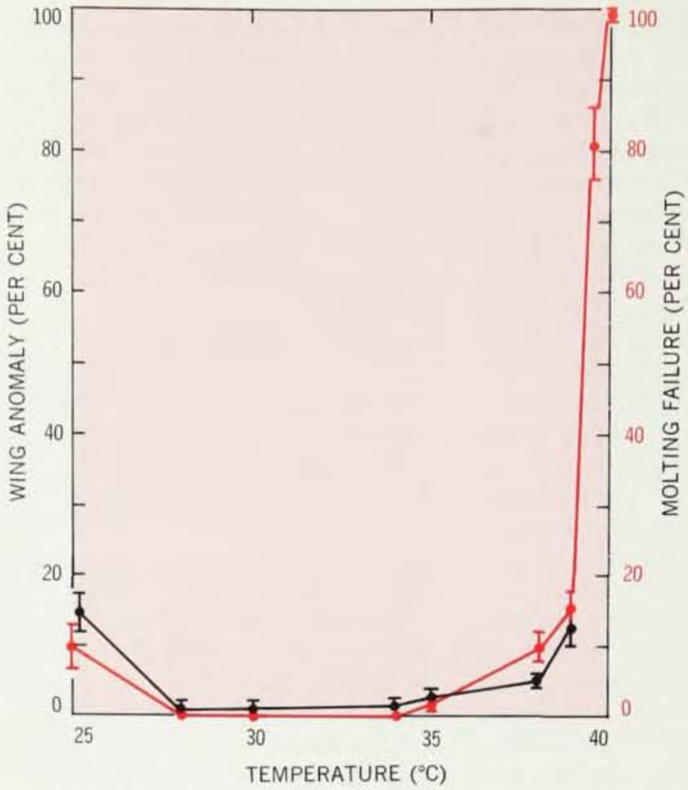
Very striking results leading to inheritable changes persisting for 30 generations were obtained by W. C. Levengood[4,5] on application of strong nonhomogeneous magnetic fields to pupae of the fruit fly *drosophila melanogaster*. One of the essential differences between his experiments and those of Amer and Tobias was that they exposed the entire animal to a magnetic field whereas Levengood endeavored to localize the application of the magnetic field to chosen target organs of the pupa. Chosen organs included the developing gonads and the head region near the imaginal disks. The most pronounced effects were obtained with pupae, although he studied all stages of metamorphosis. The effects of magnetic-field exposure ranged from alteration of development time of the pupa to death without emergence from the pupal stage. All exposure to magnetic fields was accompanied by control experiments in which pupae were exposed to a nonmagnetic replica (a brass "dummy magnet") of the electromagnet. With a cylindrical coil wound around an iron bar 6 mm in diameter that protruded about 2.5 cm beyond the coil, Levengood obtained a field strength of 21.8 ± 1.0 kilogauss at the pole-tip surface. The field gradient was 9 kilogauss/mm over the first 2 mm from the 125-micron diameter pole tip. This small pole tip enabled Levengood to treat selected regions of egg, larva, pupa and adult insect. Amer and Tobias maintained their magnetic field throughout the entire development time of the pupa; exposures in Levengood's experiments lasted from a few minutes to a half hour (the mean development time for his *drosophila* pupae was 13.6 ± 1.12 days). The age of the pupa at exposure to the magnetic field was of decisive importance. Very young pupae, close to the age of one hour, usually died as a consequence of a few minutes' exposure to the magnetic field before hatching into a fly. Pupae of various ages exposed in the head region (near the imaginal disks) proved most sensitive to the heterogeneous magnetic field. A 10-minute exposure produced more than 50% mortality, that is, more than half the pupae did not reach the stage of adult insects. Of those that did mature into imagos, 5–10% showed severe wing anomalies and body deformities. As a rule the emerging flies did not survive for more than an hour after emerging from the pupal stage.

Development time and progeny

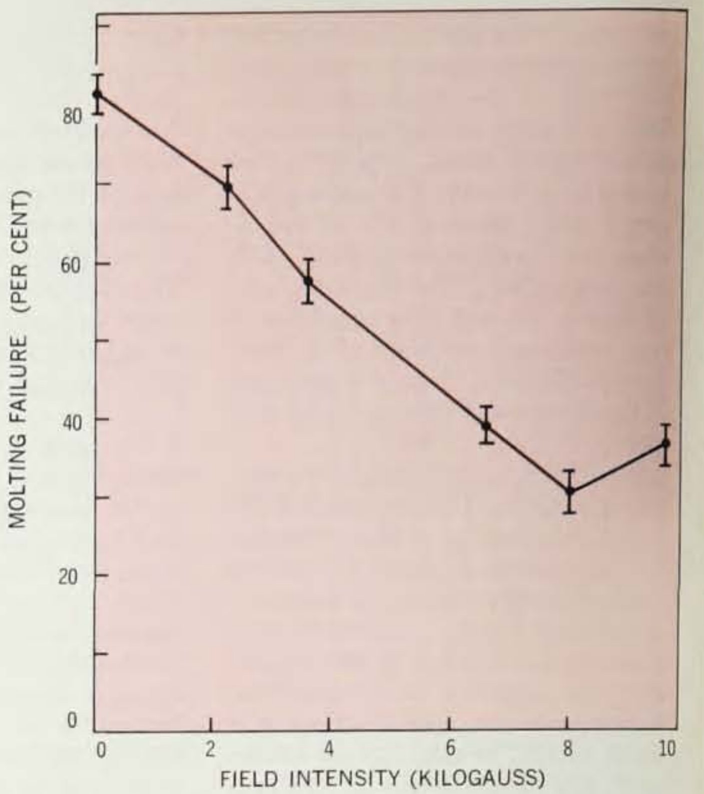
Levengood fixed his attention particularly on two inheritable characteristics of the fruit flies: the mean development time, which he defines as " . . . the number of days from the start of a new culture until . . . the new generation of flies first appeared"; and mean progeny (a measure of fecundity, determined by the number of offspring per female fly). He found that both characteristics are affected by magnetic exposure. For example, a 30 minute exposure on 110-hours-old pupae almost doubled the development time for the second generation. The increase in development time dropped for subsequent generations but could still be detected after 30 generations. As a rule, there is an inverse correlation between mean development time and mean progeny.



CRESS ROOTS and oat coleoptiles exhibit typical curvatures of magnetotropism. White horizontal line near bottom of frame marks gap between magnet edges. —FIG. 3



MOLTING FAILURE (color) and wing anomalies (black) in flour beetle as a function of temperature. —FIG. 4



EFFECT OF HOMOGENEOUS magnetic field of incidence on molting failure at 39.5°C. —FIG. 5

Of particular interest is Levengood's observation that magnetically treated fertilized adult female flies did not give rise to progeny exhibiting an increase in development time, whereas males emerging from pupae treated magnetically for 10 minutes at the age of 21 hours exhibited a development time of 28 days, more than twice the normal duration. When crossed with untreated females, the males gave rise to offspring showing a greatly increased development time that was pursued for 10 generations.

Levengood's papers contain many other interesting results and also speculations on possible mechanisms; other workers[6] also have considered possible explanations of biomagnetic effects.

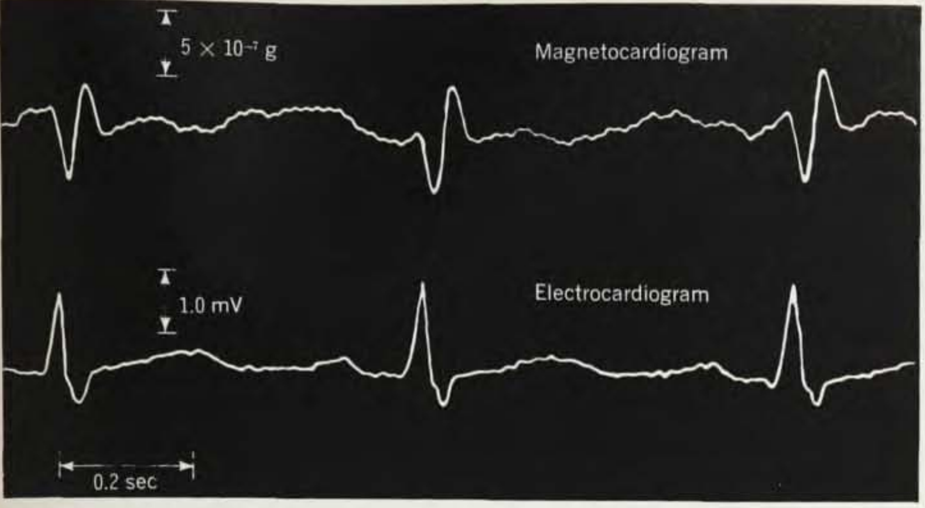
STIMULATION OF IRRITABLE TISSUES

Brain operations are often performed under local anesthesia. The patient may be able to describe his mental responses evoked by local electrical stimulation of his brain. Penfield[7] was able to induce hallucinations and recall of events from the distant past. This technique is a most valuable approach to the study of higher brain functions, but the necessity of contacting the cerebral cortex with electrodes precludes it from being used routinely on volunteer subjects. It appeared attractive to explore electrical stimulation of irritable tissues without electrodes. Hopefully, we could stimulate the brain without piercing the skull. Electromagnetic induction with an alternating magnetic field of eddy currents in tissues looked like a promising approach.[8] To begin with we showed that a nerve could be so stimulated. We took a nerve–muscle preparation, consisting of a frog's gastrocnemius muscle with the sciatic nerve attached to it, looped the nerve into a closed circle and placed it in an alternating magnetic field (6000 gauss rms at 60 Hz). Excitation of the ac magnet produced an intense tetanic contraction of the muscle and gave evidence of the nerve stimulation. When the nerve was removed and the muscle alone (or muscle segments) was placed into a flat dish filled with a suitable electrolyte (frog Ringer's solution) exposure of the submerged muscle to a vertical magnetic field resulted in strong contraction of the muscle or pieces of muscle. The contractions were strongest when the muscle was on the periphery of the circular dish and absent when it was at or close to the dish center. This is to be expected for stimulation by eddy currents that circulate along the rim of the dish.

Retinal response

The next logical step was to select a suitable irritable tissue in an intact organism whose response could be easily ascertained. Our own retinas appeared to be ideally suited. We found that a bar magnet, energized at 60 Hz and yielding approximately 8700 gauss rms at its front surface, held to the temple gave rise to intense light sensation in perfect darkness as well as in a brightly lit room.

We soon learned to our disappointment that ours was not the first observation of these visual phenomena known as "magnetic phosphenes." They were discovered several times independently by different observers. The first observation appears to have been Michael d'Arsonval's in 1896.[9] "Magnetic phosphenes" were rediscovered by Silvanus P. Thompson in 1910.[10] Thompson inserted his head into a cylindrical coil (23-cms diameter, 20-cms long) with a field of 1000 gauss rms at 50 Hz and observed an almost colorless flickering light of bluish tint spread over his entire visual field but somewhat stronger on the periphery than in the center. He subsequently learned from Birkeland of



COMPARISON of human magnetocardiogram with electrocardiogram. —FIG. 6

Christiania in Norway that workmen at the nitrate factory at Notodden reported visual sensations near the large choke coils that limited the current supplied to the electric furnace.

Investigations showed[11] that the visual sensation was neither due to stimulation of the brain nor of the optic nerve, but rather of the retina itself, presumably by eddy currents induced in the eye. Pressure on the eyeball, to stop retinal responses, is sufficient to abolish the visual sensation. This assumption of direct action on the retina is supported by application of a localized magnetic field (by a sharp-tipped bar electromagnet) to the eye, whereupon the sensation appears in the opposite quadrant of the eye. Application of the magnetic stimulator at the bottom of the eye produced visual sensation referred to the top quadrant. Placing the magnet pole near the occipital region of the skull (near the area of the cortex concerned with vision) produced no visual sensation. No sensory responses other than visual could be evoked.

MAGNETIC FIELDS OF ACTIVE ORGANS

We do not normally think of an animal (or animal organ) as a source of a magnetic dipole field. However, the conclusion is inescapable that we should see some magnetic manifestations because activity of many organs, for example nerves and muscles, is accompanied by "electrical activity" involving flow of ionic currents. How feasible would it be to pick up the presumably faint magnetic signals of such "electrical activity?" The literature contains reports of three successes. Transient magnetic fields surround the human torso; they are related to the electrical activity recorded as electrocardiograms,[12] and magnetic fields apparently related to electrical impulses traveling along stimulated nerves have been recorded by two independent teams of investigators.[13,14] Most recently, varying magnetic fields surrounding the human skull associated with the brain's electrical activity have been demonstrated.[15]

Heart and brain

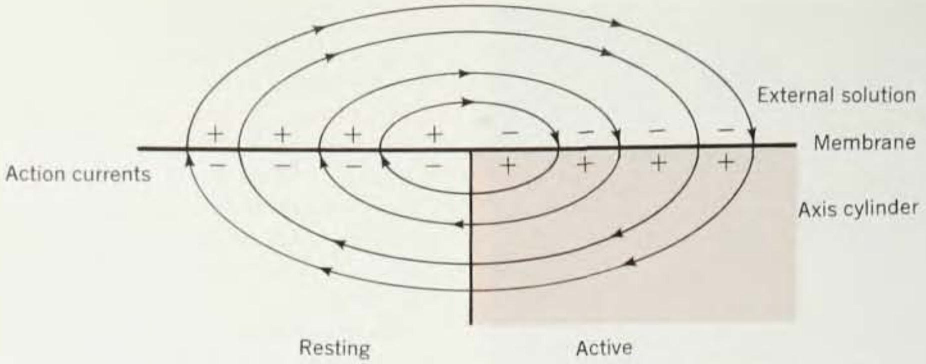
The complex pattern of periodic contractions and relaxations of the auricular and ventricular muscles of the heart gives a time dependent, complicated, spatial distribution of electric currents in the chest (a heterogeneous volume conductor) set up by the electromotive forces generated by the activity of the heart muscles. We can pick up a regular pattern of potential variations by applying electrodes at suitable standardized locations on the human torso. The electrocardiogram (ECG) thus recorded contains certain peaks of great value in diagnosing many heart diseases by deviations from the normal ECG pattern. D. Cohen[12] detected regular magnetic field fluctuations in the vicinity of a human chest demonstrably related to the ECG pattern. Figure 6 shows such a magnetocardiogram (MCG)[12] in juxtaposition to an ECG pattern.

The magnitude of the recorded magnetic fields (10^{-8}–10^{-7} gauss) is about 10^{-7} of the steady component of the earth's magnetic field and about 0.10% of the total noise composed of the fluctuating component of the terrestrial field and magnetic "city noise" in the 1–30 Hz bandwidth. Consequently Cohen used a room magnetically shielded by two layers of Moly-Permalloy surrounding an aluminum enclosure. With his parametric amplifier he could detect time-varying magnetic fields of approximately 10^{-9}-gauss amplitude on a bandwidth of 0.5–10^5 Hz.

His sensor was a series connection of several coils of 2×10^5 turns each, placed 10 cm from the torso. At this distance the magnetic-field amplitude of the MCG was of the order 10^{-8}–10^{-7} gauss. A noise-averaging enhancetron reduced the signal noise by a factor of 12. The MCG signal was not an error signal caused by ECG electrical fields; the signal remained unchanged when a copper enclosure was slipped over the pickup coil but was eliminated when a 0.36-mm enclosure of Moly-Permalloy was similarly applied. It is too early to judge if this approach to the electrical activity of the heart is an improvement upon, or at least a useful adjunct to, the currently used method. It is, however, reasonable to assume that refined detection of minute magnetic fields that accompany biological activity may lead to interesting and useful applications in the future. In particular a recent report of a magnetic concomitant of the electrical activity in the human brain will be most interesting if confirmed.[15]

An isolated nerve

Earlier investigations pursued a similar objective on a much smaller system—an isolated nerve (the sciatic nerve of a bullfrog). If we stimulate the nerve at the cut end of a nerve–muscle preparation, say by pinching, a state of excitation propagates along the nerve and makes the muscle at the opposite end contract. Two closely spaced electrodes placed somewhere along the nerve record a transient variation in potential difference, which appears as an upward "spike" followed by a gental depression below the base line. Physiologists arrived at the conclusion that the propagated potential variation is accompanied by ionic currents (we shall disregard here the nature of the ions) flowing as pictured in figure 7. Normally the membrane of the nerve is sandwiched between ionic polarization charges as pictured in the diagram in the region labeled "resting." When the nerve is stimulated, the polarization in the excited region



CIRCULATING ACTION CURRENTS which accompany the propagation of a potential variation along a polarized nerve membrane. After L. E. Bayliss, Principles of General Physiology, vol 2, John Wiley and Sons (1958). —FIG. 7

reverses sign as shown in the region labeled "active," and currents are set up. To visualize the spatial current distribution we must imagine the membrane of figure 7 as a cylindrical surface. The demarcation zone between the "active" and the "resting" region is propagated along the curve.

In accordance with this picture of the current distribution, J. H. Seipel and R. D. Morrow[14] drew the picture of the magnetic field set up by the "action currents" of an excited nerve that is shown in figure 8 and set out to detect this transient magnetic field with coils placed adjacent to the nerve. Independently and almost simultaneously, J. A. Gengerelli, N. J. Holter and W. R. Glasscock[13] embarked on the same venture. Both groups succeeded in obtaining signals that they interpreted as transient magnetic fields associated with the transient action currents accompanying the propagated nerve impulse. Each group took precautions with magnetic and electrostatic shielding to reduce their noise levels. The coil sensor of Gengerelli's group could detect a signal from a wire carrying 1.5×10^{-8} amps at 500 Hz passing through its center.

Figure 9 shows a recording by Seipel and Morrow. The initial artifact due to electric stimulation (A) could be eliminated by mechanical stimulation of the nerve (pinching). While the nerve was gradually dying the magnetic signal progressively dropped to zero.

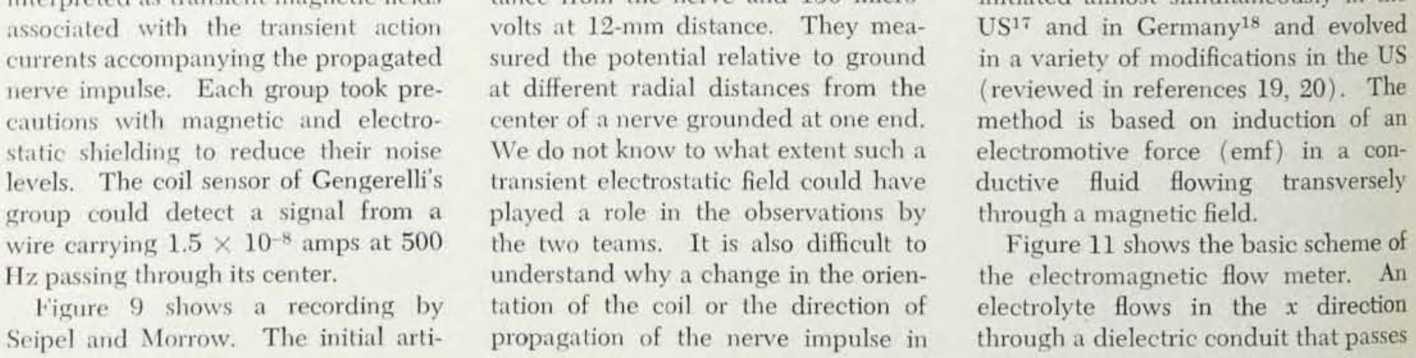
Some puzzling features

These observations have some puzzling features. It is difficult to see how an appreciable magnetic field could exist at the distances at which the detectors were placed if the electrical currents are confined to the nerve and a layer of moist electrolyte surrounding it. M. S. Burr and A. Mauro[16] demonstrated and measured the quasielectrostatic field engendered in the air around a stimulated sciatic nerve of a frog and obtained signals as large as 345 microvolts at 1-mm distance from the nerve and 150 microvolts at 12-mm distance. They measured the potential relative to ground at different radial distances from the center of a nerve grounded at one end. We do not know to what extent such a transient electrostatic field could have played a role in the observations by the two teams. It is also difficult to understand why a change in the orientation of the coil or the direction of propagation of the nerve impulse in Gengerelli's experiments produced no change in the polarity of the received signal. Figure 10 shows a recording by Gengerelli's group that was obtained by stimulation of the nerve at one end. Stimulation at the other end so that the impulse traveled in the opposite direction yielded a practically identical trace. Contrary to expectation we obtain no reversal in the tracing. More work is needed before we can better understand these intriguing results.

A BIOPHYSICAL MHD GENERATOR

We shall now turn to what may have been the first use of magnetic fields for precise biological measurements. A general method for studying the performance of a variety of organs and their response to diverse stimuli and drugs would be of great value (analogous to spectroscopy in analytical chemistry). Study of the rate of blood supply to different organs comes reasonably close to filling this need. This physiological parameter determines the supply of oxygen, hormones and nutrients to an organ while simultaneously removing metabolic products. Blood flow in an organ could be correlated to the organ's activity and used as an index of the organ's response to stimulating and inhibiting agents such as poisons, drugs, hormones, physical parameters and psychological factors. The study of blood circulation is in itself an important chapter of physiology and is equally important in clinical medicine. A method for studying blood flow was initiated almost simultaneously in the US[17] and in Germany[18] and evolved in a variety of modifications in the US (reviewed in references 19, 20). The method is based on induction of an electromotive force (emf) in a conductive fluid flowing transversely through a magnetic field.

Figure 11 shows the basic scheme of the electromagnetic flow meter. An electrolyte flows in the x direction through a dielectric conduit that passes



MAGNETIC FIELD attributed to a nerve pulse. Detection of this transient field was made with coils placed adjacent to the nerve. After Seipel and Morrow[14]. —FIG. 8

through a magnetic field between N and S poles. Positive and negative electrodes disposed along the y axis pass through the pipe to contact the fluid. Ions in the fluid experience Lorentz forces acting upward and downward along the y axis (depending on the sign of the ionic charge) as the ions traverse the magnetic field interacting with its z component. With a uniform velocity throughout the conduit and an homogeneous field we expect a voltage

$$V = 10^{-8} \times 2RBv \qquad (3)$$

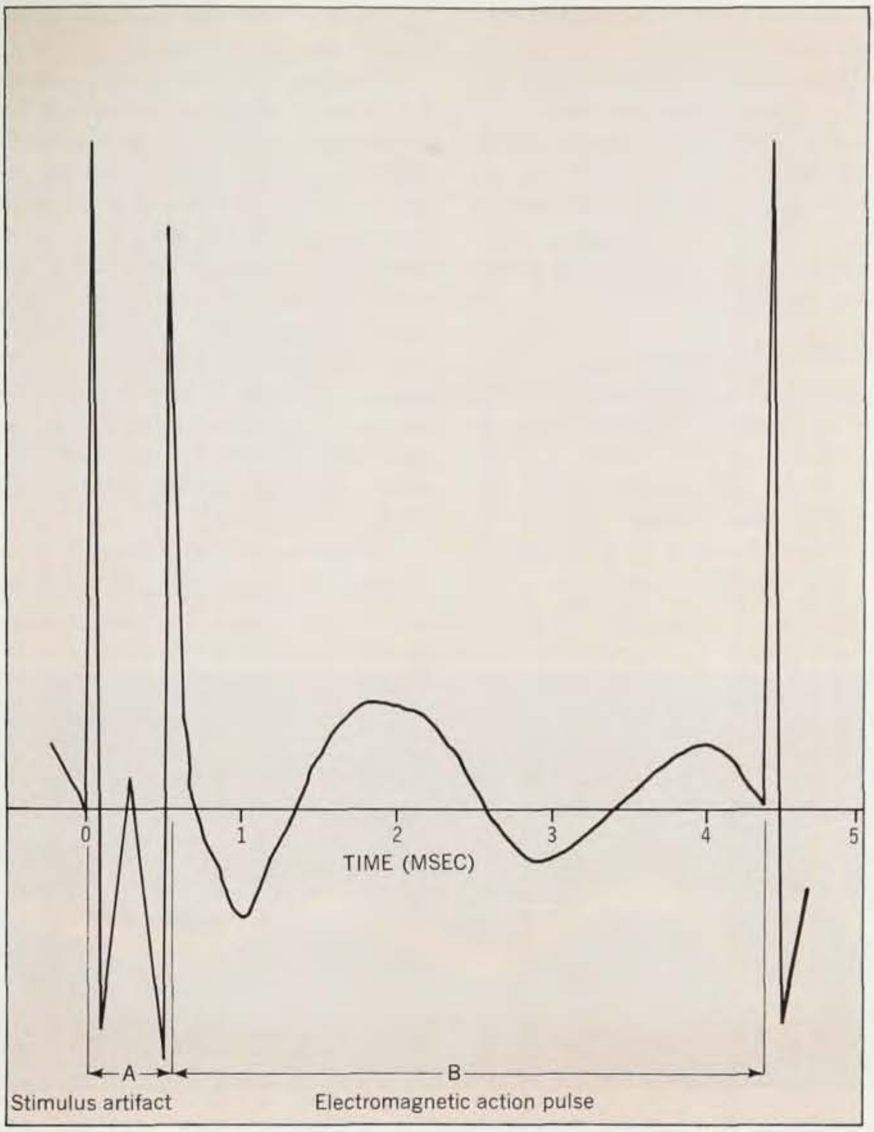
as a measure of the emf induced in the fluid, where B is the magnitude of the magnetic field in gauss, R is the pipe radius in cm and v the fluid velocity in cm/sec.

Vanishing complications

In practice the velocity is not even approximately uniform throughout the pipe cross section in laminar flow. This situation gives rise to eddy currents that greatly complicate the theoretical analysis. However, equation 3 holds generally for any cylindrically symmetrical velocity distribution. In this general case, v has the meaning of average velocity of flow in equation 3.[21] Fortunately a reliable linear performance of the electromagnetic flow meter over the laminar as well as turbulent regimes is assured. Determination of the output voltage of this magnetohydrodynamic generator permits measurement of average flow velocity v and hence the rate of volume flow through the conduit.

A second fortunate circumstance is the relatively high conductivity of the blood-vessel walls (of the same order of magnitude as the conductivity of blood). As a result we need not pierce the vessel wall to create an electrical contact between the electrodes and the blood, and so we avoid injuring the blood vessel and plugging it with a blood clot. Application of this flow meter to patients in the course of surgical procedures is safe, simple and now practiced routinely.

In early stages of development, serious experimental difficulties had to be overcome. If we use metal electrodes in conjunction with a constant magnetic field, establishment of a steady flow does not produce a steady electrical signal but a quickly decaying transient response owing to electrode polarization. So-called "nonpolarizable" electrodes are clumsy and do not fulfill the requirement of nonpolarizability



ELECTROMAGNETIC ACTION PULSE. Composite tracing of the electromagnetic action pulse obtained from a frog's sciatic nerve. —FIG. 9

well enough. The constant magnetic field was thus abandoned for an alternating one. A steady flow then generates an alternating emf, and if the frequency is high enough, electrode polarization ceases to obstruct successful flow measurements. Figure 12 shows an electromagnetic blood-flow transducer. The magnet is a split wire-wound iron toroid with a plastic sleeve inserted into its gap. The slot permits insertion of the artery that establishes contact with the electrodes. The shutter closes the slot after insertion of the artery. These transducers have been made in sizes small enough to implant into an animal as small as a rat. As we can see from figure 12a, the lead from one electrode forms a loop on its way to join the lead from the other. Owing to unavoidable slight asymmetry of construction, the magnetic field has a slight axial component that induces an emf in this loop, which in conjunction with the eddy-current signal induced in the tissues and blood enclosed in the lumen, causes an error signal independent of the flow rate. This error may be orders of magnitude larger than the signal from the flow to be detected.

Fortunately the two induced signals arise basically from two different physical phenomena that are described by different laws. The electromagnetic induction in the moving fluid is described by the Lorentz equation

$$\mathbf{E} = \mathbf{v} \times \mathbf{B} \qquad (4)$$

and the flow-independent emf induced in the loop of the input circuit is described by Maxwell's equation

$$\text{curl } \mathbf{E} = -d\mathbf{B}/dt \qquad (5)$$

Because of this difference, the flow

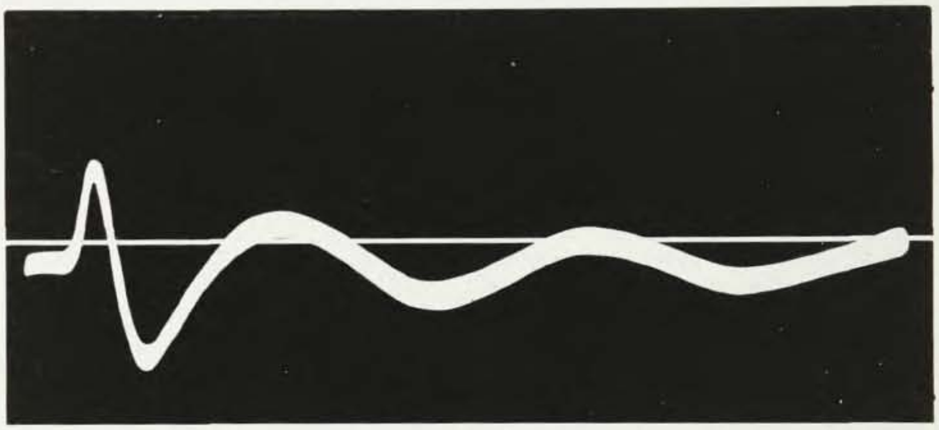
signal described by the velocity-dependent equation 4 will be in phase with the sinusoidal magnetic field **B**, and the flow-independent zero-error signal will be in phase quadrature with respect to **B**. We need look only at the flow signal with a phase-sensitive detector, while disregarding the quadrature signal, which is zero when the flow signal is maximum.

Blood flow determination

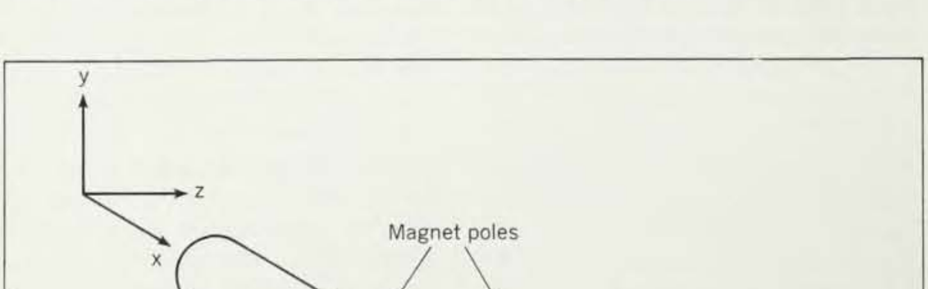
The high signal-to-noise ratio achieved by phase-sensitive detection permits very weak magnetic fields (a few gauss) to be used in transducers designed for major arteries. Figure 13 shows the skeleton of an electromagnetic flow transducer which is now in widespread use for artery lumens greater than about 4 mm.

Although the later design (figure 14) greatly reduces the bulk of the components generating the magnetic field as compared to the lumen, we should reduce the size of the implanted transducer to the utmost extent for experiments in which the blood-flow meter is to remain in the body for prolonged periods without causing irritation and possible thrombosis of the artery. Complete omission of the magnet from the flow transducer allows such miniaturization. The magnetic field must then be generated by an external magnet.

Illustrations in the figure 14 series on page 49 depict the various kinds of information that electromagnetic blood-flow meters can give. The predominant medical use of electromagnetic flow meters is in the operating room on patients undergoing heart or blood-vessel surgery. The utility of this device would be enormously increased if it could be modified to be routinely applicable to patients in the clinic; it would diagnose circulatory disorders without resorting to major surgical intervention. Such a modification has actually proved possible[23,24] and an adaption of an idea previously employed for nonbiological use[25] was recently used at the Hammersmith Hospital in London to record blood flow in the human aorta without major surgery.[26] Catheters can now be introduced routinely into the human blood vessels for diagnostic observations. It is necessary, however, to administer to the patient a drug (heparin) to inhibit coagulation of blood that normally would be provoked by a foreign object in the bloodstream. Certain materials, like silicone rubber or teflon, are less objectionable than others.



SIGNAL from a frog's sciatic nerve threaded through a toroidal coil. —FIG. 10



ELECTROMAGNETIC FLOW METER. An electrolyte flows in the x direction through a dielectric conduit that passes through a magnetic field between N and S poles. Positive and negative electrodes disposed along the y axis pass through the pipe to contact the fluid. Ions in the fluid experience Lorentz forces acting upward and downward along the y axis (depending on the sign of the ionic charge) as the ions traverse the magnetic field interacting with its z component. —FIG. 11

Electromagnetic forces on cells

Is the converse of the bioelectromagnetic generator of any use to us? If we establish an electric current between the electrodes of figure 11 we obtain an electromagnetic pump. To suppress electrolysis we would use an alternating current and an in-phase magnetic field of equal frequency. Currently there is great interest in devices that could replace or assist the heart. The electromagnetic-pump principle is very attractive because of its great simplicity and absence of parts that could wear out. A heart substitute, or at least an auxiliary heart pump, based on this principle has been the subject of experiments but no practical success has yet been achieved. However, electromagnetic pumping has been used with good success in other biological applications. A magnetic field superimposed on an electric field in a suitably designed electrophoresis apparatus moves the fluid like an endless belt, while ions of substances such as proteins, or biological particles such as cells, bacteria, viruses and chloroplasts, migrate transversely to the belt motion. They follow a helical path at the end of which they are well separated as thin streaks by differences in electrophoretic mobilities.[27] The top illustration on page 38 shows the result of such a separation; in this case a dye mixture splits into three colored components within a few seconds.

Another type of electromagnetic interaction may prove useful in applications to cells, subcellular particles and microörganisms. Consider a particle of conductivity σ', such as a living cell, suspended in an electrolyte solution of electrical conductivity σ'' (different from its own); it will experience a force if the solution is traversed by an homogeneous magnetic field and a uniform electric current perpendicular to it. The force is perpendicular to both the magnetic field and the electric current.[29,30] We shall refer to this phenomenon as an electromagnetokinetic (EMK) effect; the resulting particle migration is called electromagnetophoresis (EMP). Volume forces on the particle are caused by interaction of the ions passing through it with the magnetic field. Surface forces on the particle are caused by magnetic interaction of the ion currents flowing through the surrounding fluid, which determines the pressure distribution over the particle's surface. The force **F** upon a small spherical particle of conductivity σ' suspended in a solution of conductivity σ'' traversed by a magnetic field **B** and current of density **J** is

$$\mathbf{F} = \frac{3}{2}\,(\mathbf{J} \times \mathbf{B})\,\frac{\sigma'' - \sigma'}{2\sigma'' + \sigma'} \qquad (6)$$

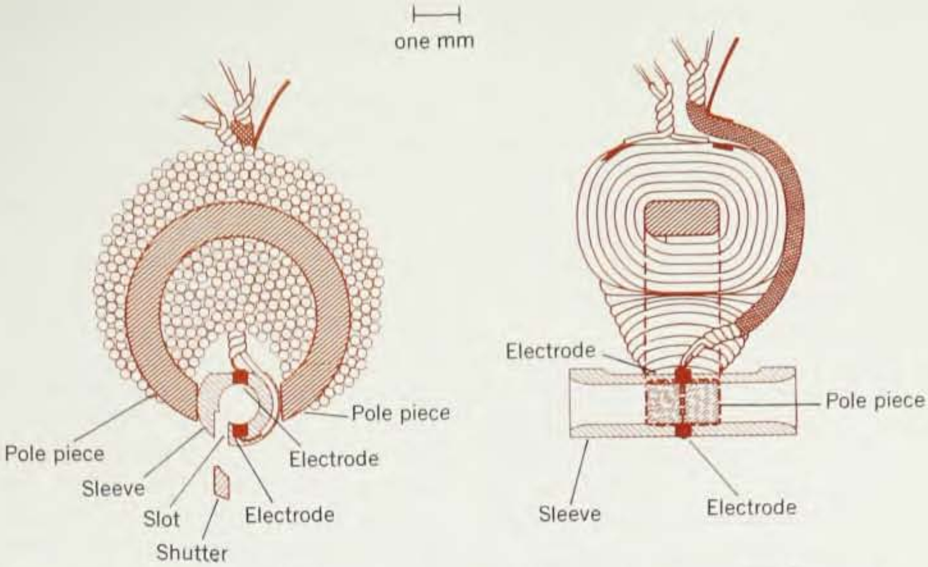
We see that $\mathbf{F} = 0$ for $\sigma' = \sigma''$ and that it reverses direction as the particle conductivity makes a transition from $\sigma' < \sigma''$ to $\sigma' > \sigma''$. We could, for instance, separate two species of cells of different conductivities by adjusting the conductivity of the suspending electrolyte to an intermediate value between σ' and σ'' that would make them move in opposite directions. If the different particles move in the same direction they can be separated by the difference between their migration velocities. From equation 6 and Stokes's law we obtain, for the speed v of a sphere of radius a migrating in a fluid of viscosity η in a magnetic field **B** at a current density **J**

$$\mathrm{v} = \left(\frac{\sigma'' - \sigma'}{2\sigma'' + \sigma'}\right)\frac{\mathbf{JB}}{3\eta}a^2 \qquad (7)$$

Figure 15 shows the basic scheme of the apparatus in which the effect can be demonstrated. Figure 16 shows a different configuration in which a straight current-carrying wire serves as a magnet. The electrical current in the separation cell is parallel to the wire and perpendicular to the circular magnetic-field lines. The force on the particles is thus radial and we have, in effect, a centrifuge without rotational motion.

As can be seen from equation 7, the EMK effect allows us to separate particles by differences in size and electrical conductivity. In addition the shape and orientation of the particles can have a strong effect on the EMK force exerted upon it . For biological particles such as cells, we must consider an additional factor: the cell membrane that surrounds the particle has the characteristics of a leaky dielectric. If we use an alternating magnetic field with a perpendicular inphase electric current to produce the EMK effect, we expect at low frequencies the permeability of the cell membrane to ions, rather than the electrical conductivity of the cell interior, to be the main factor determining the current passing through the cell and, hence, the volume force experienced by it. So we have the possibility of separating cells by differences in cell-membrane permeability, which would be of great biological interest. At a high frequency, on the other hand, the cell membrane will exhibit a low impedance and will have relatively little effect in determining the volume force on the cell because the electrical conductivity of the cell interior is the dominant factor.

Jerzy Kovalczyk[31] stabilized a fluid against convection by imbedding it in a porous medium and utilized EMP migration to separate particles. William Murphy and others[32] designed an electromagnetophoresis apparatus to separate red and white blood cells.



MINIATURE BLOOD-FLOW METER. Magnet is a split wire-wound iron toroid with a plastic sleeve in its gap. Artery is inserted in the slot, which is then closed with the shutter. Electrodes pick up the induced voltage. This flow meter can be made small enough to implant into an animal as small as a rat. —FIG. 12

MAGNETIC RESONANCE EFFECTS

We shall conclude our review with a brief reference to the most sophisticated use of magnetic fields in biological research. The biological applications of nuclear magnetic resonance (NMR) and electron spin resonance (ESR) are so extensive that even a superficial account could easily double the length of this text. The mostly biochemical applications have been thoroughly described elsewhere. (*Magnetic Resonance in Biological Systems*, A. Ehrenberg, B. G. Malmstrom, T. Vanngard, eds., Pergamon Press, Oxford, 1967). Magnetic-resonance effects occur when a given sample of matter includes particles with gyromagnetic properties. Such particles are abundant in living matter and in molecules that are essential to living processes. Electrons, protons, and nuclei such as D^2, C^{13}, N^{14}, N^{15}, O^{17} and P^{13}, which have a magnetic moment and angular momentum, are examples.

When a sample of matter is placed in a magnetic field, interactions analogous to optical resonance absorption of light quanta are possible in the microwave or radiofrequency regions of the electromagnetic spectrum, depending on the magnetic-field intensity, the magnetic moment and the spin of the particle population involved in the interaction. The magnetic field imposes a restriction upon the possible orientations for which the projection of the spin vector on the magnetic-field axis is at most equal to plus or minus the spin magnitude or differs from it by an integral number.

Thus, protons and electrons (spin 1/2) have only two possible orientations relative to the magnetic field (parallel to it or antiparallel), whereas O^{17} with spin = 5/2 can assume six different orientations. These discrete orientations of the magnetic dipoles of the nucleus and electron correspond to discrete dipole energies in the magnetic field with the lowest energy level corresponding to dipoles oriented parallel to the field and the highest to the antiparallel orientation. Absorption of electromagnetic energy can cause transitions from lower to higher energy levels with resulting absorption of radiation and re-orientation of the dipoles.

Analysis and tracer studies

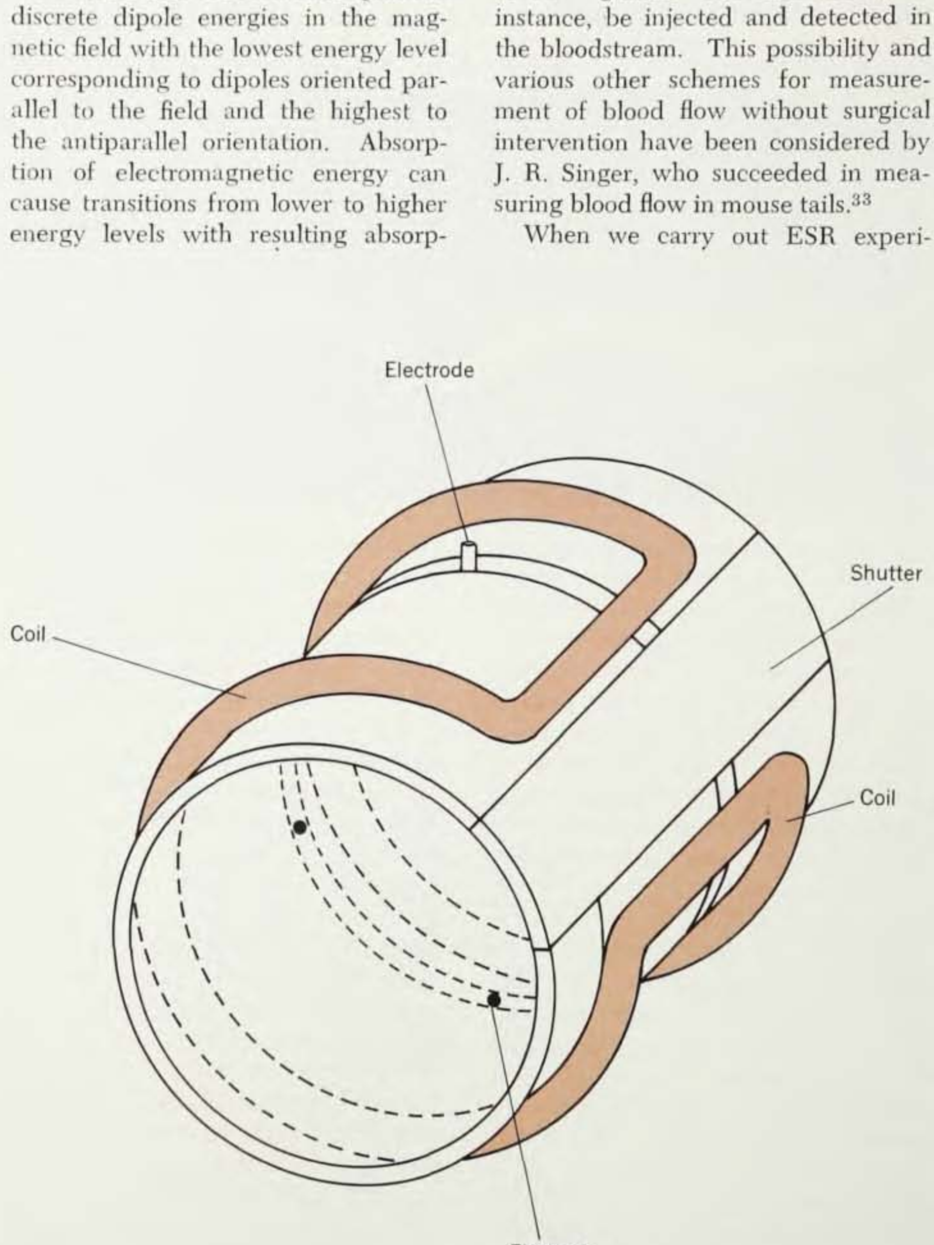
The first obvious application of NMR that comes to mind is analytical, namely qualitative and quantitative analysis for constituent elements of a biological system whose nuclei possess a magnetic moment. Both ESR and NMR can also be used for tracer studies in which introduction of radioactive isotopes into the biological system is undesirable. Stable free radicals and salts of transition metals, such as iron, cobalt and nickel, are particularly suitable and can be detected by ESR in amounts of the order of 10^{-9} grams. The salts could, for instance, be injected and detected in the bloodstream. This possibility and various other schemes for measurement of blood flow without surgical intervention have been considered by J. R. Singer, who succeeded in measuring blood flow in mouse tails.[33]

When we carry out ESR experiments or proton-resonance experiments, we normally find values for the resonance frequency ν that are different from the frequencies calculated on the basis of g values for free electrons and protons. This deviation is due to the effective local magnetic field at the site of the resonating proton or electron, which is not identical with the externally imposed field. The applied field is modified locally by the superimposed magnetic fields of neighboring nuclear and electronic magnetic dipoles as well as by the field arising from electronic orbital motions. Such frequency shifts ("chemical shifts") provide valuable clues about electronic orbital motion and disposition of various molecular structure of biologically important substances.

ESR is of importance in studies of molecules containing paramagnetic atoms, such as a number of enzymes, and particularly in detecting free radicals, which are molecular species containing an unpaired electron.

Biochemists suggests that ". . . free-radical mechanisms may be an ubiquitous attribute of the chemistry of living substance."[34]

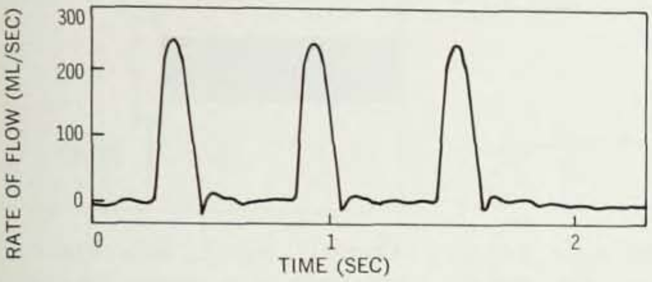
Free radicals vary in their stability from very stable molecules like triphenylmethyl to highly unstable species of very short lifetimes that cannot be expected in high concentration in a living system. The high sensitivity of ESR, enabling one to detect quantities of unpaired electrons as low as 10^{-11} moles, is ideally suited for the search for such unstable components suspected in living systems. ESR analysis promptly showed distinct electron spin resonances in materials of biological origin that had been subjected to heat treatment such as charcoal, charred cellulose and dried vegetable roots. Similar results were also obtained with presumably dead plant materials such as pine cones, fallen oak leaves and pine needles, plant materials such as seeds, roots and leaves as well as materials derived from animals, such as frog eggs and various organs of rabbits and mice–all of which yielded ESR signals corresponding to free radical concentrations of 10^{-8}–10^{-6} moles/gm of dry weight. Finally, experiments were performed that gave support to the hypothesis that free-radical formation is involved in various life processes. For instance, digitalis seeds gave no ESR signal unless they were germinating, at which time there was a signal corresponding to 10^{-7} moles/gm of dry



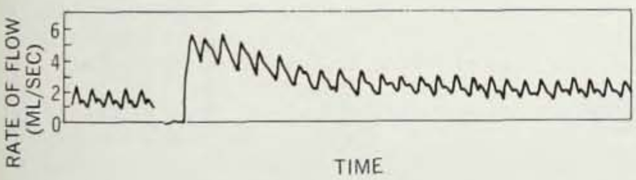
SKELETON VIEW of a single-coil coreless electromagnetic blood-flow transducer. The shutter seals the lumen after insertion of the artery. Completed transducer is potted in epoxy. This flow meter is now in widespread use for artery lumens greater than about 4 mm. From A. Kolin, R. Wisshaupt, IEEE Transactions Bio. Med. Electronics, *10* (1963). —FIG. 13

BLOOD-FLOW MEASUREMENTS

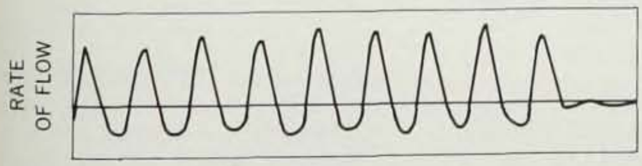
With the electromagnetic blood-flow meter we can study the effect of various stimuli on blood flow. Here we show examples of normal flow (figure 14a), interrupted flow, caused by compression of the carotid arteries (figure 14b), aortic insufficiency caused by deliberate injury to the aortic valve (figure 14c) and the blood flow in the three main branches of the coronary vascular tree (figure 14d). These four examples are all from dogs. Figure 14e is an example of the effect of an olfactory stimulus (on a cat). Figure 14f shows a psychological stimulus; the dog's heart rate increases when he first sees a cat, and his blood-flow rate falls, until he realizes that the cat is as scared as he is. Then his blood flow increases to above normal level as he gains courage.



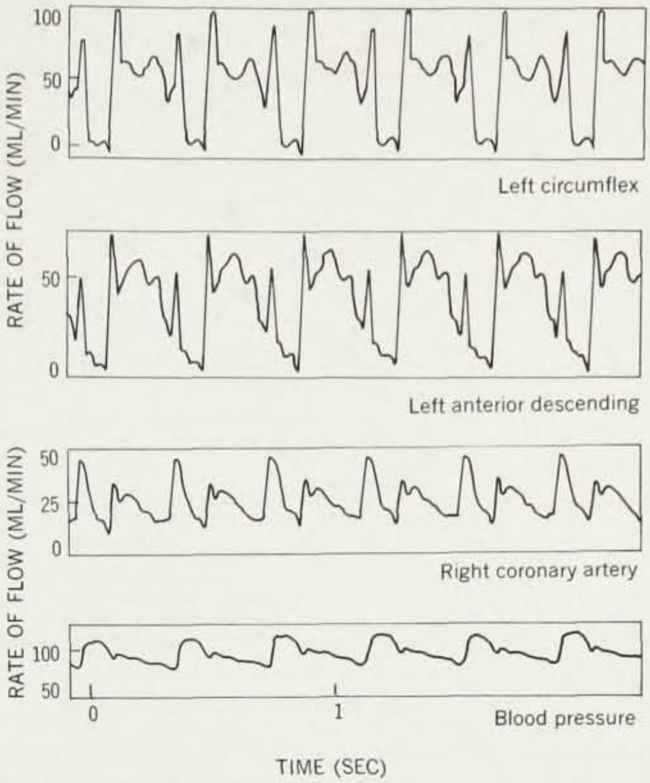
RECORD OF BLOOD FLOW in ascending aorta of conscious dog obtained with coreless blood flow meter. From A. Kolin, Science *130* 1088, (1959). —FIG. 14a



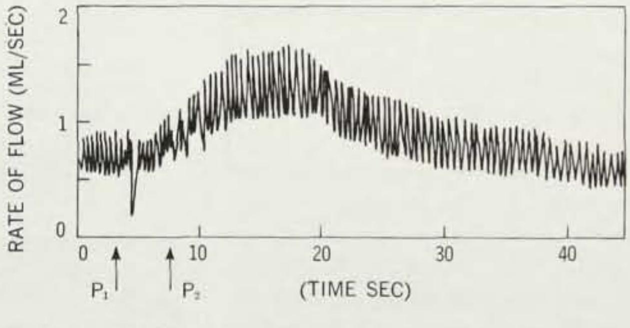
PHYSIOLOGICAL EFFECT of compression and release of both carotid arteries on dog's left carotid flow as recorded with external magnetic-field method. From A. Kolin, Rev. Sci. Instr. *23* 235 (1962). —FIG. 14b



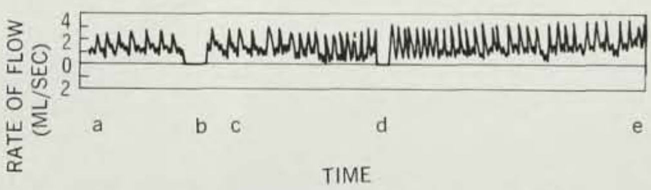
AORTIC VALVE INSUFFICIENCY, as recorded in a dog by external field method, produced by damaging aortic valve. Flow in the descending aorta is retrograde during diastole. Base line corresponding to zero flow is obtained by compression of the artery. Such heart-valve defects sometimes occur at birth. They impose a great strain upon the heart. Surgeons can now use an EMFM to record initial blood-flow pattern and then operate on the valve to eliminate back flow as verified by final EMFM record. From A. Kolin, Rev. Sci. Instr. *23* 235 (1952). —FIG. 14c



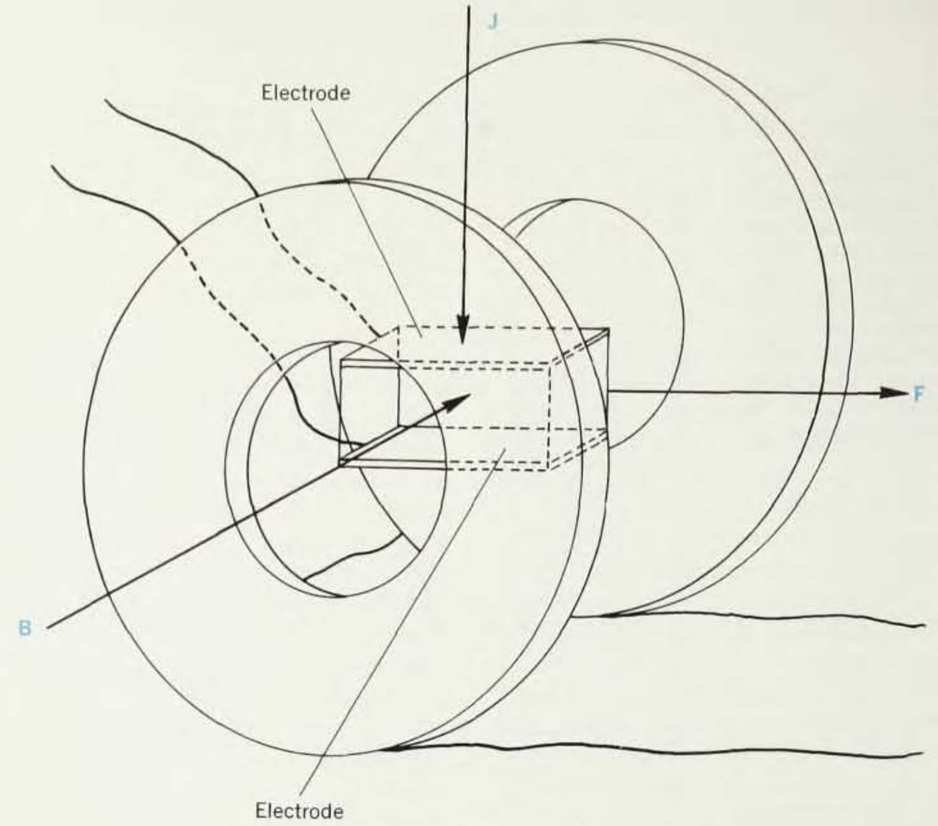
CORONARY FLOW-VERSUS-TIME patterns in the left circumflex, the left anterior descending and the right coronary arteries of a dog. From A. Kolin, G. Ross, P. Gaal, and S. Austin, Nature *203* 148 (1964). —FIG. 14d



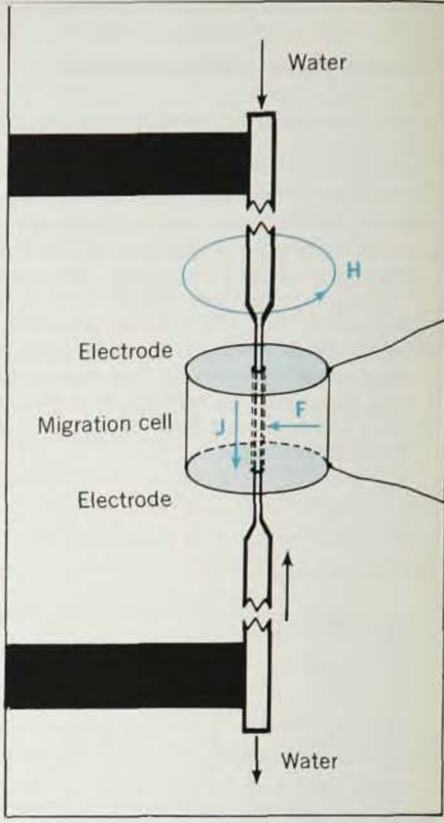
SENSORY STIMULUS. Effect of exposure of cat to ammonia odor on blood flow in carotid artery recorded between P_1 and P_2. From A. Kolin, Science *130* 1008 (1959). —FIG. 14e



PSYCHOLOGICAL STIMULUS effects on blood flow in carotid artery of a dog. Normal record is a–b. At c a cat is brought into room. At d the dog is restrained from pursuing cat. At b and d the magnet is switched off to record the zero-flow base line. —FIG. 14f



ELECTROMAGNETOKINETIC EFFECT. B is the magnetic field vector, J is the current density and F is the force exerted on suspended particles. The coils are disposed to form a Helmholtz-coil pair. From A. Kolin, Proc. of First Natl. Biophys. Conf., Yale Univ. Press, p. 133, (1959). —FIG. 15



NONROTATIONAL CENTRIFUGE. A wire carrying a current generates the magnetic field H; J is the current-density vector. A migration cell with electrodes surrounds the wire. —FIG. 16

weight of unpaired electrons. Evidence also suggests that free radicals are implicated in aging, carcinogenesis and radiation damage. ESR proved to be a particularly powerful tool in the study of photosynthesis.

This survey is by no means complete. A recently compiled bibliography[35] on biological applications of magnetic fields contains 393 entries. The present selection is an arbitrary choice of topics that were deemed to be of physical interest.

* * *

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