netic properties becomes clearly visible in magnetite by freezing-in an ordered sequence of Fe^{++} and F^{3+} below −155°C. The conductivity drops by several orders of magnitude, and if the magnetic spins are ordered by application of an external field during cooling through the transition, a magnetic axis is frozen-in, altering the hysteresis loop completely (*5, 23*) (Fig. 25). Conversely, since in the ferrites only a fraction of the interstitial sites are occupied, high temperature extends the spread of cations to less favorable positions. In consequence, by quenching-in such disorder, the magnetic properties can be greatly affected (Fig. 26).

These examples must suffice. They show that the connection between structure and properties can be of obvious directness and, in other situations, buried in prehistory effects which challenge the tenacity of a psychoanalyst for their elucidation. The principal reasons for complications are the same as in living systems: a macroscopic phenomenon may be produced by a variety of molecular causes; furthermore, the phenomenon may be related not to the ideal structure of a material but to the faults built into such a structure.

Science in previous times believed that "nature loves simplicity" and that man in his incredible complexity presents a "mighty effort contrary to nature." Dictatorships enslaving man could thus be justified as a return to nature's order. Today, this excuse of tyrants has vanished. Every day we learn with increasing insight that nature is incredibly complex and that man is one incident in its organization. At the outset we raised the question: What shall we most reasonably do with our natural resources? Molecular designing allows us to realize Jules Verne's fantasies. The answer is therefore not any longer what we can do, but what we want to do. Molecular science and molecular engineering must operate as allies of social science and political statesmanship in imaginative planning for the most beneficial transformation of the world's resources.

References and Notes

1. H. A. Meyerhoff, "Changing concepts of mineral raw materials in the national economy," paper presented at the 128th meeting of the AAAS, Denver, 1961.
2. H. Brown, "Science and government," paper presented at the 128th meeting of the AAAS, Denver, 1961.
3. The work reported in this article was made possible through support extended to the Massachusetts Institute of Technology jointly by the Navy Department (Office of Naval Research), the Army Signal Corps, and the Air Force, under ONR contract Nonr-1841 (10), NR-018-801; also by the Air Force under contract AF 33 (616)-8353. I am greatly indebted to my co-workers C. W. Nelson and J. J. Mara for help in preparing the figures.
4. See, for example, J. L. Greenstein, *Am. Scientist* **49**, 449 (1961).
5. See, for example, A. von Hippel, *Molecular Science and Molecular Engineering* (Massachusetts Institute of Technology Press and Wiley, New York, 1959).
6. See L. Pauling, *The Nature of the Chemical Bond* (Cornell Univ. Press, ed. 3, Ithaca, 1960).
7. See, for example, J. C. Slater, in *Handbuch der Physik*, S. Flügge, Ed. (Springer, Berlin, 1956), p. 1.
8. A. von Hippel, *J. Chem. Phys.* **16**, 372 (1948).
9. A. S. Balchan and H. G. Drickamer, *ibid.* **34**, 1948 (1961).
10. See *Progress in Very High Pressure Research*, F. P. Bundy, W. R. Hibbard, Jr., H. M. Strong, Eds. (Wiley, New York, 1961).
11. *Sci. Am.* **205**, No. 9 (1961).
12. L. W. Tilton, *J. Res. Natl. Bur. Std.* **59**, 139 (1957).
13. J. Biscoe and B. E. Warren, *J. Am. Chem. Soc.* **21**, 287 (1938).
14. A. H. Silver and P. J. Bray, *J. Chem. Phys.* **29**, 984 (1958).
15. S. D. Stookey, in *Ceramic Fabrication Processes*, W. D. Kingery, Ed. (Massachusetts Institute of Technology Press and Wiley, New York, 1958), p. 189.
16. W. N. Lipscomb, in *Advances in Inorganic Chemistry and Radiochemistry*, H. J. Emeleus and A. G. Sharpe, Eds. (Academic Press, New York, 1959), vol. 1, p. 117; ———, A. R. Pitochelli, M. F. Hawthorne, *J. Am. Chem. Soc.* **81**, 5833 (1959); J. A. Wunderlich and W. N. Lipscomb, *ibid.* **82**, 4427 (1960); E. B. More, Jr., L. L. Lohr, Jr., W. N. Lipscomb, *J. Chem. Phys.* **35**, 1329 (1961).
17. A. L. Loeb, *Acta Cryst.* **11**, 469 (1958); I. L. Morris and A. L. Loeb, *ibid.* **13**, 434 (1960).
18. H. C. Gatos, *Surface Chemistry of Metals and Semiconductors* (Wiley, New York, 1960), p. 399.
19. W. J. Merz, *Helv. Phys. Acta* **31**, 625 (1958).
20. H. Welker and H. Weiss, in *Solid State Physics*, F. Seitz and D. Turnbull, Eds. (Academic Press, New York, 1956), vol. 3, p. 1.
21. See, for example, "Semiconductors," *American Chemical Society Monograph Series* (1959); *J. Appl. Phys.* **32**, No. 10 (1961).
22. See, for example, J. Smit and H. P. J. Wijn, *Ferrites* (Wiley, New York, 1959).
23. B. A. Calhoun, *Phys. Rev.* **94**, 1577 (1954).

Cell Disruption by Ultrasound

Streaming and other activity around sonically induced bubbles is a cause of damage to living cells.

D. E. Hughes and W. L. Nyborg

Ultrasonic methods for injuring or disrupting microorganisms or animal cells in vivo are now widely used (*1, 2*), but there is as yet no generally accepted theory to explain their disruptive effects (*3*). In connection with fragmentation of microorganisms in suspension, it is an accepted view that a major role is played by a sonically maintained activity known as "gaseous cavitation." This activity occurs in liquids containing dissolved gases and takes place especially readily in the presence of solid or quasi-solid surfaces containing tiny cracks or crevices. These surfaces may be presented by the vessel walls, or by tiny particles suspended in the liquid. Alternations of pressure in the sound field cause bubbles (containing gas or vapor, or both) to grow and take part in a complex and extremely energetic motion. Noltingk and Neppiras (*4*) have shown that under suitable conditions a tiny pocket of air of, say, a few microns in radius expands to a size thousands of times greater than the original volume, then violently collapses to a fraction of the original size, all within a time less than that for one cycle of the sound. In the collapse phase Noltingk and Neppiras predict instantaneous temperatures of the order of 10^4°K and pressures of the order of 10^6 atmospheres. The equations for such nonlinear behavior of the bubbles have recently been developed further by Flynn (*5*). Among the effects attributed to cavity collapse are local heating and electrical discharges, sonoluminescence, chemoluminescence, and free radical formation (*6, 7*).

Dr. Hughes, a member of the Medical Research Council, Unit for Cell Metabolism Research, department of biochemistry, Oxford, England, is at present visiting professor in the department of microbiology, Dartmouth Medical School, Hanover, N.H. Dr. Nyborg is professor of physics at the University of Vermont, Burlington.

In addition to such possible action, gas bubbles are capable of resonance vibration. The resonance radius a of an air bubble in water at atmospheric pressure is given rather accurately (at frequencies of less than 10^6 cycles per second) by the equation

$$a = 3.0/f,$$

where a is in millimeters and the frequency f is in kilocycles per second. Bubbles of less than resonance size attract each other; in a representative high-amplitude sound field such as is used in cell disintegration they collide at high speed and coalesce. By such coalescence and by a "rectified diffusion" process (*8*), bubbles grow to resonance size (*9*). Violent volume and surface vibrations then occur (*10*). As a consequence of this vibration, probably by way of a complex surface motion, the resonantly vibrating bubble surrounds itself with a cloud of very tiny bubbles, or microbubbles, of its own creation (*11*). Also a vigorous eddying occurs very near the bubbles (*9, 12*). This eddying or microstreaming is of itself sufficient to accelerate certain types of reactions (*13*), to induce surface modes of the exterior of cells (*14*), or to break cells (*15*).

Activities such as bubble growth, coalescence, surface excitation, microbubble production, and bubble-associated eddying occur, under favorable conditions, at moderate pressures; typical pressures are in the range of 0.01 to 1.0 atmosphere. The threshold for "collapse" type cavitation is usually somewhat greater than 1 atmosphere and may be much greater. This article describes part of a study undertaken to follow by high-speed cinematography the development of sonically induced bubble growth and cavitation and to correlate the various stages seen by this means with the effect on cells and other biological material.

It has been previously shown that when a needle (end diameters 10 to 15 μ) vibrating at 85 kilocycles per second at amplitudes from 0.05 to 5 microns, is placed next to a cell wall, it causes the contents of plant cells to become violently agitated (*16*). The motions agree with those predicted from an approximate theory of microeddying in that particles in the cell at first tend to move along the wall toward the region of contact with the needle. The pressures were too low for the formation of bubbles and for cavity collapse. In the work reported here a similar vibrating needle was tested with suspensions of microorganisms and other cells to see whether eddying in the liquid phase would develop sufficient shear to injure the cells.

Suspensions of fresh erythrocytes in 0.9-percent saline were treated in the apparatus shown in Fig. 1, which consists of a small plastic container (0.2-ml volume), mounted on the stage of a microscope in such a position that the vibrating needle can be dipped into it with the aid of a micromanipulator. Cell breakage was estimated by measuring the amount of hemoglobin released from the cells into the liquid after removal of cells by centrifugation at 2000*g* for 5 minutes. Under a variety of conditions it was found that erythrocytes were readily damaged; the number of cells damaged increased as amplitude of vibration increased (Fig. 1). Neither bubble formation nor cavitation was detected under these conditions, and it is clear that the cells were broken by shearing due to the eddying motions (indicated by arrows in Fig. 1) which are induced by the vibrating needle. These may be of the order of 10 meters per second near the tip of the needle. Suspensions of the protozoan *Tetrahymena pyriformis* were treated under the same conditions. Various degrees of injury, from temporary inhibition of motility to complete disruption, were found, depending mainly upon the amplitude. A film was taken at 3000 frames per second of *Tetrahymena* treated under relatively mild conditions which produced no visible disruption. It was seen that not only were the cells violently distorted as they entered the region of highest streaming speeds near the needle tip but that the contents of the cells tended to move in a circular manner relative to the cell motion. Both erythrocytes and *Tetrahymena* are relatively easily disrupted by low rates of shear, produced for instance by filtration through sintered glass filters. It was of interest, therefore, to test the disruptive effect of the vibrating needle on bacteria, which need much higher shear rates for disruption (*17*). Suspensions of *Escherichia coli* in water or in 0.9-percent sodium chloride [50 mg (dry weight) of cells per milliliter] were treated for various lengths of time and at different amplitudes. Injury was estimated by measuring the amount of protein re-

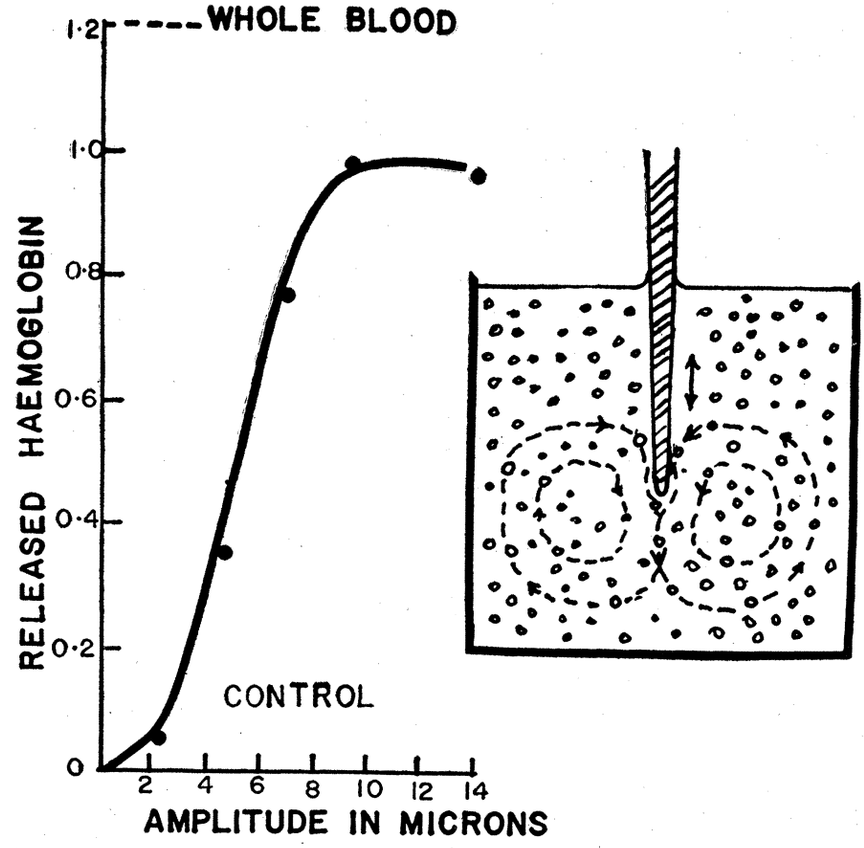

Fig. 1. (Left) The effect of amplitude of vibration on human erythrocytes as measured by hemolysis. Released hemoglobin is expressed as optical density at 490 millimicrons. (Right) Diagram of vibrating needle and cell. The double arrow indicates the direction of vibrations; the dashed line indicates the streaming motions.

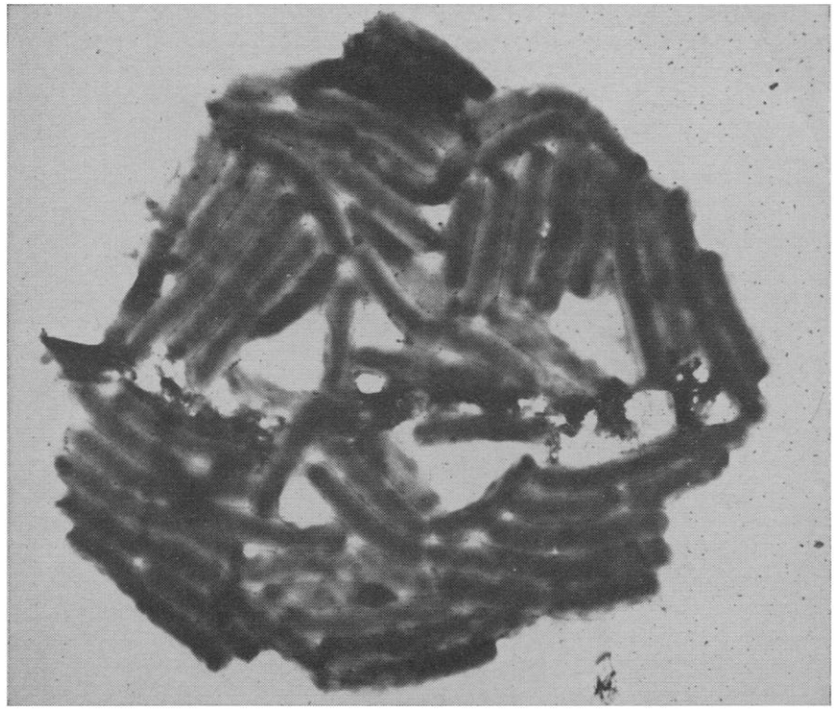

Fig. 2. Electron micrograph showing empty and partly empty hulls of *Escherichia coli*, which accumulated on the needle tip during treatment for 30 minutes.

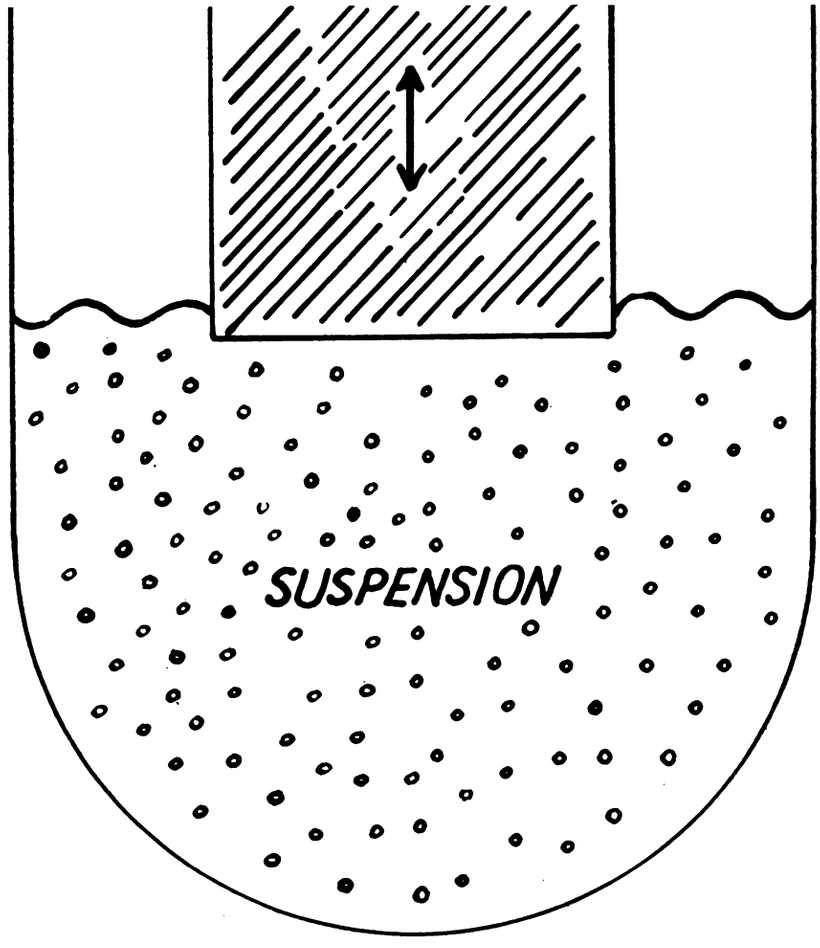

Fig. 3. Diagram showing the arrangement of a vibrating probe dipped into a cell suspension, such as is used in the M.S.E. 20-kilocycle-per-second cell disintegrators.

leased from the cells and remaining in the supernatant after centrifugation at 6000 to 8000*g* for 10 minutes (*18*). Significant amounts of protein were released from the cells upon treatment for relatively long periods (up to 1 hour), and the amount of protein depended approximately linearly on the amplitude of the needle vibration. Examination by light and electron microscopy showed many empty cells in the treated suspensions. In particular, clusters of empty cells were found in a small sheath of material which often accumulated on the needle just below the tip (Fig. 2).

Cavitation Streamers

It is evident from these preliminary results that streaming motions induced by the vibrating needle produce sufficient shear to injure red blood cells, *Tetrahymena*, and bacteria. In the latter case, however, the damage is small compared with the usual effects of ultrasound, despite the fact that treatment periods were very long (up to 1 hour) compared with the time (3 to 5 minutes) required for complete disruption of *Escherichia coli* under the usual conditions (*18*).

The question arises whether the mode of action of ultrasound in commercial disintegration devices is like that of the vibrating-needle arrangement. One's first impression is that the situations are quite unrelated. The M.S.E. disintegrator (*19*), in which vibrations of 10- to 20-micron amplitude are generated by a vibrating bar (19 to 20 kcy/sec), is in fairly common use for disintegrating bacteria (Fig. 3) (*18*, *20*). This instrument may be tuned by ear for maximum hissing noise or with the aid of signals from a strain gauge or accelerometer. The hissing noise is associated with so-called "cavitation streamers." This term is generally used to describe transient clouds of bubbles formed in a liquid by sound intensities above the cavitation threshold. These give the appearance of cloudy lines, often originating at the point of highest pressure amplitude, in this case on the vibrating bar or probe. Under suitable conditions, sound-induced chemoluminescence and sonoluminescence can be seen to originate in such streamers.

We have made high-speed motion pictures of the development of cavitation streamers on the surface of a bar probe. The streamers appear to be formed by the continued appearance,

growth, and coalescence of small bubbles attracted to each other and to larger ones which grow to approximately resonance size. An unexpected finding was that as these large bubbles reach a given size, near that for resonance, they suddenly vanish, leaving in their place a cloud of tiny bubbles (Fig. 4). It is possible that this kind of bubble collapse is a catastrophic form (occurring at sufficiently high amplitude) of the Willard phenomenon, referred to earlier, of microbubble production associated with surface vibrations. Its relationship to the simple, radially symmetrical collapse considered by Noltingk and Neppiras (*4*) is of course not known. The small bubbles formed at the time of collapse hasten to coalesce and join larger bubbles, thus maintaining a continuous coalescence-growth collapse cycle.

The formation of cavitation streamers is often associated with the formation of free radicals and sonoluminescence (*21*), which are thought to occur at the collapse of cavities (*7*). Cell breakage, however, is independent of free radical formation (*22*). One is led to suggest that cell breakage is not dependent on violent collapse but may well be the result of shearing action associated with bubble-induced eddying and related motions.

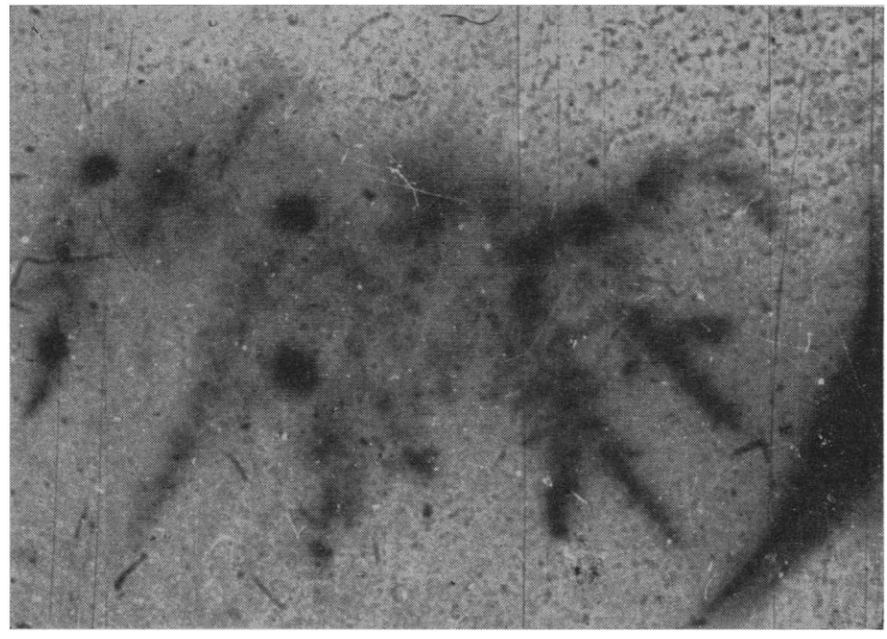

Fig. 4. A single frame from a film of cavitation streamers taken at about 6000 frames per second. The large bubbles appear as dark spots, and the streamers, consisting of masses of smaller bubbles, appear as the branching, less dense background. The edge of the vibrating bar is at lower right.

Low-Amplitude Bubble Activity

To test this suggestion, means were considered for obtaining bubble activity at relatively low amplitudes at which collapse would not occur. From the experiments with the vibrating needle it seemed likely that at least a slow rupture of cells could take place under these conditions. However, a valid test of the effectiveness of low-amplitude bubble activity requires a special arrangement. Commonly the amplitude must be relatively high in order to produce the bubbles themselves. A method described below proved satisfactory for causing bubbles of suitable size and numbers to appear at low amplitude. Using this, we were able to study the effects of vibrating bubbles over a range of amplitudes; at very low values the bubbles appear to act as simple (secondary) sound sources, while at high values streamer formation and collapse events are observed.

The face of a brass probe (2 cm in diameter) was drilled with a series of about 50 holes, each slightly smaller than a resonant bubble at 20 kilocycles per second, 200 microns in diameter and 200 microns deep (Fig. 5, bottom right). At low amplitudes (about 3 μ), bright and shining bubbles appeared to grow from the trapped air in the holes and extruded from the surface of the probe into the liquid but did not leave the holes. With increasing amplitude, the bubbles became slightly opaque and the surfaces appeared to be actively vibrating. Occasionally at this stage a bubble would leave the hole and move either toward another bubble or to the center of the probe. Slight hissing was generally heard at this stage. A further increase in amplitude caused most bubbles to leave the holes and caused small opaque bubbles to move about the surface of the probe. Marked hissing could then be heard. Increasing the amplitude still further caused marked movement in the surface of the liquid next to the probe. Small bubbles, both from the holes and from the surface, then moved toward the larger bubbles, and streamer activity (in terms of growth by coalescence and collapse, with small-bubble formation) was established. The threshold for streamer formation, 1.3 microns, is indicated by the vertical dashed line in the graphs shown in Fig. 5. By carefully adjusting the amplitude, each of the described stages of bubble activity could be held for periods up to 60 minutes at the lower amplitudes and for shorter periods (because of heating) at the higher amplitudes. A highly polished probe without holes drilled in the surface did not show streamer formation until it was driven at much greater amplitudes than the probe with holes in the surface. The efficiency of these probes for disrupting *Escherichia coli* is shown in Fig. 5 (bottom left), where it may be seen that cell breakage occurs at much lower amplitudes with the drilled probe than with the polished probe. With the former, significant breakage occurred at the first stage of visible bubble formation and increased almost linearly as the amplitude increased.

As previously described, no phenomenon resembling the collapse stage of cavitation was evident at low amplitudes. Cavitation streamers occurred only when the amplitude was great enough to result in coalescence and collapse—that is, about 1.3 microns (Fig. 5, top left and top right). Free radical formation, as indicated by the formation of iodine from potassium iodide in the presence of carbon tetrachloride, was measured (*18*). No free radical formation was detected at amplitudes below the streamer threshold during periods of up to 40 minutes, whereas rapid iodine release was detected in a significant amount after a few seconds of marked streamer formation. The onset of free radical formation occurred suddenly when the amplitude reached 1.3 microns (Fig. 5, middle right).

Breakdown of Large Polymers

The breakdown of a large polymer such as deoxyribonucleic acid (DNA) was of interest under these conditions, as this molecule may be broken by liquid shear (*23*) and also by free radical attack. Shearing in the absence of free radicals is thought to reduce the molecular size by producing breaks across the phosphate-sugar backbone, whereas free radical attack breaks the hydrogen bonding between bases and reduces hyperchromicity. It was found that rapid breakdown of DNA, as judged by reduction in viscosity, occurred at the lower amplitudes and, in the absence of free radicals, at amplitudes below the threshold for streamers; there was no reduction in hyperchromicity (Fig. 5, top right and middle right). Although the breakdown of DNA occurred more rapidly at the higher amplitudes, denaturation, as judged by an increase in optical density, also occurred (Fig. 5, top right). Thus the chemical effects of free radical formation were clearly separated from the chemical effects resulting from shear due to violent eddying of the liquid around bubbles.

The finding that cells such as bacteria may be disrupted by ultrasound in the absence of free radical formation is particularly important for the preparation of biologically active material such as enzymes from the cells. It has been shown, for instance, that in certain cases enzyme inactivation is entirely due to oxidation by free radicals (*18*) and may be partly prevented by the addition of a scavenger such as cysteine. In other instances, the passage of hydrogen may also reduce enzyme inactivation by reducing free radical formation (*3*). It has also been suggested that shearing alone may inactivate certain enzymes—for example, polymetaphosphatase (*18*). It would be of interest to see whether the lower shear produced by bubbles would also inactivate this enzyme.

Implications

The apparatus used in these studies cannot be regarded as having many practical applications since the volumes treated are relatively small and the times of treatment are long. However, the results suggest that modification of the M.S.E. disintegrators may improve their overall performance as well as give more control over the disintegrative effects. For instance, the effects of the small bubbles formed in the holes drilled in the face of the probe appear to be related to the effects of adding powders on disintegration by the higher powered M.S.E. instruments. It was found that the addition of diatomaceous earth (Embacel) could, under certain conditions, triple the rate of cell breakage (*18*). Embacel traps a considerable amount of air in the form of small bubbles of somewhat less than resonance size. Nonwettable solid particles of the same size, which were suggested as a source of nuclei, were without effect (*24*). Powdered glass and other materials that trap less air than Embacel were also less effective. At first it was thought that these results might be explained by assuming that the Embacel and other powders served as a source of nuclei, particularly as their effect was most marked under conditions where air exchange between liquid and air was difficult. However, an alternative possibility, suggested by the experiments described, is that the increase in the number of air bubbles throughout the liquid provides a greatly increased

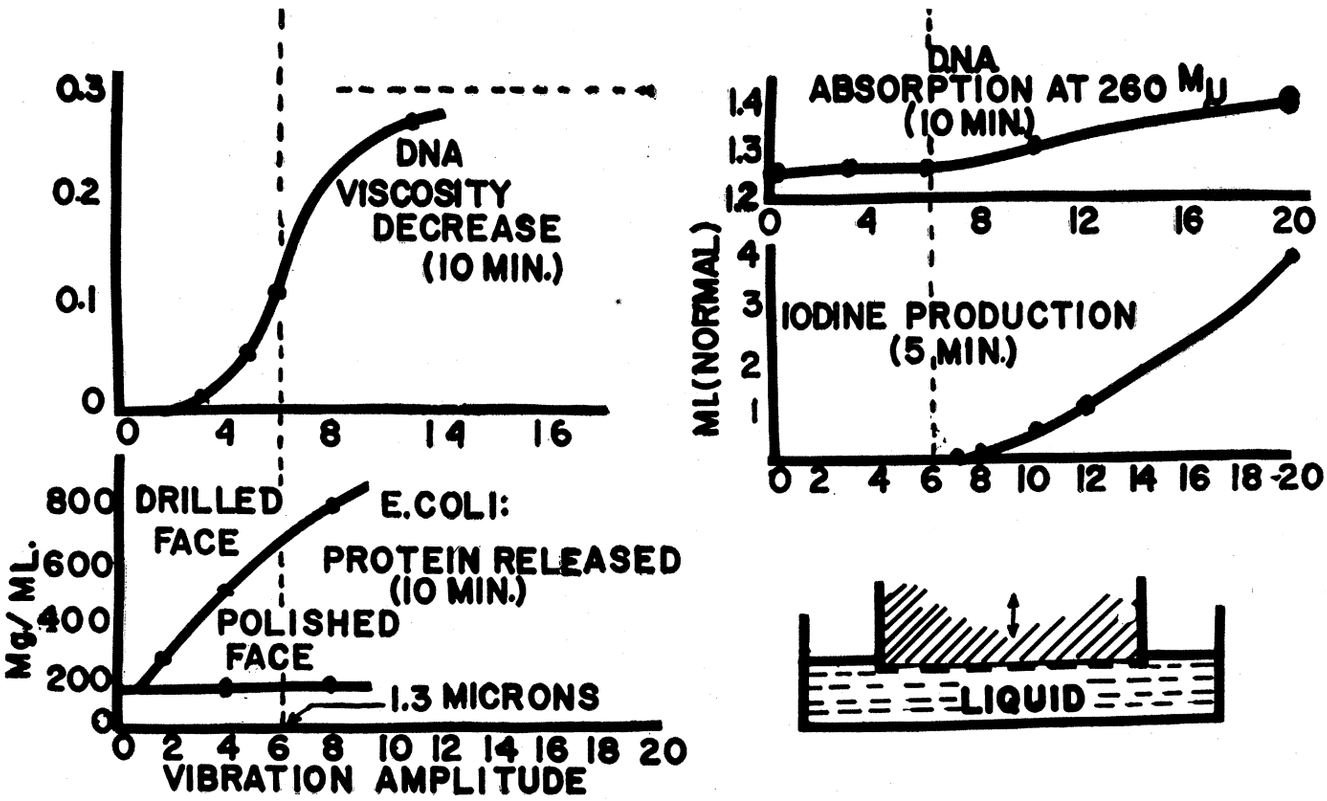

Fig. 5. (Bottom right) Drilled probe. (Bottom left) Disruption of *Escherichia coli* by drilled and polished probe. The other graphs show the effect of amplitude on DNA breakdown and on free radical formation. In each case the amplitude is expressed in microns. The decrease in viscosity of DNA (top left) is expressed as a fractional decrease. The absorption of DNA (top right) is expressed as the optical density with a 1-centimeter light path. The release of protein was estimated by means of the Folin reagent.

number of rapidly moving objects as well as of centers of eddying activity, each of which contributes toward the total disruptive effects. The results also suggest that cavitation streamers per se may be unnecessary for cell damage and that the improved rate of disruption generally observed when these are present is due mainly to the increased number and activity of bubbles, and not to the effects of the collapse of bubbles, as is generally assumed to be the case.

Ultrasonic methods of disrupting microorganisms are generally found to yield extracts containing finer fragments than are yielded by other methods—for example, use of a Hughes press or Milner press (*21*). However, recent studies on time constants for the release of various cell components of yeast, together with electron microscope studies, suggest that the initial cell rupture may not differ radically in the various methods and that the fine fragments produced by ultrasonics result from further comminution after release from the broken cells. In addition, there is a suggestion that some components may be released by ultrasound even before major damage has been caused to the cell wall. This is illustrated in Fig. 6, which compares the rate of release of total protein with the rates of release of two enzymes—alcohol dehydrogenase, which is regarded as a "soluble" enzyme, and succinic dehydrogenase, which is bound to particles resembling mitrochondria (*25*). Such experiments strongly suggest that examination of the actual process of disruption may give valuable information about the structure of the cells and the location of enzymes within them (*26*).

With regard to the surgical use of ultrasound for producing brain lesions and destroying the labyrinth (*27*), there is still no agreement about the mechanism of the disruptive effects which result in the death of the cells, generally after some delay following application (*2*). There is evidence suggesting that the effects are not due to cavitation, but whether they are due to local heating is in some doubt (*2, 28*). In experimental animals no immediate gross histological changes are found, but the rapidity of loss of motor or sensory activity suggests that some immediate biochemical lesion is caused. It is likely that such immediate effects may be produced by causing motions of cell contents similar to those caused by the vibrating needle in plant cells or *Tetrahymena*. In animal cells such violent motions might destroy cell function by injuring membrane systems such as the endoplasmic reticulum or other parts of cells not normally detected by the histological method used. A mechanism by which such motions may be brought about by focused sound fields is suggested by the experiments described, which have shown that a vibrating bubble as well as a vibrating needle may act as a sound source in setting up eddying systems of its own within a larger sound field. Such point sources might occur particularly at cell junctions or at membrane interfaces within a nonuniform sound field, such as is used for labyrinth destruction. The presence of small bubbles cannot be altogether dismissed on the basis of histological examination because it is not likely that they would persist after the sound source has been turned off (*29*).

In addition to giving a description of the events leading to ultrasonically induced cavitation, the experiments briefly reported here are of interest in showing that cell rupture, normally associated with "gaseous cavitation," can occur in the absence of the collapse phenomenon and at surprisingly low power. This finding is important for its practical application in preparing extracts of microorganisms and other cells with ultrasonic vibrations, and important for the further insight it gives into the disruptive action of sound on free cell suspensions and on cells in tissue aggregates (*30*).

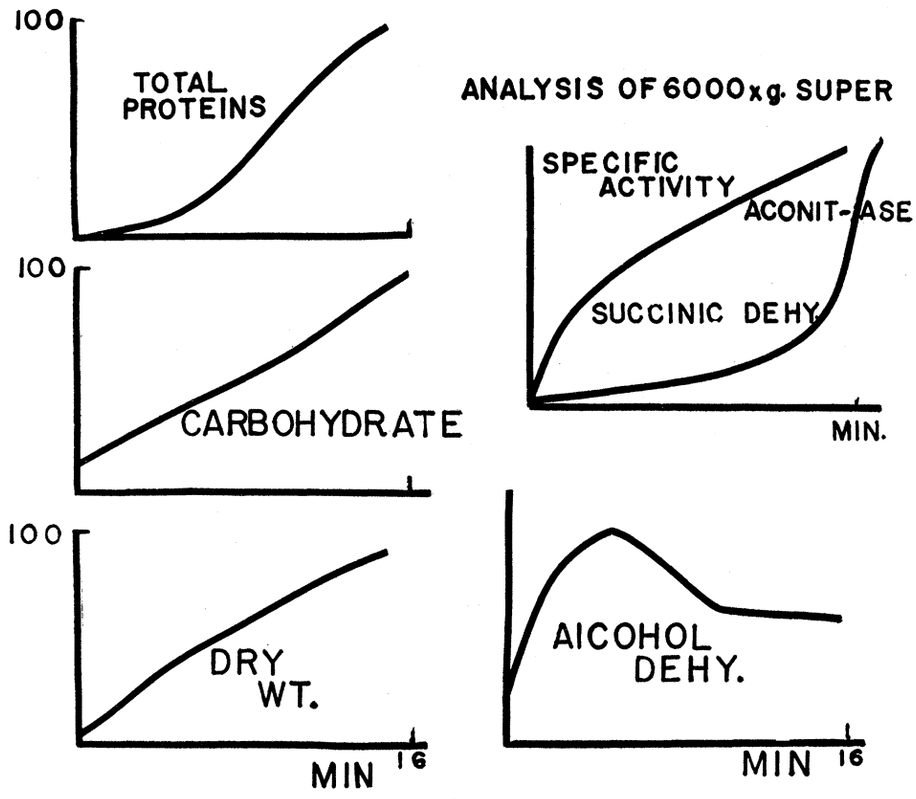

Fig. 6. Time constants for the release of cell components by treating yeast suspension with ultrasound. Yeast (30 ml of a 1.5 wt/vol suspension in water) was treated with the small titanium probe at power setting 4 in the 500-watt M.S.E. disintegrator. Samples were centrifuged at 6000*g* for 10 minutes, and the components in the supernatants were estimated. Protein, carbohydrates, and dry weight are expressed as percentages of the totals released when all the cells are broken. The enzymes are expressed as specific activities—that is, units of enzyme released per unit of protein released.

References and Notes

1. W. B. Hugo, *Bacteriol. Rev.* **18**, 87 (1954).
2. W. G. Fry, *Advances Biol. Med. Phys.* **4**, 282 (1958).
3. P. Grabar, *ibid.* **3**, 191 (1958).
4. B. E. Noltingk, and E. A. Neppiras, *Proc. Phys. Soc. London* **63B**, 6 (1950); *ibid.* **64B**, 1032 (1951).
5. H. Flynn, in preparation.
6. O. Lindstrom, *J. Acoust. Soc. Am.* **27**, 68 (1956).
7. P. Jarman, *ibid.* **32**, 1459 (1960).
8. F. G. Blake, *Office Naval Res. Tech. Rept. No. NR 014-903* (1949); Rosenberg, *Office Naval Res. Tech. Rept. No. NR 384-903* (1953).
9. J. Kolb and W. L. Nyborg, *J. Acoust. Soc. Am.* **28**, 1237 (1956).
10. M. Kornfeld, and L. Surorov, *J. Appl. Phys.* **15**, 495 (1944).
11. G. W. Willard, *J. Acoust. Soc. Am.* **26**, 933A (1954).
12. S. A. Elder, *ibid.* **31**, 54 (1959); R. K. Gould, thesis, Brown University (1961).
13. W. L. Nyborg, R. K. Gould, F. I. Jackson, C. E. Adams, *J. Acoust. Soc. Am.* **31**, 706 (1959).
14. E. Ackerman, *Proc. Intern. Congr. Med. Electron. 3rd, London* (1960).
15. R. E. P. Smith, thesis, Brown University (1961).

16. H. J. Dyer and W. L. Nyborg, *IRE (Inst. Radio Engrs.) Trans. Med. Electron.* **7**, 163 (1960).
17. D. E. Hughes, *Brit. J. Exptl. Pathol.* **32**, 97 (19[illegible] H. W. Milner, N. S. Lawrence, C. S. French, *Science* **111**, 633 (1950).
18. D. E. Hughes, *J. Microbiol. Biochem. Eng. and Technol.* **4**, 405 (1962).
19. The M.S.E. disintegrator is manufactured by Measuring and Scientific Equipment, Ltd., Westminster, England.
20. E. A. Neppiras and D. E. Hughes, in preparation.
21. E. N. Harvey, *J. Am. Chem. Soc.* **61**, 2392 (1939).
22. D. E. Hughes and A. Rogers, *Medical Electronics* (Illiffe, London, 1960), p. 397.
23. P. Doty, B. B. McGill, S. A. Rice, *Proc. Natl. Acad. Sci. U.S.* **44**, 432 (1958).
24. G. Bradfield, *Symposium on Cavitation in Hydrodynamics* (Her Majesty's Stationery Office, London, 1953).
25. M. F. Utter, D. B. Keech, P. M. Nossal, *Biochem. J.* **68**, 431 (1958).
26. A. G. Marr and E. H. Cota-Robles, *J. Bacteriol.* **74**, 79 (1957); M. M. Matthews and W. R. Sistrom, *ibid.* **78**, 778 (1959).
27. A. R. James, G. A. Dalton, M. A. Bullen, M. F. Freundlich, J. C. Hopkins, *J. Laryngol. Otol.* **54**, 730 (1960).
28. H. T. Ballantine, E. Bell, J. Manaplatz, *J. Neurosurg.* **17**, 858 (1960).
29. E. N. Harvey, A. H. Whiteley, W. D. McElroy, D. C. Pease, D. K. Barnes, *J. Cellular Comp. Physiol.* **24**, 23 (1944).
30. We are indebted to Sir Hans Krebs and to E. Neppiras for advice and criticism. The experiments were aided by a loan of equipment from Measuring and Scientific Equipment, Ltd., and by grants from the U.S. National Institutes of Health and the Rockefeller Foundation. The investigations were carried out while one of us (W.L.N.) was on leave of absence at Oxford in 1960–61.

"Gulliver"—A Quest for Life on Mars

Radioisotopes are used in a miniature instrument designed to detect life during early probes of the planet.

Gilbert V. Levin, Allen H. Heim, John R. Clendenning, Mary-Frances Thompson

Biologists are late-comers to the field of space exploration. The development of systems capable of launching satellites and space probes requires a highly coordinated and intensive effort in the physical sciences. It was only natural that such a program, developed largely by physicists, should emphasize physics in early space experiments. Moreover, many experiments in physics were necessary first steps into space. As payload capacity for probing space was actually achieved, biologists, who hitherto had had little cause for more than general interest in rocketry, became more attentive to the possibilities thus opened for biology and stressed the need for including their science in space program planning. Experiments were incorporated in instrument packages, and effects of the space environment on the metabolism and genetics of microorganisms and small animals were studied. The manned-flight and space-medicine efforts have also provided biological information, although these programs are directed toward accommodating man in space. Now, with the continued growth of thrust and guidance capabilities, biologists suddenly find themselves on the brink of one of man's most tantalizing experiments—the search for life beyond his planet.

With the beginning of modern science, information slowly accumulated bearing on the possibility that life exists on other planets, a question hitherto thought approachable only through philosophy and theology. The search for scientific data on this question had been confined to our solar system because of technological limitations. From feeble rays of light, carefully gathered and analyzed, astronomers and physicists deduced some pertinent facts or indications. Recently, radar and light waves have been directed at the planets so that the reflected energy might bring back with it information concerning surface conditions. Observations of the moon and planets have been summarized by Kiess and Lassovsky (*1*), by Kiess and Birney (*2*), and by the Space Science Board of the National Academy of Sciences (*3*). Most recently, Salisbury (*4*) discussed findings pertaining to the question of life on Mars. On the basis of observations and deductions, interest had focused on both Venus and Mars. However, recent data obtained by Mayer and his associates (*5*) have convinced these workers and others that the surface temperature of Venus is above the melting point of lead. Consequently, Mars is now thought to be the planet (with the exception of the earth) most capable of supporting life, and it has been selected by the National Aeronautics and Space Administration as the first planet to be probed by instrumented landings in an effort to find evidence of life forms. Landings within this decade are planned (*6*) which conceivably could resolve this age-old speculation. Among the instruments tentatively selected for the first landing is "Gulliver," a miniature mechanical device which, like the Gulliver after whom it is named, will seek exotic forms of life.

The authors are affiliated with Resources Research, Inc., Washington, D.C.

Exploration of Mars

While some biologists doubt that life exists elsewhere in our solar system, even the doubters generally agree that life-detection experiments should be included in the exploration of Mars. There are also "believers" who think, or at least hope, that the search will be fruitful. Surface features and atmospheric features provide the principal evidence in support of the two views. The surface features include (i) a relatively smooth and mountain-free land surface; (ii) extensive, light-colored areas which have been called deserts; (iii) polar caps, probably of water ice, which change seasonally; (iv) darker areas or bands of gray (or perhaps green or other colors), which some attribute to moisture advancing