treatments under study have been observed at this time.

Women whose cancer had spread to the lymph nodes received either a radical mastectomy or a total mastectomy plus radiation to kill cancer cells in the lymph nodes. Again, no differences were observed in the cancer recurral rates in patients receiving the two treatments.

If the results of the study hold up, the next step may be a determination of the effectiveness of the segmental mastectomy or lumpectomy. In this procedure, the tumor plus the surrounding tissue is removed but the bulk of the breast is left intact. This operation is even more controversial—and raises even more ethical questions—than the total mastectomy, but Fisher believes that it is imperative to test its effectiveness because some surgeons are already doing it.

The results described by Fisher indicate that the more disfiguring radical operation, which is by far the most commonly used, may not be necessary for most women. Whether they will be accepted and applied by the medical profession remains uncertain in view of the controversy that has raged for years about breast cancer surgery. Although the physicians treating Mrs. Betty Ford, for example, were aware of the results of the NSABP study, they still elected to perform a radical mastectomy on the President's wife.

The inability to detect all positive nodes by clinical examination—almost 40 percent may be missed—is one reason some surgeons prefer the radical operation. Fisher said, however, that it is possible to remove nodes for pathological examination without doing a radical.

Adequate detection of positive nodes is important because the presence or absence of cancer in the lymph nodes is the most accurate indicator of a patient's prognosis. When the nodes are negative, 80 percent of the patients survive at least 5 years. The survival rate drops to less than 40 percent for those with nodal involvement, but another NSABP study described by Fisher showed that chemotherapy with L-phenylalanine mustard (L-PAM) may prolong the survival of such patients.

Administration of the drug is begun right after surgery when the patient is clinically free of disease. Until recently chemotherapy was not attempted until cancer recurred and was in the advanced stages. The increased survival was particularly striking for premenopausal patients but less significant for patients above the age of 49. Fisher said that he now routinely prescribes L-PAM for all younger patients with nodal involvement.

Additional chemotherapeutic trials with drug combinations are now planned. Paul Carbone of the National Cancer Institute said that clinical studies have indicated that combinations of extremely potent chemotherapeutic agents increase the remission rate or prolong the survival of patients with advanced breast cancer. Such studies will now be extended to postoperative patients who appear disease-free but are in the high risk group. Patients who do not have nodal involvement will not receive chemotherapy because their prognosis, which is already good, does not warrant exposing them to the hazardous side effects—including carcinogenicity—of the drugs.—J.L.M.

(Continued on page 284)

RESEARCH NEWS

Diagnostic Medicine: The Coming Ultrasonic Boom

Current predictions are that the medical applications of ultrasound will equal or even surpass those of x-rays within 10 years. In fact, if these predictions are borne out, a veritable revolution in diagnostic medicine is in the making, for there appear to be few—if any—medical specialties in which ultrasound cannot play a role. At present, its clinical applications are most advanced in obstetrics, cardiology, neurology, and ophthalmology, but research is moving forward on a broad front and numerous additional applications are foreseen if not yet available.

Many investigators think that ultrasound may be the ideal diagnostic tool. It is externally applied and noninvasive; unlike x-rays it can distinguish between different soft tissues; and there is no evidence that ultrasound as it is used in diagnostic procedures damages biological tissues. The investigators stress, however, that additional research on the biological effects of ultrasound is required to definitively establish its safety. Ultrasound examinations are limited mainly by the fact that both bone and gases strongly reflect high-frequency sound waves and thus interfere with their transmission through certain areas of the body including the skull, lungs, and gastrointestinal track.

The ultrasound procedures now used for medical diagnoses are essentially clinical forms of radar and can be called pulse-echo sonography. Ultrasound is generated by a transducer, made of piezoelectric material, that is incorporated into a probe. Piezoelectric materials vibrate at high frequencies when a pulse of electricity is applied to them. Ultrasound is defined as sound with frequencies greater than 20,000 hertz, but the frequencies of diagnostic ultrasound are usually above 1 million hertz. For most diagnostic procedures the transducer transmits sound waves for about 1 millionth of a second.

As the ultrasound travels through the body, it is reflected by interfaces between tissues with different acoustic properties. Reflected sound returns to the transducer, which serves as the detector during the time it is not transmitting, where the vibrations are reconverted to electrical signals that are recorded on an oscilloscope. The time required for the reflected sound wave to return to the transducer depends on the distance between interface and transducer and the properties of the structures through which it passes. Since ultrasound does not travel well in air, the transducer must be coupled to the body by a liquid.

Ultrasound has been extensively applied in the practice of obstetrics and gynecology (Fig. 1). There are two major reasons for this. The pregnant uterus is filled with fluid that is an excellent transmitter of ultrasound. And diagnostic ultrasound, which is not associated with known hazards to the developing fetus, is the preferred diagnostic alternative to x-rays, which are associated with known fetal hazards.

Ultrasound scanning of the uterus

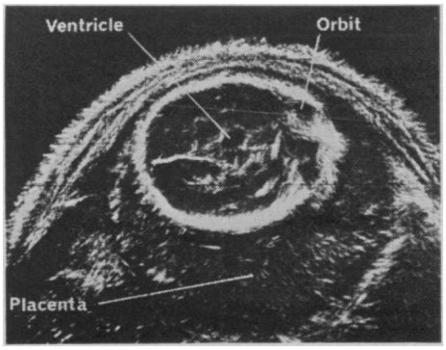

Fig. 1. Transverse scan of the uterus of a pregnant woman that shows the fetal head and the location of the placenta. The orbit, the bony structure that encases the eye, and the brain ventricles can be seen in the fetal skull. The scan is a two-dimensional scan in the B (brightness) mode. In this mode, the ultrasound echoes are displayed as a series of dots on an oscilloscope screen, with the brightness of the dots determined by the intensity of the echoes. A two-dimensional image can be built by moving the probe over the body surface and recording the echoes on a storage oscilloscope. [Source: G. Kossoff, National Acoustics Laboratory, Sydney, Australia]

can be used to detect pregnancy as early as the sixth to eighth week; to determine the number of fetuses; to measure the size of the fetus; to determine the fetal position—whether it is in the normal position for delivery with the head down, or whether the head is up; to locate the placenta—if it is in the area of the uterine cervix a cesarean section is indicated to prevent the woman from hemorrhaging; to monitor the position of the needle during amniocentesis; and to detect gross fetal abnormalities such as anencephaly (absence of all or most of the brain) or hydrocephaly (enlargement of the head caused by abnormal accumulation of fluid within the fetal skull).

Because of their capacity to distinguish between different soft tissues, ultrasonic techniques are also proving to be valuable diagnostic aids in cardiology. Physicians use "echocardiograms" (Fig. 2) for diagnosing abnormalities of heart valves, congenital heart defects, and the presence of fluid inside the membrane that surrounds the heart.

Diagnosis of the first two types of conditions would otherwise require invasive and somewhat hazardous techniques. They are also extremely difficult to perform on very young children. The noninvasive character of ultrasonic methods makes them especially suitable for infants and for patients weakened by disease. A problem is that the transducer must be directed between the ribs in order to scan the heart. Although the angle of the beam can be altered so as to pass through different heart structures, the bony ribs do somewhat restrict the sound beam's access to the heart.

The use of diagnostic ultrasound in neurology is restricted, but by no means prevented, by the skull. The probe must be positioned above the ear where the skull is relatively thin. Ultrasound can be used to locate the midline of the brain (Fig. 3). Displacement of the midline to the side could be caused by the presence of tumors or cysts or result from edema (abnormal accumulation of fluid) or hemorrhage following a stroke or traumatic injury.

In ophthalmology, ultrasound is used to measure the eye, to diagnose detached retinas, and to locate foreign bodies for surgical removal. Since the eye is both accessible and fluid-filled, it is an excellent target for ultrasonic examination.

There are a large number of additional ultrasound applications, most of which are still in the research stage and not yet routinely available in the clinic. Among these are locating tumors and differentiating between benign and malignant growths, especially those of the breast and the abdominal regions. Radiologists may use ultrasound to determine the size and position of tumors to be treated by radiation therapy. A method of using ultrasound to visualize the prostate gland is also being explored. This gland is prone to a variety of abnormal conditions, including cancer, and is difficult, if not impossible, to examine by other techniques. When the prostate gland is examined the probe must be inserted into the rectum.

One area of research now receiving considerable attention is the development of a noninvasive technique for determining blood flow through arteries. The carotid artery is of special interest because the internal branch of this artery carries blood to the brain. If clots or atherosclerotic plaques blocking these blood vessels could be detected before they completely occlude the arteries and cause a stroke and irreversible brain damage, they could be surgically removed. Current arteriographic techniques for doing this are invasive and carry an element of risk. (In arteriography, contrast dyes are injected into the artery so that the structure may be visualized with x-rays.)

William McKinney, James F. Toole, and their colleagues at the Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, North Carolina, have used conventional pulse-echo sonography to scan the carotids. After comparing their results with those of arteriographic studies, they concluded that this ultrasonic procedure could be used to screen patients for carotid occlusions. The results of the two determinations agreed for 73 percent of the arteries. Where there was disagreement the sonograms gave false positive results—indications of occlusions not found in arteriograms; none of the sonograms gave false negative results.

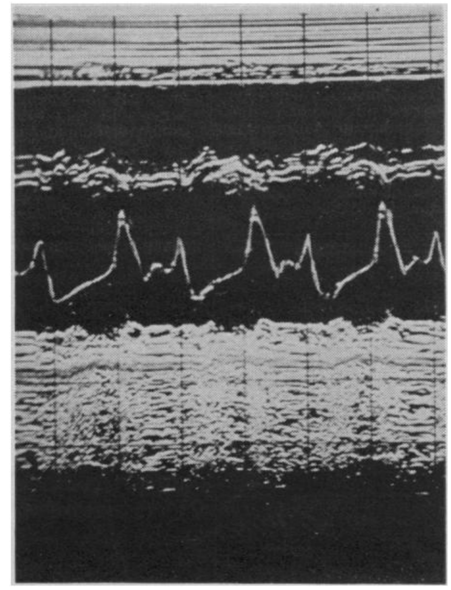

Fig. 2. Echocardiogram of a heart with a normal mitral valve (the valve between the left atrium and the left ventricle). In M (motion) mode recordings such as this one, the reflection from a moving structure (here the mitral valve) appears as a line with peaks and valleys. The other reflections are from other heart structures through which the beam has passed, and the intense reflection at the bottom is from the lungs. [Source: Bowman Gray School of Medicine, Winston-Salem, North Carolina]

Other investigators are making use of the Doppler effect to measure arterial blood flow. When a sound wave impinges on a moving object, the frequency of the wave is shifted. The direction of the shift depends on the direction in which the object is moving; the magnitude depends on its speed. Thus the frequency shift can be used to measure blood flow.

Doppler probes can be applied externally to determine the direction of blood flow in the ophthalmic arteries. A probe placed on the closed eyelid can detect whether blood is flowing toward the probe as it normally does or away from it. The latter situation is usually indicative of obstruction in the internal carotid artery.

Investigators such as John M. Reid and his colleagues at the Institute of Environmental Medicine and Physiology, Seattle, Washington, are developing an external Doppler system for measuring blood flow in the carotid arteries. They examined 60 patients with their technique. Where arteriograms were available for comparison, the results of the two techniques agreed in 29 of 41 cases.

Reid points out that the two types of examinations provide different information. X-ray arteriography examines anatomic structures while the ultrasonic technique measures function. Blood flow may appear normal even if the vessel is partially blocked. Reid thinks that the Doppler technique will complement rather than replace arteriography. The former has the advantage that it may be used repetitively to follow a patient's progress without submitting him to the hazards of x-rays.

Because most Doppler probes emit a continuous sound wave, they require two transducers; one generates the ultrasound and the other detects the frequency shift of the echo. However, James Meindl and his associates at Stanford University in Stanford, California, have developed a unit with a single transducer. The transducer, which is only 1 or 2 millimeters long, emits pulses of ultrasound and functions as a detector between pulses. This device must be placed directly on the exposed blood vessel, but it can be used to monitor blood flow during and after cardiovascular surgery. No wires are required because the signal is transmitted to the receiver by radiotelemetry. The Stanford group is working on a device that can be used externally.

The ultrasound apparatus presently in clinical use suffers from major handicaps, which is not surprising for first-generation equipment. The information is often presented in a one-dimensional and nonanatomical format that requires special training to interpret. Since the beam travels in a narrow path through tissue, only a small portion of the target is examined. For some uses, these disadvantages can be overcome by moving the probe and building a two-dimensional image on a storage oscilloscope. But several minutes may elapse during which fetal movement or breathing may cause blurring of the resultant picture. The quality of the image is also highly dependent on the skill of the technician.

To overcome these handicaps, investigators are developing ultrasound systems that give immediate, anatomical pictures. If these are displayed on a television screen or recorded on videotape, the clinician would, for example, be able to view the beating heart. One way of achieving this is to use transducer arrays.

A second generation of ultrasonic diagnostic equipment is based on linear transducer arrays. Frederick Thurstone of Duke University in Durham, North Carolina, has developed one such system designed primarily for cardiac examinations. It contains a linear array of 16 transducers that can scan a sector-shaped plane and produce a minimum of 20 scans per second. Since this gives an immediate, moving image of a plane through the heart it should provide much more information, in a

Assessment of Ultrasound Research

Not all the problems in the development of ultrasonic medicine are scientific. Some involve the translation of experimental devices and techniques into commercial products acceptable to the medical profession. Others relate to the need to train large numbers of medical and paramedical personnel to perform and interpret the tests.

The Office of Experimental Research and Development Incentives of the National Science Foundation (NSF) commissioned a nine-member team in March 1973 to conduct a state-of-the-art survey of diagnostic ultrasound research throughout the world. The team's goal was to provide the information needed to facilitate practical application of basic research. The participants in the study concluded that commercial exploitation of ultrasonic research lags in the United States, even though much of the research is done here and existing knowledge would permit production of improved instruments (*1*).

The survey team recommended that the federal government support programs, including training programs for physicians and related health personnel, that would remove barriers to clinical use of diagnostic ultrasound in this country; that basic research leading to enhanced diagnostic capabilities be coordinated; and that information exchange programs between scientists and engineers in the industrial, clinical, and academic worlds be fostered.

As a result of the recommendations of this panel, NSF sponsored a series of studies conducted by the Alliance for Engineering in Medicine and Biology. Task groups assessed, and established priorities for, research on four aspects of ultrasonic imaging: the interaction of ultrasonic energy with biological structures, ultrasonic transducers, displays and scans, and signal processing (*2*).

The potential market for new ultrasonic equipment is great. The NSF survey team reported that sales of ultrasonic diagnostic instruments in the United States increased 300 percent between 1971 and 1973. According to a "pessimistic" estimate, sales of ultrasonic instruments will match those of x-ray equipment within 10 years.

The explosive growth of clinical applications of ultrasound will require an equally explosive increase of programs to train qualified personnel. The American Society of Ultrasound Technical Specialists now has about 1,000 members; William McKinney estimates that 20,000 to 80,000 additional technicians will be needed within 10 years. Where—and how—all these specialists will be trained is unclear. But the growth potential of ultrasonic medicine is clear.—J.L.M.

References

1. *Prospectives for Ultrasonic Imaging in Medical Diagnosis; Report of the NSF Survey Team on Ultrasonic Imaging* (National Science Foundation, Washington, D.C., 1973).
2. *An Assessment of Selected Medical Instrumentation* (N-1974-1, Task Group 1; N-1974-2, Task Group 2; N-1974-3, Task Group 3; N-1974-4, Task Group 4) (Alliance for Engineering in Medicine and Biology, Chevy Chase, Md., 1974).

format more readily appreciated by physicians, than the essentially one-dimensional record currently produced by echocardiography.

A two-dimensional array of transducers is theoretically capable of producing a simultaneous, three-dimensional image of the target tissues. According to William Beaver, an associate of Meindl's at Stanford, the Stanford group is working on a diagnostic ultrasound system that includes a two-dimensional array of 100 transducers. They plan to have a prototype model installed at Stanford University Hospital within the year, but this is just the beginning. They eventually plan to build the array to include as many as 10,000 transducers. Increasing the number of transducers can increase the size of the field examined or the resolution of structures within the field, or both.

The major problem with a system such as this is that highly complex electronics are needed to process and store three-dimensional information. The image will necessarily be displayed in two dimensions because all current display systems—film, television screens, and so on—are two-dimensional, but the investigators will be able to select successive planes through the target for viewing and thus examine the entire structure if desired.

Acoustic holography, which is analogous to optical holography, is another method of extracting information in three dimensions from sound waves. The idea is to generate an interference pattern between a reference beam of ultrasound and a beam reflected from the sample and then to reconstruct the sample image from the pattern. The problem is that there is no equivalent of photographic film for recording the pattern. A number of approaches to signal processing are being explored. One of these taken by David Vilkomerson, K. F. Etzold, and their colleagues at the RCA Laboratories in Princeton, New Jersey, is to record the interference pattern electronically and use a computer to reconstruct the image from the stored data. Etzold estimates that it will be 2 to 3 years before they have an instrument ready for market.

Essentially all investigators interviewed said that there is no evidence that ultrasound at the frequencies (usually less than 10 megahertz), intensities (approximately 1 milliwatt per square centimeter), and pulse duration (1 millionth of a second) used for diagnosis constitutes any hazard to human health. There have been no reports of defects or other problems either in women who were scanned during obstetric examinations or in the children who were scanned in utero. In studies with laboratory animals, the investigators have generally concluded that there are thresholds of frequency, intensity, and duration below which damage does not occur and that diagnostic ultrasound is well below these thresholds.

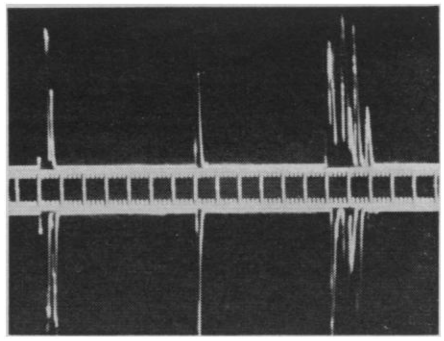

Fig. 3. Normal echoencephalogram indictating the position of the brain midline. This recording is in the A (amplitude) mode in which the horizontal axis represents time (or the distance between the reflecting interface and the transducer) and the echoes are displayed as peaks; the peak amplitude is proportional to the intensity of the reflected sound. Two tracings, made from equivalent positions on each side of the head, are shown in the recording. The intense reflections on the left and right sides of the photograph are from the skull; the central peak is from the brain midline. The complete ultrasonic examination requires determination of the midline position at three separate positions on the skull. [Source: Bowman Gray School of Medicine, Winston-Salem, North Carolina.]

For example, Francis Fry, now at the Indianapolis Center for Advanced Research, and Floyd Dunn of the University of Illinois, Urbana, found that the ultrasound intensities and durations used for diagnostic work were several orders of magnitude below those producing detectable lesions in the brains of cats. Frederick Kremkau, with Walter Bo, at Bowman Gray School of Medicine, exposed the ovaries of pregnant rats to ultrasound after implantation occurred. They observed no effect of this treatment on maintenance of pregnancy (for which functioning ovaries are required in the rat) or on the gross morphology of the fetuses, nor did they observe defects in fetuses treated with ultrasound. Other investigators, including a group in Japan, did find developmental problems after exposing rat embryos to ultrasound.

Although the preponderance of evidence favors the safety of diagnostic ultrasound, a number of investigators pointed out that ultrasound is a form of energy and may yet be associated with unexpected hazards just as x-rays proved to be. Because of this possibility, they think that more research is needed to characterize ultrasound emissions from diagnostic equipment and their interactions with living tissue. A better understanding of the acoustic properties of different types of tissue will aid in designing new techniques and equipment and in identifying abnormal conditions, including malignant tumors.

Ultrasound may be used for therapy as well as for diagnosis. Since ultrasound can be focused, high intensities can be used to selectively destroy tissue. Although there have been clinical studies of ultrasound as a surgical tool in humans, it is much more frequently used to produce lesions in the brains of laboratory animals. The advantage is that with good focusing, high intensity ultrasound can destroy an area deep in the brain without damaging intervening tissue. Fry said that it is at least theoretically possible to locate a brain tumor with diagnostic ultrasound and destroy it with high intensity ultrasound while monitoring the process with ultrasound.

According to Kremkau, ultrasound can inhibit mitosis in rapidly dividing cells such as those in regenerating rat liver. Whether this effect is harmful or beneficial depends on the circumstances. If it can be applied to inhibiting tumor growth it would be beneficial.

In another experiment, Kremkau found that ultrasound enhances the toxic effect of nitrogen mustard, a drug used for cancer chemotherapy, on a highly malignant line of mouse leukemia cells. He thinks that it may act by increasing uptake of the drug by the cells. Since ultrasound can be accurately focused, it may eventually be feasible to increase the uptake of chemotherapeutic agents by tumors without producing a similar effect on normal tissue.

Except for applications in physical medicine, in which ultrasound has long had uses such as generating heat and breaking up calcium deposits in joints, its therapeutic applications lag behind the diagnostic ones. But ultrasound appears to be sparking a revolution in diagnostic medicine, and there are hints that with a better understanding of its effects on tissue, new therapeutic applications may also evolve.

—JEAN L. MARX