FURTHER PILOT ECHOGRAPHIC STUDIES ON THE HISTOLOGIC STRUCTURE OF TUMORS OF THE LIVING INTACT HUMAN BREAST*

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The object of this study was to examine further the effect of living intact tumor tissue of the human breast on a pulsed electrosonic beam directed into tumors from the overlying skin.[1] More specifically, this investigation was planned to determine the preoperative diagnostic possibilities of the method on the basis of the histologic structure of palpable lesions, with a view to future applications to other sites. The investigation was not planned to detect tumors and was not necessarily intended to replace existing methods of diagnosis of breast lesions.

HISTORY OF THE METHOD

The principle of creating bursts of sound energy and studying the echoes returning has been used for years in the detection of flaws in metals. The highest frequency used commercially is 5 megacycles. Ludwig and Struthers[2] reported the application of the commercial machine to the biologic field. They demonstrated that gallstones and foreign bodies buried in the muscles of dogs could be detected at a frequency of 2½ megacycles.

However, theoretically, the approach to the examination of tissues in terms of cellular composition required a considerably higher frequency, greatly increasing the technical difficulties. A machine specifically for the simulation of "radar" on a small scale was developed by the U.S. Navy during the last world conflict. This complex ultrasonic training machine operated at a frequency of 15 megacycles. Thus the opportunity arose to carry out pilot studies on the measurements and echo-producing properties of biologic tissues, including a stomach containing a carcinomatous ulcer freshly removed at operation.[3]

Encouraged by striking differences observed in echo patterns of the carcinomatous ulcer, the infiltrated stomach wall, and the normal stomach wall used as a control, pilot work was carried out on fresh malignant cerebral tissue.[4,5] It was found possible to detect malignant tissue in the brain substance through the dura mater post mortem.

Experiments were carried out on the brains of living animals,[6] and

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on the living intact human arm[1] to determine possible effects. No harmful effects from the method have been observed to date.

A limited clinical trial was attempted.[1] The histologic structure of 2 nodular lesions of the human breast was correctly forecast before biopsy in terms of malignancy and benignancy without apparent harm to the patients. Results of further pilot work carried out on the human breast, using a machine specifically designed for biologic application, are recorded in this report. This investigation is not concerned with detecting unsuspected lesions but with the histologic differentiation of living intact tumors.

Principle

Sound energy can be produced from electrical energy by means of the piezo-electric phenomenon. Piezo-electric substances can be mechanically deformed by application of electric charges. Conversely, when piezo-electric substances are mechanically deformed, electric charges are produced. Sound waves can be produced by mechanical motion so that a piezo-electric substance can convert sound energy into electrical energy or, conversely, can convert electrical energy into sound energy. When a piezo-electric substance is arranged for the production or reception of sound in electrosonic terms, the name electro-acoustic transducer is applied to the instrument. By suitable design, a narrow beam of sound energy can be produced from such a transducer. This sound beam can be directed into a system under examination. Two technics can be applied. In the first, termed a transmission technic, the sound energy from the transmitting crystal can be driven through the system under examination and "collected" by a receiving crystal placed at the point of exit of the sound beam from the system. From this arrangement the amount of sound energy absorbed by the system between the two transducers can be observed. This type of observation is termed a measurement of attenuation of the sound beam. The value of such a system will depend upon the amount of information required. If the sound beam is moved through the tissues, a record of intensity variation analogous to an x-ray can be obtained. The transmission technic has been attempted in order to outline the ventricles of the brain in the living human subject.[7-9]

The second technic is termed reflection, and is the type believed more useful where more information is desired, as in the present study. In this method, sound energy is driven into the tissues, and the echoes returning to the transmitting transducer from the interfaces between the various elements in the path of the sound beam are studied. It is obligatory with this technic to pulse the sound energy so that a time

interval is available for the detection of the returning echoes just as in the case of shouting at a mountain face where a pause is necessary in order to hear the echoes. Thus, the time of exposure of the tissues to the sound beam is short. With this arrangement, at a suitable frequency, distances from the surface of the interfaces, in addition to more detailed information about attenuation of the sound beam by the various tissue elements, can be obtained.

Discussion of Possible Harmful Effects

A review of the extensive literature, going as far back as 1928, on the damaging effects of ultrasonic energy is beyond the scope of this communication. Much of the work on damaging effects is in our opinion not directly applicable to our investigation, since the operation of our machine is without precedent in the biologic field. Results of workers specifically interested in damaging effects on tissues are extremely difficult to apply because of the great differences existing in the conditions of experimentation. The result of the intensive work on damage has tended to implant the impression that ultrasonic energy must be handled with caution. When this impression is coupled with the all too recent memory of the terrible sequelae of x-radiation unsuspected by pioneer workers, it is not surprising that a very cautious attitude toward the diagnostic possibilities of ultrasound should be manifest.

The suffering of the early workers with x-rays was not in vain, since it has been possible to control x-radiation to an apparently "safe" level for therapeutic and diagnostic procedures, though even today a casual observer of the skin of some patients after deep x-ray therapy would conclude that the skin had been "damaged permanently." It is therefore necessary to consider carefully what is meant by the words "harmful" and "damage." Such factors as time scale, completeness of recovery, restoration of function, and the object in mind in risking the damage, must be taken into account.

No late sequelae comparable to those seen after x-radiation have yet been demonstrated with ultrasonic energy. Theoretically, there is no reason to expect such sequelae since ultrasonic energy is a form of mechanical energy. The pressure wave produced as sound energy causes displacement in the medium and imparts velocity and acceleration to particles composing the medium. The passage of the pressure wave gives rise to internal friction producing heat over the period of application; in addition, dissolved gases may be released from liquid media and tearing apart of the medium may produce cavitation. If the

medium is not homogeneous, as with tissues, local concentration of the effects can occur.

Lynn and Putnam[10] described the histologic effects of high intensity ultrasonic energy at a frequency of 835 kilocycles on the scalps, skulls, and brains of dogs, cats, and monkeys at 10 to 15 minute exposures. The end result was dry gangrene with sequestration of the exposed area.

Because of the unusual operation of our machine at high frequency and of the short, widely spaced pulses, the absence of specific precedent in the literature made extension of other work impossible in the assessment of possible damage. Even had it been possible to extend previous fundamental work, the practical difficulties of measuring sound intensities with our machine would introduce further uncertainty.

The complexity of the problem of damage and the understandable uncertainty of expert opinion forced a direct biologic approach. Accordingly, since no obvious damage was observed in the original pilot experiments in freshly removed tissues, direct application of the echoscope to the exposed brains of animals[6] was carried out. The animals recovered from the anesthetic and maintained unimpaired function. Sacrifice and microscopic examination of the brains at suitable intervals up to several weeks after exposure failed to produce any evidence of damage.

It seemed a reasonable risk to expose the extensor muscles of the left arm of one of us[1] for a 30-minute period. No sensations of heat or pain were experienced. There were no immediate after-effects and no sequelae have appeared to date (20 months later).

It was therefore possible to make a cautious approach to the patient. No complaints of pain were received from any of the patients in this series, either at the time of application or subsequently. No sensations or complaints were admitted upon being questioned. One normal breast exposed for short periods during "tuning-up" experiments is lactating efficiently at the time of writing (8 months after exposure). The living human brain has been exposed through the dura mater during experiments aimed at localization and diagnosis of tumors at operation. No unusual microscopic findings were reported in the removed specimen (glioblastoma multiforme). A scientific evaluation of loss of function was impossible owing to the effects of the operation from which the patient recovered "uneventfully."

Sound Intensity Used in the Experiments

Peak Power. The power actually transmitted while the crystal is vibrating is called the peak power. The maximum figure used in our

experiments, based on calculations assuming a uniform sound beam, is 644 watts per square cm. The value is higher than that reported by most investigators, but the peak intensity is applied for only one-half millionth of a second. We believe that various workers have shown that greater intensities can be used with short exposures than can be used continuously. Fry *et al.*[11] worked on intact frog spinal nerves, and Hueter and co-workers[8] on human periosteal pain thresholds. Unfortunately, their results are not directly applicable to our extremely short exposures.

Average Power. The peak power averaged over a cycle of operation is based on an equivalent energy concept. The average intensity at the surface of our patients was similarly calculated as not more than 1.3 watts per square cm. This figure is below the human periosteal pain threshold found by Hueter and Bolt.[9] We have tried the echoscope on our own tibiae under comparable conditions and have not experienced pain.

It should be noted that our figures are probably high because harmonic voltages across the crystal give the very high peak voltages used in the calculations. Harmonic voltages contribute very little acoustic output.

We think at present that only direct biologic confirmation, such as already described, can give reliable indications of safety. A cautious but positive approach to an area of the patient provided with sensory organs responsive to heat and pain, after all advantage has been taken of the experimental animal, is recommended for testing untried ultrasonic apparatus. In the final test of safety, someone has to be the last link in the chain. We consider our echo-ranging studies as concerned with the effect of tissues on sound rather than the converse.

Terminology

When the sender-receiver unit was designed for clinical work, the name ultrasonoscope[4] was originally used. The words ultrasonography and ultrasonogram were coined in a later publication.[1] It is proposed to simplify the terminology and to refer to the ultrasonoscope as the echoscope, to correspond with the word stethoscope. The electronic machine will be referred to as an echograph and the records of the echographs produced by the machine will be referred to as echograms to correspond with the terminology used in electrocardiography. The entire subject of sound reflection from biologic tissues can be called echography. Recent applications of radar technics[12] make it necessary to introduce further terminology.

Sound energy can be driven into tissues in a narrow beam as de-

scribed, but, also, this narrow beam can be moved through tissues to record continuously the pattern traced out by the returning echoes according to the structure of tissues. Therefore, the echographic structure of tissues can be obtained in one dimension, in a manner analogous to a needle biopsy, or in two dimensions, in one plane. Accordingly, the concepts of uni-dimensional and two-dimensional echography with the corresponding nomenclature can be introduced. Further developments could produce three-dimensional echography.

This communication is concerned mainly with uni-dimensional echography at a frequency of 15 megacycles per second, though some pilot two-dimensional echograms are shown in Figure 8 (case 6) to show how further information can be obtained from biologic tissues.

The Apparatus

The arrangement of the apparatus designed for clinical research is shown in Figure 1. It should be noted that the apparatus was built primarily for general research and can be designed in a more compact form for specific application. The echoscope can be seen clamped to the right hand side of the table top. To the left is the cathode-ray oscilloscope with the camera in position for recording.

The echoscope (ultrasonoscope) has been described elsewhere[4] and consists of a chamber filled with water, one end containing the piezo-electric crystal (quartz). The other end is closed by a sheet of condom rubber. The distance between the crystal and the rubber membrane is 2 cm. in the instrument used in the studies to be described. The echoscope is handled in a manner analogous to a stethoscope, the wetted rubber membrane being applied to the skin. The crystal is 0.008 inches thick and has a working face of 9 mm. in diameter.

The relationship of the electronic units comprising the machine is shown in Figure 3. An electronic clock (1) times the bursts of sound energy and starts the trace of the electron beam on the fluorescent face of the cathode ray oscilloscope tube. The sound transmitter (2), upon receipt of the pulses from the electronic clock (1), creates the electrical energy necessary to cause the piezo-electric crystal (3) to produce sound energy for the period of the pulses. The sound pulses leave the crystal in a narrow beam and penetrate the tissues. Echoes returning from the tissues are received by the same crystal between the transmitted pulses, are amplified by unit (4), and are caused to deflect the trace as shown. The process is continuously repeated and is carried on at such a rate as to give a stable trace which can be seen and photographed to produce echograms.

The machine has been described in more detail.[13]

Method of Control

Operation of the system is complicated, involving not only the electronic complex but also the effects of tissues, which are heterogeneous when related to wave length (approximately 0.1 mm.), upon sound energy. Because of the possible number of variables, biologic control was used exclusively in the series presented. As more exact knowledge becomes available from fundamental work, it is expected to be able to apply other methods of control. In each case the echograms of the lesion and of the normal tissue of origin were recorded with the echoscope positioned in exactly the same manner and without change of machine setting. In most of the cases the opposite breast was used for control. In cases 5 and 9, adjoining normal subcutaneous tissue and the opposite axilla were recorded respectively as controls.

Clinical Results

A series was made up of 19 consecutive cases of breast tumors as admitted to the hospital for treatment. The original 2 cases[1] were included, bringing the total to 21.

Method of Echographic Examination

Adjustments of the echographic machine, including gain, were made on the basis of experience. The echoscope was applied to the tissues under examination (Fig. 2). No change was made in the controls of the machine between the echogram of the lesion and the echogram of the normal tissue of origin in order to insure control of the experiments. Thus, echograms of the normal tissue of origin could be compared. The method of control makes a comparison from case to case possible only on the basis of observed differences between the echogram of the lesion and the control echogram of the same case. It is not valid to compare individual echograms from case to case.

Subjective Interpretation of Records

It has been found from previous studies that certain definite characteristics appear to distinguish echograms believed, at the present stage, to be associated with malignant tissue from the control echograms obtained from the tissue of origin. These characteristics can be distinguished subjectively on the oscilloscope screen and a probable diagnosis can be made at the time of examination. The subjective basis of interpretation of the records is explained later.

It is necessary to state the axes of the uni-dimensional echograms. Figure 4 shows a typical pair of uni-dimensional echograms from case 2. The time base runs horizontally from left to right. From this base

the depth in the tissues from which the echoes are returning can be computed. The total distance across the record corresponds to about 2 cm. of penetration into the tissues. (Each horizontal scale division is 3.0 micro-seconds and represents a distance of 2.30 mm., taking the average velocity of sound in tissues at 1540 meters per second.) The height from the baseline in the vertical axis indicates the strength or loudness of the echoes returning from the tissue.

The saturated signal "X" should be noted. This signal indicates that the echoes returning from the rubber-membrane-body-surface interface, or the point of entrance of the sound into the tissues, are so strong that

TABLE I

A Composite of the Clinical Data, the Results of the Subjective and Objective Evaluation of the Echogram Pairs in Each Case, and the Microscopic Diagnosis Made after Echographic Examination

Case no.	Hospital no.	Age	Lesion	No. of echoes†	Area†	Baseline†	Diagnosis	
							Echographic	Pathologist
				Malignant group				
1	832576	32	Whole breast	$\frac{9}{6}=1.5$	$\frac{796}{574}=1.39$	$\frac{44}{37}=1.2$	Malignant	Adeno-carcinoma
2	832585	69	Breast nodule	$\frac{11}{6}=1.8$	$\frac{508}{361}=1.40$	$\frac{48}{28}=1.7$	Malignant	Adeno-carcinoma
3	832270	38	Breast nodule	$\frac{5}{5}=1$	$\frac{580}{431}=1.35$	$\frac{28}{29}=0.1$	Malignant	Adeno-carcinoma
4	832284	55	Breast nodule	$\frac{5}{1}=5$	$\frac{698}{446}=1.57$	$\frac{42}{10}=4.2$	Malignant	Adeno-carcinoma
5	832016	66	Axillary node	$\frac{7}{5}=1.4$	$\frac{603}{507}=1.19$	$\frac{35}{32}=1.1$	Malignant	Adeno-carcinoma
6	767222	47	Breast nodule	$\frac{8}{2}=4$	$\frac{421}{329}=1.28$	$\frac{34}{12}=2.8$	Malignant	Adeno-carcinoma
7	809359	79	Breast nodule	$\frac{6}{5}=1.2$	$\frac{477}{278}=1.72$	$\frac{32}{27}=1.9$	Malignant	Adeno-carcinoma
8	661916	61	Breast nodule	$\frac{3}{4}=0.8$	$\frac{324}{247}=1.31$	$\frac{15}{13}=1.2$	Malignant	Adeno-carcinoma
9	834912	80	Subcutaneous plaque	$\frac{6}{1}=6$	$\frac{317}{298}=1.06$	$\frac{20}{8}=2.5$	Malignant	Adeno-carcinoma
10*	816988	51	Breast nodule				Malignant	Adeno-carcinoma
11	827694	87	Breast nodule	$\frac{7}{1}=7$	$\frac{426}{313}=1.36$	$\frac{30}{9}=3.3$	Malignant	Intraductal carcinoma
12	833986	51	Half breast	$\frac{10}{11}=0.9$	$\frac{739}{567}=1.30$	$\frac{54}{57}=0.9$	Malignant	Sarcoma

TABLE I (Continued)

Case no.	Hospital no.	Age	Lesion	No. of echoes†	Area†	Baseline†	Diagnosis	
							Echographic	Pathologist
				Non-malignant group				
13	833951	80	Breast nodule	$\frac{2}{1}=2$	$\frac{166}{166}=1$	$\frac{13}{8}=1.6$	Non-malignant	Intraductal papillomatosis
14	680930	37	Breast nodule	$\frac{4}{5}=0.8$	$\frac{680}{697}=0.97$	$\frac{29}{33}=0.9$	Non-malignant	Fibroadenoma (pericanalicular)
15	824906	39	Breast nodule	$\frac{3}{3}=1$	$\frac{270}{338}=0.80$	$\frac{25}{20}=1.3$	Non-malignant	Fibroadenoma (intracanalicular)
16*	813490	40	Breast nodule				Non-malignant	Fibroadenoma (pericanalicular)
17	833908	33	Breast nodule	$\frac{7}{9}=0.8$	$\frac{599}{696}=0.86$	$\frac{49}{70}=0.7$	Non-malignant	Lipoma
18	833546	54	Breast nodule	$\frac{6}{6}=1$	$\frac{150}{150}=1$	$\frac{35}{35}=1$	Non-malignant	Fibrocystic disease
19	827789	56	Breast nodule	$\frac{3}{2}=1.5$	$\frac{116}{244}=0.48$	$\frac{19}{11}=1.7$	Non-malignant	Fibrocystic disease
20	827692	47	Breast nodule	$\frac{6}{4}=1.5$	$\frac{193}{177}=1.09$	$\frac{24}{20}=1.2$	Malignant	Fibrocystic disease
21	834609	42	Breast nodule	$\frac{11}{10}=1.1$	$\frac{409}{355}=1.15$	$\frac{52}{52}=1$	Malignant	Fibrocystic disease

* Original cases.

† Echographic ratios $\frac{\text{tumor}}{\text{control}}$.

the range of the machine is exceeded. The signal "X" is a convenient landmark, since subsequent signals (to the right) are coming from tissues beneath the skin.

Casual inspection of the two echograms without prior knowledge of the principles of echography reveals a definite difference between the two. The following points may be noted and compared in the subjective examination of each pair of echograms:

1. The number of echoes to the right of point "X."

2. The distance the echoes extend along the baseline to the right of point "X."

3. The character of the echoes and the distance at which they occur along the baseline, relative to the point "X."

4. The vertical height to which the echoes rise from the baseline.

When these four points are compared in the two echograms in Figure 4, it will be noted that: The echogram of the lesion "B" shows a greater number of echoes (approximately 10) than the control echogram "A" (approximately 3). The echoes in the echogram of the tumor extend along the baseline to a far greater extent than those of the control echogram. Thus the tumor was returning echoes from a greater depth than was the normal breast tissue. The closeness of the lesion to the skin, noted clinically and microscopically, can be seen in the echogram "B" at "Y" occurring with the bifid entering signal "X." Finally, the signals returned from the tumor echogram "B" are considerably higher, or stronger, than those from the normal "A." (The signal "Z" shown in the normal echograms was frequently observed in the series and is considered a normal signal from the human breast.) From experience gained in previous work, a diagnosis of a malignant neoplasm was made on the basis of the positive differences between the two echograms.

In contrast, the pair of echograms from case 15 shown in Figure 5 can be examined. Both echograms show about the same number of echoes. But the echoes in the echogram of the lesion "B" show less amplitude. Both show about the same horizontal extent. The lesion of "B" shows a somewhat smaller over-all echo pattern than does the control "A" of normal tissue. A diagnosis of benign tumor was made on this negative difference between the control and the lesion, again on the basis of hypothesis.

The echograms from case 12 (sarcoma) are shown in Figure 6. The control is shown at "A" and the lesion at "B." In this case, the number of echoes and the baseline extent were approximately the same. But a diagnosis of a probable malignant lesion was made on the basis of the group of echoes under the broken line (see point 3).

The preoperative echographic diagnoses, based on the hypothetic points of comparison between the two echograms in each case, are shown in Table I, together with relevant clinical data and the microscopic diagnoses. Cases 1 to 12 were diagnosed microscopically as malignant lesions, and cases 13 to 21 as non-malignant.

Objective Evaluation

Subjective examination of the echograms suggested three possibly significant characteristics which seemed amenable to quantitative analysis. These characteristics are: the number of echoes, the baseline extension of echoes, and the area beneath the trace (average returned sound). The numerical data for these variables are shown in Table I.

Echoes were not counted as such unless higher than baseline thickness. Baseline extension of echoes was measured in millimeters from the beginning of the entering signal "X" to the beginning of the last counted echo.

Area, which is proportional to the average energy received from the system, was computed by tracing the echo pattern from the original records, including the entering signal "X" and the last counted echo, upon paper ruled in millimeters in both directions. The difficulties of handling trace line width in connection with area determinations led us finally to accept only whole square-millimeter units as contributors to total area. Thus the areas given in Table I are minimal.

Ratios of tumor to control were determined for every case. The malignant and non-malignant groups were then compared with respect to the average values of these ratios. The "t" test of "Student" was used for the statistic evaluation of probability that the observed differences in these averages might arise purely through chance. With 17 degrees of freedom pertinent to each "t" value (1.9 for echo number, 4.9 for area, and 1.8 for baseline extension) the resultant probabilities are .071, .0002, and .09 respectively for echo number, area, and baseline extent. The only clearly significant ratio appears to be that for area where it will be noted that all cases diagnosed microscopically as malignant had a ratio above unity. The lowest area ratio in the malignant group (case 9) was 1.06 as compared to the highest area of 1.15 in the benign group (case 21). Thus overlapping of the two groups is very small.

TABLE II
Clinical Composition of Series

Malignant Neoplasms		Non-Malignant Lesions	
Adenocarcinoma in breast	8	Intraductal papillomatosis	1
Adenocarcinoma remote	2	Fibro-adenoma (pericanalicular)	2
Intraductal carcinoma	1	Fibro-adenoma (intracanalicular)	1
Sarcoma	1	Lipoma	1
		Fibrocystic disease with fat necrosis	2
		Fibrocystic disease without fat necrosis.	2
Total	12	Total	9

Table II shows the composition of the series based on microscopic structure.

TWO-DIMENSIONAL ECHOGRAMS

The adenocarcinomas showed the usual variation of cellular and fibrous components from section to section, but the differences between the uni-dimensional echograms of case 6 (Fig. 7) were not as striking subjectively as the other cases. Since at this time, pilot apparatus for

two-dimensional echography had come to hand, the opportunity arose to try to obtain more evidence in this case. Figure 8 shows the results of the attempt, and is believed to be the first record of its kind taken from the human breast. The principles of two-dimensional echography have been fully described elsewhere.[12] The deeper echo pattern of the lesion "B" can be readily seen. (The time axis is from below upward.) The records are of small sectors of tissue in one plane.

With development of the apparatus it is hoped to draw a picture in terms of echo pattern which will define a tumor directly, thus greatly facilitating interpretation. The tumor in this case was too large for the available range of the instrument.

The area of control echograms "A" (Fig. 8) (on the original records) was 580 square mm. and that of the tumor "B" (Fig. 8) 1121 square mm., giving a ratio of 1.93.

It was interesting to note that, although the subjective interpretation of the uni-dimensional echograms of case 6 revealed only a moderate difference between the two records (Fig. 7, A and B) as compared to the other cases of which Figure 2 is typical, the objective evidence obtained from both the uni-dimensional and the two-dimensional echograms indicated a malignant tumor.

Case Discussion

The secondary deposits in regional lymph nodes (case 5) and in the subcutaneous tissues (case 9) gave similar patterns to those of lesions within the breast on other cases. Case 9 also exhibited massive involvement of the thyroid gland, which gave the same pattern of echoes as the subcutaneous plaques, though control from the thyroid gland itself was not possible.

Case 8 was recorded as doubtful subjectively because of only a moderate difference of echo pattern in one of three records (the other two being conclusive). The pathologist reported the lesion as well circumscribed, necrotic in parts, and that the histologic diagnosis was less clear-cut than for the rest of the cases, and that "there was room for an honest difference of opinion." However, the area ratio of the doubtful echogram fell into the malignant range.

Case 11 (Paget's disease) gave quantitative data indicating a malignant lesion whereas case 13 (intraductal papillomatosis) fell into the "normal" (area ratio) quantitative zone. Cases 13, 20, and 21 were subjectively designated as malignant in the interest of the patients, but case 13 did not warrant this designation on the basis of the quantitative analysis.

In the quantitative study, the ratio of areas under the echograms appears to be a significant entity agreeing completely with the microscopic diagnosis in the malignant group.

Consideration of Production of Echoes by Tissues

From the beginning, echographic studies on effects of tissues in terms of cells have been hampered by the absence of precedent, so that approach has of necessity been experimental. As experimental data have become available, it has been possible to attempt application of the theory of sound. Most of the exact knowledge of sound is predicated upon homogeneous mediums. At a frequency of 15 megacycles, the present upper practical limit of echographic application, the wave length is about 0.1 mm., or 100 μ, so that if a cell diameter is assumed at 10 μ, the theoretic limit of resolution at 15 megacycles could be about ten cells. Unfortunately, tissues must be considered not only as heterogeneous on a possible scale of ten-cell units, but also extremely complex geometrically, so that a theoretic approach to the problem becomes overwhelmingly difficult at 15 megacycles. It is possible, however, once this fact is appreciated, to apply some of the known theory cautiously and to devise experiments with at least some of the variables controlled. Fundamental work is in progress designed to elucidate some of the observed phenomena in relation to the problem.

The difficulties of the purely theoretic approach and the necessity for clear biologic thinking become apparent when attempts are made to obtain physical constants from biologic tissues. Ludwig,[14] measuring velocity of sound in isolated tissues at 1.25 to 2.5 megacycles by a transmission technic, found a variation of 1506 to 1585 meters per second in brain, liver, kidney, spleen of dog, and hog and beef muscle. In the living subject for various groups of muscles in several individuals the range was from 1490 to 1610 meters per second.

Ludwig[14] found that within the limits of experimental error the velocity of sound did not differ significantly when the sound energy traversed the tissue parallel to the muscle bundles or across them. Hüter,[15] using a transmission technic, measured the absorption of sound by similar blocks of tissue. He found that the absorption of sound was greater when the sound energy was directed across muscle bundles than when directed along the muscle bundles.

We have helped to explain this effect of anisotropy (fiber direction) of beef muscle by the echographic technic used in this communication. We have found that sound is reflected back toward the source in the

crosswise direction and practically not at all along the fibers. Thus the natural orientation of beef muscle presents interfaces at which sound can be absorbed or reflected when the sound energy is directed normally to the plane of the fibers (across). We found echographically that the orientation was destroyed by grinding the meat.

We have noticed also a marked difference of echo pattern with and without intact blood supply.

The echographic method of examination will make possible more exact measurement in terms of small units of tissue in the future, but in the meantime advance can be made with empirical procedures such as the study described.

Our hypothesis relative to the present study is based upon the greater concentration of nuclear material found mainly in malignant growths, since we may be differentiating groups of ten cells theoretically. The evidence for this hypothesis is based partly on the fact that necrotic malignant tissue apparently does not return echoes as compared to a living cell mass. If this fact is true, the one doubtful subjective verdict (of three echograms) in the malignant group (case 8) might be explained.

It should be appreciated that the present apparatus is extremely crude when compared to possible future development. Echography appears to be applicable to all accessible sites of tumor growth.

Summary

An echographic study was made of 21 cases of tumors associated with the human breast (Table II). Control was biologic throughout the series. The cases were examined as presenting in the clinic for preoperative diagnosis. An echographic diagnosis based on hypothesis was made before operation (Table I), and compared with the subsequent microscopic diagnosis.

The original records were subjected to quantitative analysis. The quantitative echographic diagnosis based on the records obtained appeared to agree completely with the microscopic diagnosis in the malignant group on the basis of a statistically significant entity, the area (average returned sound) ratio.

Differentiation between intraductal papillomatosis (case 13) and intraductal carcinoma (case 11) was possible. Some typical records illustrate the discussion.

Two-dimensional echograms of the human breast (Fig. 8) are believed to be the first recorded.

The patients examined did not complain of, or admit, any sensa-

tions when examined. The pathologist did not comment upon any unusual appearances of the specimens when examined. The operators of the machine have not experienced any untoward effects to date (7 months). No precautions were taken by the operators.

Echography appears to be applicable to tumors at all accessible sites. Further inquiry along the lines described would seem justified.

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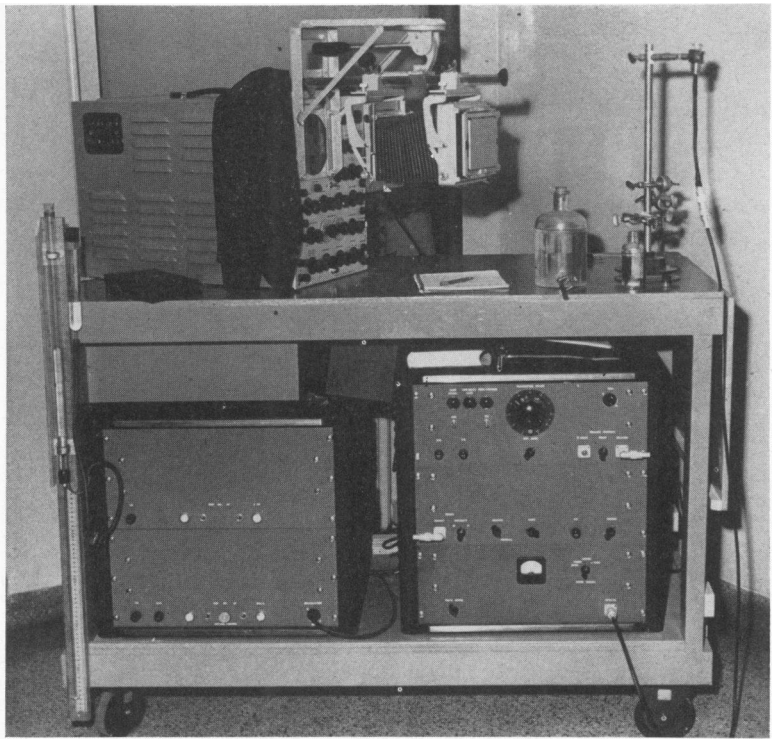
DESCRIPTION OF PLATES

PLATE 129

FIG. 1. The 15 megacycle echograph arranged for clinical work. The power supply unit is to the left and the transmitter, receiver, and control units to the right of the substage. The echoscope is seen on the table top, clamped to a stand. The camera is shown in position for recording. It can be swung clear for detailed examination of the oscilloscope. The boiled distilled water used for filling the echoscope is shown stored under oil in the bottle between the clamp stand and the oscilloscope.

FIG. 2. Method of examination of the patient. The echoscope is shown applied to a lesion of the right breast.

1



2

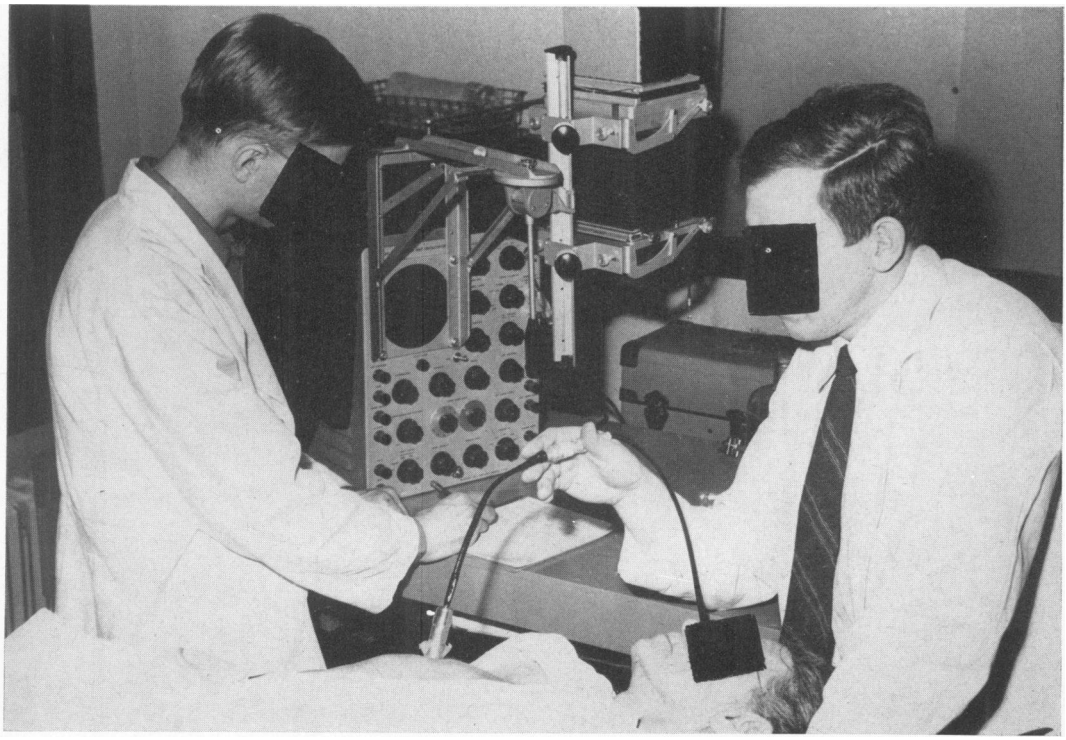
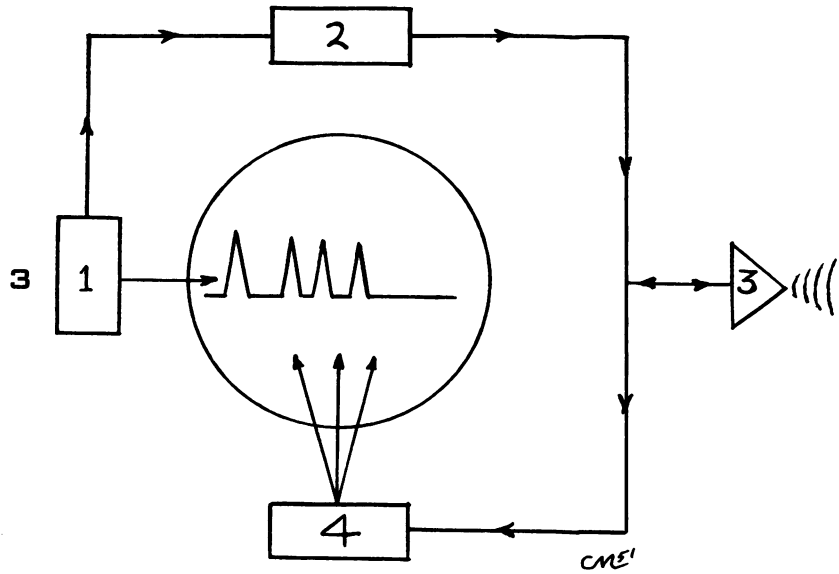


PLATE 130

FIG. 3. A schematic diagram of the apparatus. The electronic "clock" (1) starts the trace on the oscilloscope and times the bursts of sound energy produced by (2) into the piezo-electric crystal (3). Returning signals pass to amplifier (4), and are recorded continuously on the oscilloscope as shown.

FIG. 4. A typical pair of echograms obtained from a malignant lesion (case 2, adenocarcinoma). The control echogram ("A") is from normal breast tissue. The entering point of the sound into the tissues is designated "X." (The echo "Z" was frequently seen in the normal breast.) The echogram of the lesion ("B") demonstrates the greater number and strength of the echoes arising deeper in the lesion. The interpretation is described in the text. (Time base 3.0 microsecs. per division horizontally.)



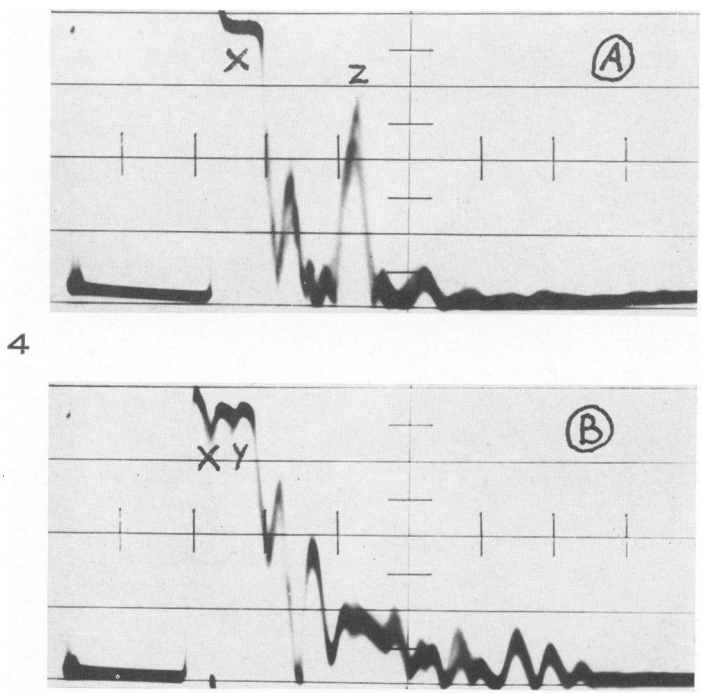


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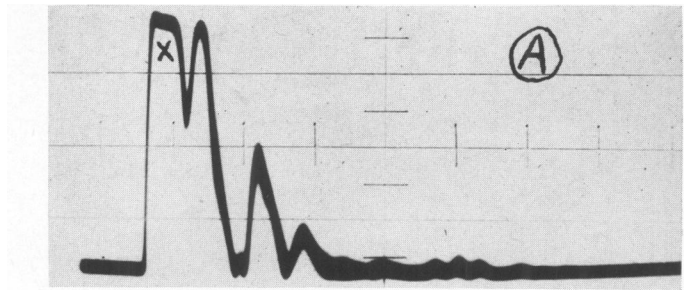
PLATE 131

FIG. 5. A pair of echograms of a benign lesion (case 15, fibro-adenoma). The normal echogram "A" shows a slightly fuller echo pattern than does the lesion "B." (Time base 3.0 microsecs. per division horizontally.)

FIG. 6. A pair of echograms from case 12 (sarcoma). The normal ("A") should be compared with the lesion ("B"). The greater strength of the echoes arising deep in the lesion is demonstrated under the broken line. (Time base 3.0 microsecs. per division horizontally.)



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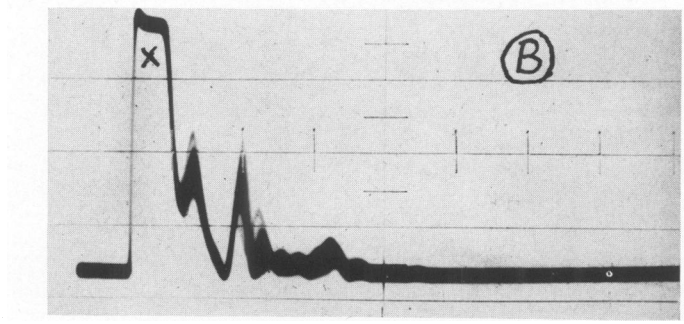
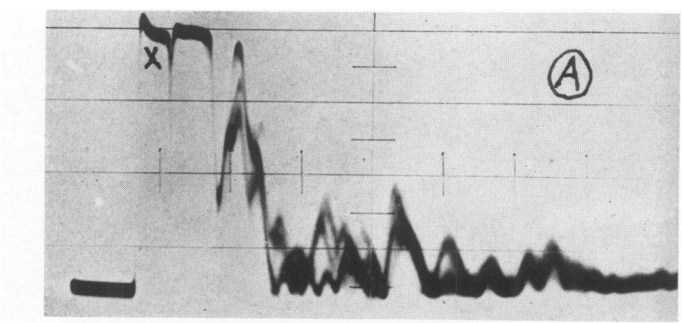




6

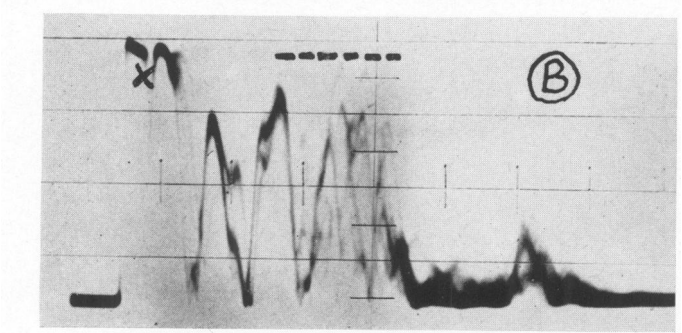
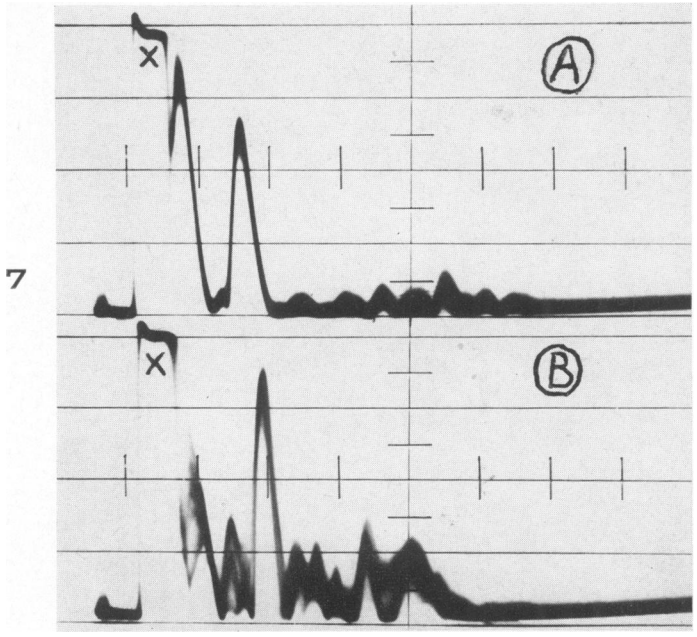
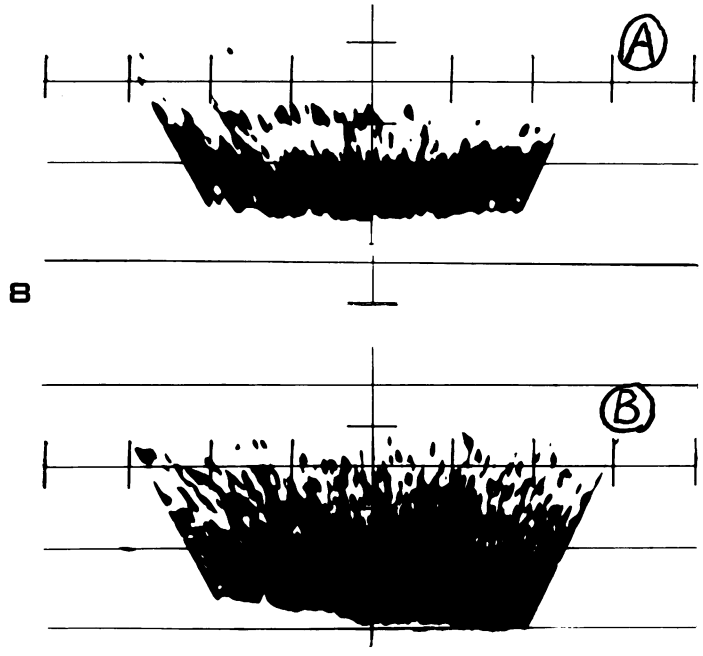


PLATE 132

FIG. 7. An apparently less marked difference in the uni-dimensional echograms from case 6 for comparison with Figures 4 and 8. (Time base 3.0 microsecs. per division horizontally.)

FIG. 8. The two-dimensional echograms of case 6. The *difference* between the normal ("A") and the lesion ("B") should be compared with the difference in Figure 7. (Time base vertical.)


7
X
A
X
B


8
A
B