17 February 1961, Volume 133, Number 3451

SCIENCE

INSTRUMENTS AND TECHNIQUES

Electromagnetic Radiation as a Tool in the Life Sciences

Radio waves, long used for communications, are becoming an important tool in biophysics research.

Tom Jaski and Charles Süsskind

Although certain types of radiation, notably ultraviolet and x-radiation, have long been used in altering the life cycle, the physical and chemical structure, and the reproductive processes of biological organisms, much less attention has been paid by researchers in the life sciences to electromagnetic radiation at lower frequencies. Yet it now appears likely that the use of this type of radiation may provide new approaches to hitherto unsolved problems and may eventually contribute toward the understanding of life processes.

Considerable attention has been given at recent scientific conferences to the biological effects of microwave radiation, as used in communications and in radar. Several papers on this topic were presented at the 12th Annual Conference on Electrical Techniques in Medicine and Biology, in Philadelphia, the 3rd International Conference on Medical Electronics, in London, and the 4th Tri-Service Conference on the Biological Effects of Microwave Radiation, in New York, all held within the past year.

The reason for the increased interest in these radiations is the much expanded application of microwaves in industry and for military purposes. The military services have been interested for some time in possible harmful effects of microwaves (*1–4*), partly because of a genuine concern for the safety of personnel and partly as the result of unfavorable publicity given to the matter by some of the less conscientious mass-communication media. An academic rather than an industrial and military approach to the subject has resulted in a great deal of interest, on the part of university researchers assigned hazard investigations, in the possibilities of the radiations as a scientific tool.

Radio waves have been used for many years in medicine as a therapeutic technique called "diathermy." However, diathermy applications and experiments have proceeded primarily on an empirical basis. A more quantitative approach was required for the use of radio waves in physics and chemistry, where they have been utilized for radio spectroscopy in its various forms and in other ways. More recently, direct radiation under precise quantitative control has been applied to the determination of important biological parameters.

Although there is no fundamental difference in the radiation from various parts of the electromagnetic spectrum, including visible light and x-rays, the various radiations affect living organisms quite differently. The action of x-rays, for example, is primarily ionization, a process that requires energy of the order of several electron volts. The energy E associated with electromagnetic radiation is proportional to the frequency ν, and its value ($E = k\nu$, where k is a constant) is sufficiently high to produce ionization at the frequency of x-rays and in the ultraviolet and visible portion of the spectrum. At the much lower radio frequencies and in the microwave range the energy is much too low to produce ionization. There, the principal effect is one of heating, due to the resistance to the electromagnetic wave passing through a "lossy" dielectric; we speak of "nonionizing" radiation. However, there is reason to believe that nonionizing effects other than heating are involved. An increasing amount of current research is being devoted to these athermal effects of radio waves.

Medical Therapy and Research

The biophysical basis for experiments with alternating currents on human beings was formulated by Nernst (*5*). He showed that the conduction of high-frequency electric currents is made possible by the motion of ions in an alternating-current field. Next, von Zeyneck in 1908 grasped the possibilities inherent in heating body tissues by the conduction of a high-frequency current through them, a therapeutic method for which he coined the name *diathermy* (*5*). His technique was to apply electrodes directly to the skin of the body—a rather ineffective method, since the various tissues have markedly different ohmic resistance, so that the heating was not very uniform. As the frequencies available increased with technological advances, it became apparent that generation of heat in tissues depends on frequency.

Beginning in 1928, Schliephake (*5*) employed higher frequencies (approxi-

The authors are engaged in a project sponsored by the U.S. Air Force at the Electronics Research Laboratory, University of California, Berkeley. Dr. Süsskind, associate professor of electrical engineering, is director of the project.

mately 30 megacycles) for therapeutic experiments. At these higher frequencies, the predominant effect was one of induction rather than conduction, and a much more uniform depth penetration could be achieved. It became possible to heat the deeper layers without overheating the skin and the subcutaneous tissues. Broadly speaking, penetration increases with frequency; future diathermy equipment may operate in the same high range as certain radar transmitters, at frequencies of several thousand megacycles.

The history of the use of radio waves reveals many attempts to employ them experimentally for the generation and investigation of poorly understood phenomena. The methods employed by some of these early researchers were, to say the least, of somewhat doubtful validity; so were some of the conclusions they drew from their results. Yet these investigators deserve mention because of renewed interest in the type of experimentation which they undertook, some of which is being repeated with modern methods, under carefully controlled conditions.

For example, the Italian physician Cazzamalli attempted in the 1920's to elicit heterodyned radiation from human brains by exposing them in vivo to the field of a relatively powerful radio transmitter (*6*). He claimed to have observed and recorded a variation in such radiation when his hapless subjects were emotionally aroused or engaged in creative pursuits. Among his results was the finding that hallucinations could be induced in highly suggestible individuals by radiation.

Even less acceptable are the results reported by the French physician Lakhowski (*7*), who believed that multifrequency radiation introduced in the vicinity of his subjects was responsible for their recovery from malignant growths, and who concluded that this type of radiation contained the key to the secret of life. This thought forms the central theme of the book reporting his observations; the volume is a curious mixture of apparently incontrovertible testimonies of successful cures and near-mystical "theoretical" considerations.

Considerably more plausible are the results produced with microwave radiation by a Dutch physician, van Everdingen, a tireless and careful as well as persistent and imaginative researcher. He reported (*8*) the reduction of certain types of growths by carefully planned procedures that included injecting irradiated substances. The results included control of the appearance of growths in healthy animals exposed to time-tested coal-tar stimulants and the induction of growths by the reversal of certain steps in his procedure. Van Everdingen observed that microwaves affected the heart action of the chicken embryos and that this effect did not occur until glycogen first appeared in the affected hearts. He concluded that some action on the glycogen was responsible for the result. Further experimentation revealed that the microwaves produced a measurable change in the plane of optical polarization in the glycogen if the concentration and viscosity of the substance were precisely controlled. The amount by which the polarization plane was rotated proved to be an accurate indicator of dosage at a given frequency. Van Everdingen concluded that it was this kind of "unnatural" mechanism that controlled tumor growth. Extracts from the livers of healthy mice, when irradiated, would affect the resistance to tumor growth of mice injected with the altered substance.

We have been unable to determine any specific results of extensions of van Everdingen's work to experiments with human patients. But only last August Bach reported (*4*) that the U.S. Army Medical Research Laboratory at Fort Knox, Ky., was engaged in extending some of these early experiments.

Numerous other experiments have been performed to study the effect (other than heating) of radio waves on biological specimens. As an example, Nyrop (*9*) reported specific effects on bacteria, viruses, and tissue cultures resulting from experiments in which heating was carefully excluded by applying the radiation in short pulses, with intervals long enough (and increasing as the experiment progressed) to prevent the temperature from increasing. Although experiments of this sort have elicited considerable skepticism in the past (*10*), more recent results, described below, suggest that a physical basis may indeed exist for some of the earlier observations.

Another aspect that has attracted attention in scientific circles both in this country and in the Soviet Union is the possible neurological effect of electromagnetic radiation. The much-publicized rhesus-monkey experiments performed at the U.S. National Institute for Neurological Diseases (*3*) fall in this category, as do the experiments on isolated nerves performed at Tulane University and reported by McAffee (*3*). Owing to the relatively high power levels employed in McAffee's experiments, it is very likely that most of the effects observed are related to the stimulation of nerve fibers by heating.

In the Soviet Union, interest in this aspect of electromagnetic radiation has been very high; one Soviet review article (*11*) cites many results that cannot be dismissed as thermal effects. At the London conference last summer the Soviet scientist Gordon reported (*12*) that after irradiation with microwaves at a low level, the delay between stimulus and conditioned reflex in dogs increased, and the employment of a larger stimulus became necessary. Moreover, histological examinations of brain tissues revealed physiological and chemical changes such as globular concentrations of acetylcholine along nerve fibers.

Microwave and Radio-frequency Spectroscopy

Radio waves have been extensively used in chemistry in spectroscopy. Three categories of radio spectroscopy may be distinguished: transmission spectroscopy and two forms of magnetic resonance—nuclear magnetic resonance and electron paramagnetic resonance. In transmission spectroscopy, the techniques of light spectroscopy (that is, the classification of the content of a sample through the identification of specific absorption bands) are extended to a range of lower frequencies, where measurements of molecular rotational energy levels can be made with extremely high resolutions and sensitivities. In nuclear magnetic resonance the precession of the spinning nuclei of atoms of the materials under investigation is affected by the simultaneous application of a radio-frequency electromagnetic and a direct-current magnetic field. (Either the frequency of the electromagnetic field or the strength of the magnetic field must be varied.) At specific frequencies and field strengths characteristic of the elements in the substance, energy is absorbed, because of the realignment of the nuclear spins. Upon relaxation of the fields, this energy is released and detected by a radio receiver. In electron paramagnetic resonance, electrons rather than nuclei are affected; because the precession rate is much faster, microwave frequencies must be employed in electron paramagnetic resonance, whereas much lower frequencies are used for nuclear magnetic resonance.

The field of spectroscopy below infrared frequencies has given rise to an entire new branch of chemistry and has been the subject of several exhaustive treatments (*13*). Of particular importance is the recently developed electron-paramagnetic-resonance technique for observing the formation of free radicals, the formerly theoretical intermediate products of chemical reactions. Although all of the techniques decribed above utilize electromagnetic radiation as a tool in the study of chemical substances, many of them of biological interest, it is not the intention of the investigators to change the substances under study through the measurement procedure.

Physical Chemistry

In addition to the use of radio waves for the passive study of compounds, attempts have been made to employ such waves for the purpose of changing the structural arrangement of substances such as proteins and enzyme systems. Beginning in the 1930's, de Pereira Forjaz (*14*) investigated the rate of reaction of chemical systems under irradiation by ultrashort waves and found a substantial acceleration. More recently, Gilkerson (*15*) has utilized this phenomenon for the measurement of the rates of extremely fast ionic reactions in solutions.

Lepeschkin (*16*) investigated differences in changes in the molecular weights of constituents of human blood serum when it was heated and when it was irradiated by microwaves. He found that he could bring about more stable alterations in the substances by microwave radiation than he could by heating. Fleming (*17*) observed a difference in bacterial growth according to whether the sample was irradiated with electromagnetic irradiation or with heat, and discovered a frequency and power dependence.

Other phenomena that have been studied by means of electromagnetic radiation have to do with the detailed nature of aqueous solutions. The electrical charges associated with water molecules are disordered. Under the action of an electromagnetic field, these randomly oriented charges tend to line up (and the molecules with them). As the frequency of the alternating electromagnetic field is increased, the charge reorientations have difficulty in following the rapid variations. As in radio spectroscopy, it is this frequency dependence that can be utilized to yield information about the structure of aqueous solutions of biologically important molecules. The details of the techniques employed must be modified to take into account the fact that at microwave frequencies water absorbs electromagnetic energy rather strongly and resonance lines of individual molecules cannot be readily resolved. However, these structural details can be inferred from measurements of bulk properties such as the dielectric constant and conductivity, for which measurements microwave techniques are very well suited (*10*, *18*).

As an example, Buchanan *et al.* (*19*) have shown that microwave measurements can be used to estimate the

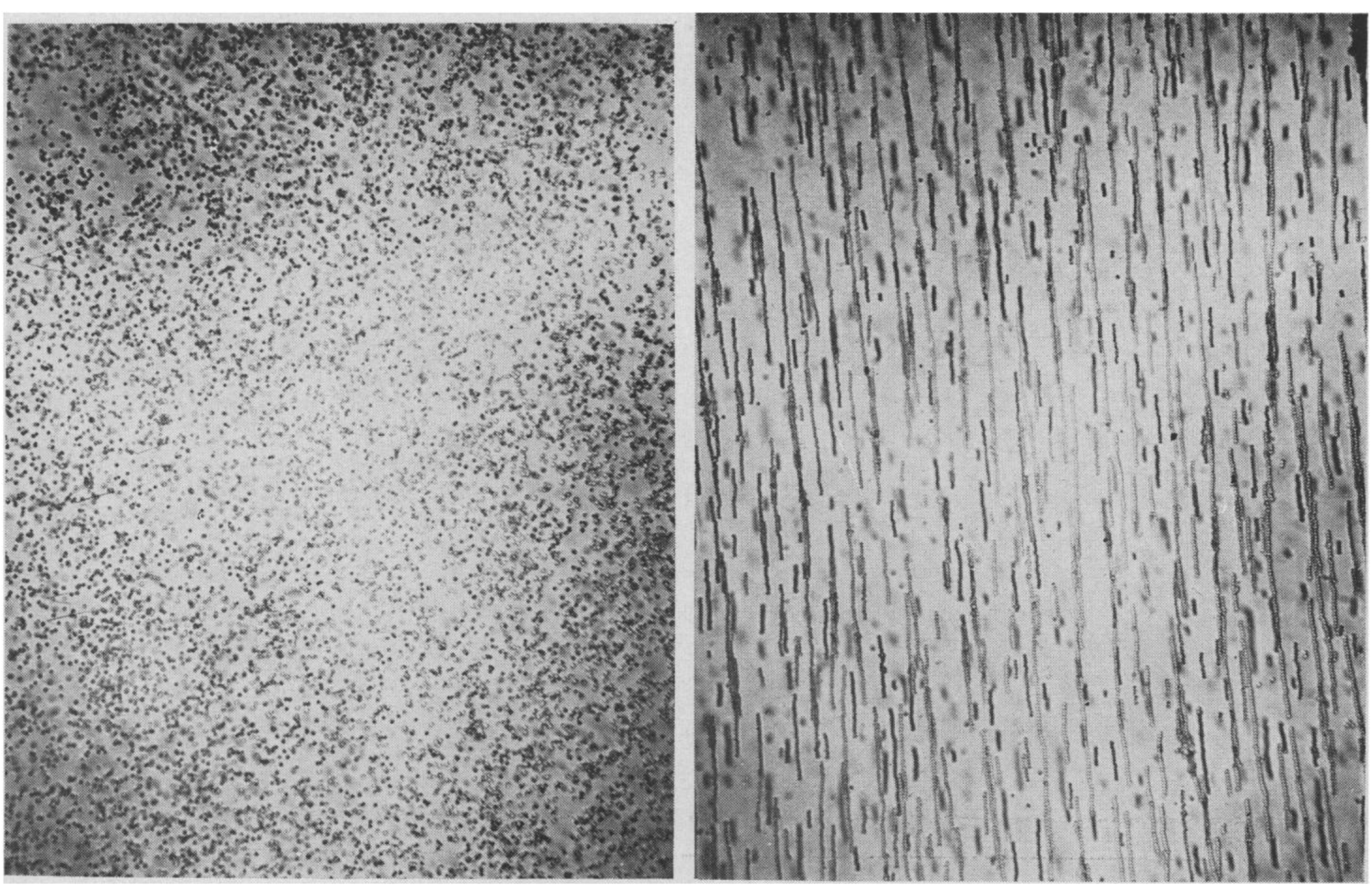

Fig. 1. Polystyrene spherules 1.171 microns in diameter suspended in water (left) at random, and (right) forming "pearl chains" under the action of an electromagnetic field (26 megacycles). [Courtesy Dr. J. H. Heller, New England Institute for Medical Research]

maximum amount of chemically bound water in proteins. The precise amount of bound water is of vital importance in determination of the weight and size of a protein molecule, and these, in turn, are among the fundamental data required in many biological investigations.

Dielectric and conductivity measurements have also been used by Schwan (*18*) to yield information about the nature of a cell membrane, its composition, and the composition of the cell interior. This investigation represents one of the most spectacular instances of the use of high-frequency electromagnetic radiation for obtaining new results in biology.

Saito and Schwan have recently reported (*4*) another instance of the use of dielectric theory, to explain the phenomenon of "pearl-chain" formation observed by previous investigators (*20*). Like molecules, microscopic particles in suspension tend to align (Fig. 1) under the influence of an electromagnetic field; the ordering influence depends on the frequency and strength of the electromagnetic field. A similar phenomenon is observed with ellipsoidal motile microorganisms (Fig. 2), whose motion under the action of an electromagnetic field tends to be either in the direction of the lines of force or at right angles to them, depending on the frequency (*21*). Saito and Schwan's theory may account for these observations on the basis of an extension of dielectric theory to suspensions of microscopic particles.

Applicability to Research Problem

A difficult problem that faces an experimenter unfamiliar with electrical instrumentation techniques, and one in which precedent is of least value, is that of deciding whether irradiation with some form of electromagnetic energy is at all applicable to the research at hand. Where the interest centers around a method of uniformly heating an object or biological entity very rapidly, radiation in the microwave region is probably the most effective method. Where surface heating without the use of flame or other energy-transfer media is desirable, ultrahigh-frequency radio waves are more likely to be satisfactory. But where nonthermal phenomena may have to be evoked, a pilot study should definitely precede a full-scale investigation, to indicate whether or not the approach can be expected to be a fruitful one.

Radiation "Hazard" Problem and Dosimetry

With the general acceptance of a safe level for whole-body microwave irradiation, interest in the "hazard" aspect of electromagnetic radiation has somewhat decreased. For continuous whole-body irradiation, this level has been set (*10*, *22*) at 0.010 watt per square centimeter—a power density that can be quite reliably detected by commercially available radio equipment if the frequency is known beforehand, and yet one that is several times smaller than any value known to yield any physiological indication. Several relatively minor aspects of the hazard problem, still under investigation, may well result in revision of the safe-dosage level by a factor of 2 under varying conditions related to frequency, duration, orientation with respect to the electromagnetic field, and allied considerations; but the interest of the principal investigators has largely reverted to possible uses in pure research.

The history of our own project at the University of California (*23*) has been fairly typical of work in similar laboratories throughout the country. Starting with an effort to establish a significant irradiation level for a study of longev-

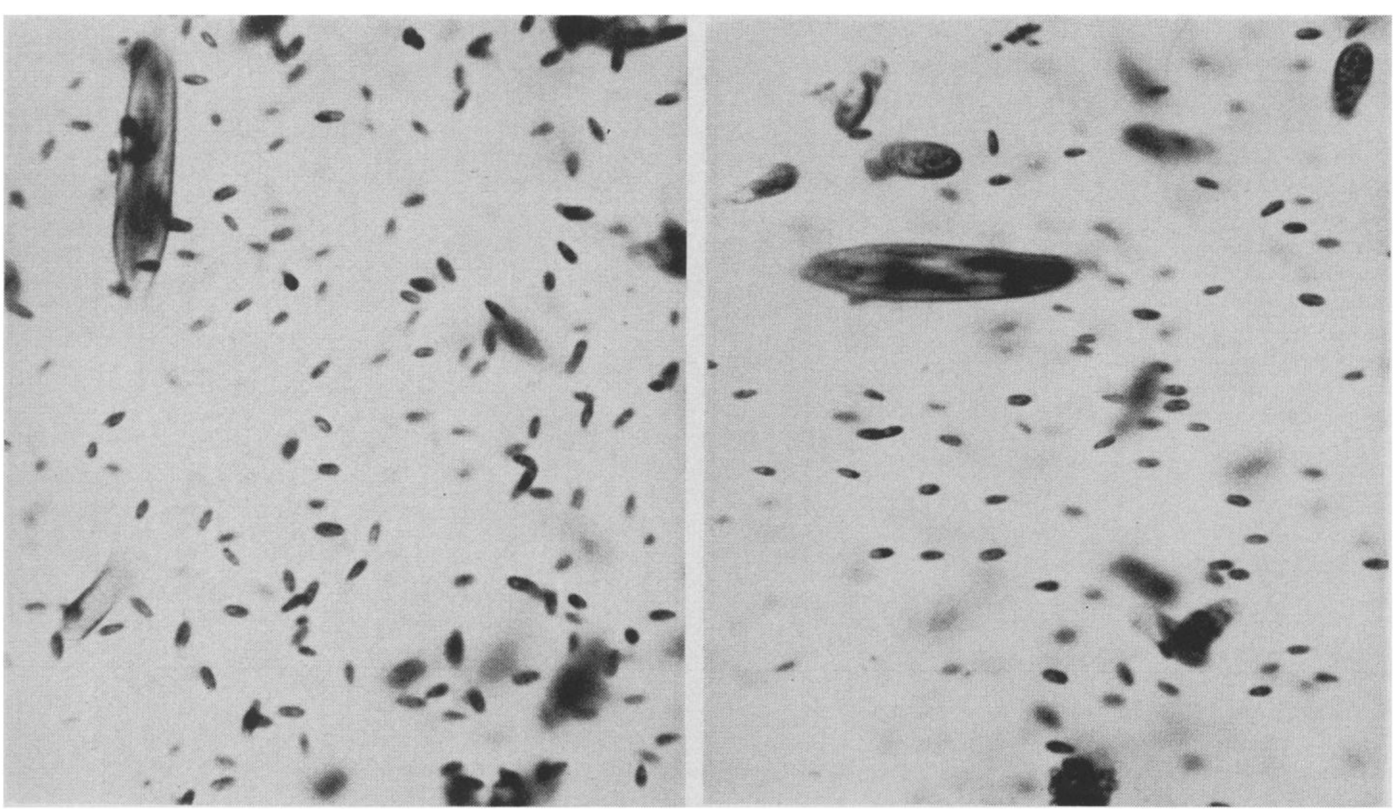

Fig. 2. Ciliates (left) moving at random, and (right) under the influence of an electromagnetic field (100 10-microsecond pulses per second, at 6 megacycles), moving parallel to the lines of force. Above a certain frequency, the direction of motion changes by 90°. The larger organisms are paramecia. [Courtesy Dr. J. H. Heller, New England Institute for Medical Research]

ity in a large colony of mice exposed to a 3-centimeter U.S. Air Force radar, we accumulated some data in the process of precise calibration that may prove to be of interest to workers in a number of fields, ranging from antenna design to zoology. The laboratory (among the first to utilize the radiation-as-tool approach) next demonstrated how microwaves could be used, for instance, for the study of thermal balance in mammals (*24*). The daily irradiations of the experimental colony of mice below lethal levels continue. The investigators have also had time to study such aspects of the problem as the effect of "fractional" on-off irradiation, simulating exposure to a rotating radar antenna. However, an increasing proportion of their effort is being devoted to basic investigations.

As a result of such investigations at a number of universities, the safety level remains at 0.010 watt per square centimeter. An obvious sort of hazard exists in the case of a person entering a field in which the power density is above the safe level without being aware of it. In areas where electromagnetic radiation is likely to be present, all personnel should be equipped with some sort of indicator comparable to the survey meters used by workers subject to danger from ionizing irradiation. Several manufacturers have developed radiation meters for use at microwave frequencies; these meters are becoming available commercially.

However, the problem of dosimetry is not a simple one. Radiation at a given frequency can be readily measured, but the equipment usable at one frequency is rarely suitable for another frequency. Power density alone is not a sufficient indicator; the effect of the energy absorbed by a subject may vary a great deal, depending on his absorption and reflection characteristics and on ambient conditions (*25*). Moreover, power-density measurements do not really show the "dosage" received, since they are in no way indicative of the actual physiological effects. "Dosimeters" based on absorption have been proposed; one version, described by Richardson (*2, 3*), would employ a quantity of a gelatin-like substance simulating the properties of human tissue and a temperature-sensing device to produce an electrical signal, capable of being amplified, that is proportional to the total heating. Such a device would not be very sensitive to frequency and could be employed in situations where instruments of several frequencies might be radiating simultaneously, as on warships. But it has been found difficult to make the device wholly independent of its environment.

It is probable that ordinary intensity meters, one for each possible frequency of radiation in a given situation, will continue to satisfy most safety requirements. Such meters can be arranged to serve as warning devices, producing an audible signal whenever the radiation exceeds the safe level. But no matter which of these schemes is employed, there is little doubt that nonionizing radiation, handled with quite minimal safety precautions, presents no greater hazard than ordinary electric current or x-radiation from unshielded high-voltage electronic devices such as the very klystrons or other tubes that produce the supposedly hazardous high-power electromagnetic radiation. In fact, what we have tried to show is that, instead of considering electromagnetic radiation purely a hazard, from the biological viewpoint, research workers have become increasingly conscious of the growing importance of such radiation as a tool in the life sciences (*26*).

References and Notes

1. Proceedings, Tri-Service Conference on Biological Hazards of Microwave Radiation, Rome Air Development Center, N.Y. (1957).
2. Proceedings, 2nd Tri-Service Conference on Biological Effects of Microwave Energy, Rome Air Development Center, N.Y. (1958).
3. Proceedings, 3rd Annual Tri-Service Conference on Biological Effects of Microwave Radiating Equipments, Berkeley, Calif. (1959).
4. Proceedings, 4th Annual Tri-Service Conference on the Biological Effects of Microwave Radiation, New York (1960).
5. H. Alm, *Einführung in die Mikrowellen-Therapie* (Fürst, Berlin-Schönberg, 1958).
6. F. Cazzamalli, *Neurologica* **6**, 193 (1925); *Quaderni Psichiat.* **16**, 81 (1929); *Neurologica* **16**, 47 (1935).
7. G. Lakhowski, *The Secret of Life* (Heinemann, London, 1939).
8. W. A. G. van Everdingen, *Ned. Tijdschr. Geneesk.* **82**, 1873 (1938); **84**, 4370 (1940); **85**, 3094 (1941); **87**, 406 (1943).
9. J. E. Nyrop, *Nature* **157**, 51 (1946).
10. H. P. Schwan and G. M. Piersol, *Am. J. Phys. Med.* **33**, 371 (1954); **34**, 425 (1955).
11. N. N. Livshits, *Biofizika* **3**, 426 (1958).
12. Z. W. Gordon, paper presented at the 3rd International Conference on Medical Electronics, London (1960).
13. W. Gordy, W. V. Smith, R. F. Trambarulo, *Microwave Spectroscopy* (Wiley, New York, 1953); D. J. E. Ingram, *Spectroscopy at Radio and Microwave Frequencies* (Butterworth, London, 1955); G. H. Townes and A. L. Schawlow, *Microwave Spectroscopy* (McGraw-Hill, New York, 1955).
14. A. de Pereira Forjaz, *Biochem. Z.* **280**, 53 (1936).

W. R. Gilkerson, *J. Chem. Phys.* **27**, 914 (1957).

16. W. W. Lepeschkin, *Biochem. Z.* **318**, 15 (1945).
17. H. Fleming, *Elec. Eng.* **63**, 18 (1944).
18. H. P. Schwan, in *Advances in Biological and Medical Physics*, J. H. Lawrence and C. A. Tobias, Eds. (Academic Press, New York, 1957), vol. 6, p. 147.
19. T. Buchanan, G. H. Haggis, J. B. Hasted, B. G. Robinson, *Proc. Roy. Soc. London* **213A**, 379 (1952).

E. Muth, *Kolloid-Z.* **41**, 97 (1927); P. Liebesny, *Arch. Phys. Therapy* **19**, 736 (1938).

A. A. Teixeria-Pinto, L. L. Nejeleski, Jr., J. L. Cutler, J. H. Heller, *Exptl. Cell Research* **20**, 548 (1960).

22. "Radio Frequency Radiation Hazards," *U.S. Air Force T.O. 31-1-80* (1958).
23. This project is sponsored by the U.S. Air Force under contract No. AF41(657)-114.
24. B. S. Jacobson, S. B. Prausnitz, C. Süsskind, *IRE Trans. on Med. Electronics* **ME-6**, 66 (1959).
25. H. P. Schwan and K. Li, *Proc. I.R.E. (Inst. Radio Engrs.)* **44**, 1572 (1956); **47**, 1841 (1959).
26. We gratefully acknowledge the aid of P. O. Vogelhut in the preparation of this article and the helpful critical comments of Professor H. C. Mel of the University of California's Donner Laboratory of Biophysics and Medical Physics.