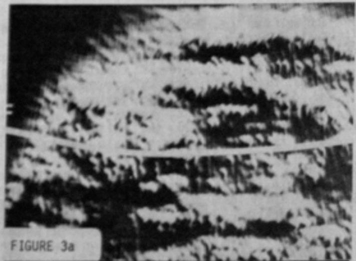

FIGURE 3a

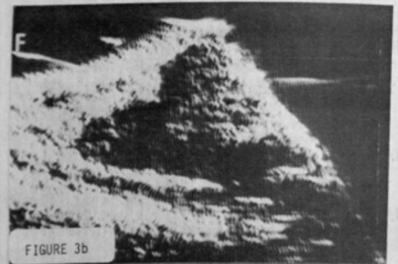

FIGURE 3b

FIGURE 4a

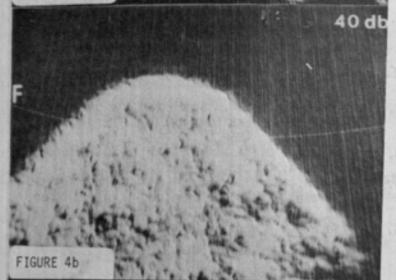

FIGURE 4b

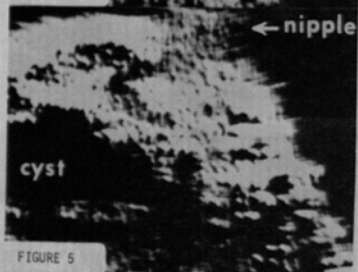

FIGURE 5

FIGURE 6

FIGURE 7

FIGURE 8

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THE POTENTIAL OF ULTRASOUND VISUALIZATION FOR DETECTING THE PRESENCE OF ABNORMAL STRUCTURES WITHIN THE FEMALE BREAST*

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ABSTRACT. At the present stage of knowledge regarding successful treatment of breast malignancies, early detection is the most significant factor in the survival of the patient. The extent to which ultrasound visualization methods can act as an adjunct to present techniques is discussed in this paper.

Introduction

Based on statistical data for the American female, in the past 35 years there has been essentially no change in the death rate from cancer of the breast.[1] In the United States, approximately 75 women per day die as a result of the disease of breast cancer.[1] In rounded figures there are, in the United States, approximately 25,000 deaths per year (27,304 in 1966) from cancer of the breast and an incidence of 65,000 new cases each year.[1]

Despite the advances in medical technology in the past half century, over 90% of patients discover their own breast tumors and, on the average, such tumors are over 5 cm in largest diameter at the time of discovery.[2,3] Further, at the time of diagnosis, more than 50% of the breast tumors have already spread to regions beyond the breast.[3] (It should be understood, of course, that there are a number of factors other than tumor size associated with the question of mortality rate and survival time following initial discovery of a malignancy.[4,5,6] Neither these aspects nor Macdonald's theory that "cure rate" is more dependent on original biologic activity of the tumor than on its stage of development at the time of detection will be discussed here[7]). The present evidence on the poor prognosis of patients with large tumors, as well as the data of a number of investigators regarding a possible relationship between stage of development of the disease and mortality rate, justifies a serious effort on the part of scientists and engineers to consider new approaches to the problem of early detection of breast malignancies.[8-12]

The primary methods available to the medical profession at the present time for detection of cancerous growths within the breast are manual palpation, (a major component of the broad category of "clinical examination" in which the physician obtains information from a number of sources, other than instrument examination, such as patient history, specific breast symptoms, etc.), X-ray examination (mammography and the more recently available technique designated xerography or xeroradiography) and thermography, an infrared detection method dependent on the thermal characteristics of the breast in the area of the tumor.[13] All of these methods are of considerable value but each has serious limitations in regard to solving the problem of <u>early</u> detection of breast carcinoma. Insofar as manual palpation is concerned, the most serious natural limitation is the location of the tumor (that is, apart from the obvious limited ability of the fingers to detect a small tumor embedded in soft, resiliant tissue). A tumor deeply embedded in a large breast could reach considerable size before manual detection was feasible. It is of interest in that regard to note that manual palpation (or the clinical examination) and mammography are considered complementary, that is, in screening studies it has been found that each modality is capable of detecting malignant tumors that the "other" misses.[3,14] Although mammography has been shown to have potential as a screening technique, it has limitations both in regard to ability to detect tumors (as emphasized by the above mentioned finding that tumors detectable to the touch may, in some instances, be unidentified on a mammogram) and in regard to possible deleterious effects of the ionizing radiation to the patient.[3,15,16] Further, mammography has its greatest potential for the middle aged and older patient. It is less successful in finding tumors in the dense, young breast and the hazards of ionizing radiation is more serious for the younger individual.[17] Thermography may have excellent potential as a screening modality. Apparently one limitation of the thermographic technique for detection of breast cancers may be associated with the presumption that the presence of a breast cancer <u>always</u> results in a detectable increase in temperature in a limited region of the breast. The reliability of this awaits confirmation since investigators using the thermographic technique have found that, on occasion, very large carcinomas are missed and no temperature variation is found despite the fact that the presence of the cancer is without question;[12,14] further, it has also been found that certain benign patholgies can also produce breast surface thermal gradients which are indistinguishable from the thermal gradients of breast cancer.[14,16]

As early as 1951, 1952, Wild and associates, using 15 MHz ultrasound, demonstrated the potential of ultrasound visualization techniques for detecting benign and malignant conditions within the female breast.[18,19] During this same period, Howry and co-workers developed the so-called ultrasound compound scanning technique and using a lower frequency than Wild, applied this method to study of the breast (20). Both of these early investigators indicated the necessity for solving instrumentation problems before the ultrasonic technique could realistically be used as a clinical tool, especially in regard to the differentiation of the differences between benign and malignant echogram patterns.[21-24] Howry, in particular, pointed out specific problems associated with true identification of anatomical structures with complex geometry or steep angular borders and emphasized the type of identification errors resulting from poor axial or azimuthal resolution. Japanese investigators carried out considerable clinical research on the use of ultrasonic techniques for breast examination.[25-30] Other investigators, in various parts of the world, have carried out individual studies on possible application of ultrasonic visualization techniques for detection of breast pathologies.[31-36] The results to date of all of these investigations are of considerable interest, but are not sufficiently definitive, particularly in regard to succinct differentiation between <u>solid</u> benign tumors and malignant tumors to recommend that immediate application of this technique as a reliable clinical method - except in terms of a research clinical tool.

The present paper concerns a specific experimental approach in regard to application of ultrasonic visualization methods to the study of breast pathologies. This "approach" may be summarized as follows: in the initial studies, design the acoustic visualization system as an advanced laboratory instrument which can be used for basic studies on excised tissue and on experimental animals, yet is a safe and reliable system for scanning the human subject, but is <u>not</u> a prototype of a clinical instrument; second, after obtaining sufficient basic data on the potential of the visualization technique for detecting pathological states of the female breast, then design a prototype clinical instrument which meets the requirements of reliability, safety and simplicity of operation but also incorporates those features of operation, found in the study of the more elaborate instrumentation, as necessary components for obtaining definitive diagnostic information. The first part of this approach is based on the success of this method in earlier studies on brain tissue and on liver tissue with a computer based visualization system [37-44]. The overall rationale of the above approach of using elaborate instrumentation included a number of considerations, such as accuracy of location of any apparent abnormality within the breast, but its primary aim was detection of abnormalities in the early stage of their development. Further, the problem of early detection was approached from two viewpoints, namely, the straightforward one of having instrumentation capable of recognizing and accurately defining a solid tumor or cyst of quite small dimensions, that is, of the order of a few mm., secondly, a more fundamental approach, namely, determination if acoustic characterization of the normal breast (for all age ranges of the adult female) can be obtained by study of the breast echogram pattern, with the specific long range goal of developing the capability for detection of pathological changes in breast tissue prior to the formation of a tumor, by noting significant changes in the normal echogram pattern.

Materials and Methods

The basic system used in this study is an ultrasonic pulse echo method in which short bursts of low intensity (average intensity less than 50 milliwatts) ultrasound are generated in a piezoelectric transducer, and transmitted through a water path to the breast. Part of this ultrasound wave is transmitted through the breast tissue and part is reflected back from the various structures within the breast; these reflected sound waves are received by an acoustic transducer (this may be either the sending transducer or a separate receiving transducer), are converted into electrical signals, amplified and displayed on an oscilloscope. Photographs (Polaroids in the studies reported here) of these two dimensional images of the reflected ultrasound constitute the so-called echogram. In a general sense, the sound leaving the transducer can be considered a pencil beam which penetrates the tissue from the skin surface to the base of the breast; this pencil beam is moved across the breast (by motion of the transducer) so that a thin "cut" (of the order of 1 mm in thickness) is made by the sound wave as it penetrates the tissue. (So-called intensity-modulated, or brightness modulated (B-mode) display, in combination with the relative motion between subject and transducer yielding a B-mode scan presentation.)The brightness of the spots on the CRT are proportional to the intensity of the reflections received back from specific tissue structures and the relative positions of these bright spots correspond with the position of each reflection source of the scanned plane of tissue. Sector scanning (transducer rotated about its axis to produce a "pie-shaped" section of tissue) was used in the computer based instrumentation; linear scanning (simple lateral motion of transducer across breast) was applied in a relatively simple, non-computer based, clinical prototype instrument.) Unlike an X-ray image, which displays a view through the whole breast structure, each individual echogram represents an image of the structures encountered in a 1 mm slice (this may be either horizontal or sagittal (see Fig. 1) of breast tissue; in fact, such echograms might be thought of in terms of whole breast histological sections. Any number of such single scans can be taken at whatever spacing interval is desirable; for example, in most cases,in the present program, a series of horizontal scans were carried out, starting at the superior border of the breast taking a scan every 5 mm (except over the nipple region and areola where scans were taken every 2 mm), completing the scans at the inferior border.[45-47] Earlier publications discuss the specific details of the acoustic, electronic aspects of the system.[37,38]

The majority of the studies considered in this paper were carried out with the wide aperture, focused mirror type transducer system outlined in the previously cited publication; studies were also carried out with wide aperture, focused transceivers (i.e., same transducer acts as both sending and receiving unit). Two relatively broad banded transceivers were used in these studies (1) a lead zirconate titanate (PZT-7) unit of 9.0 cm in diameter with a machined curvature providing a focal length of 20.5 cm; this unit has a mid-band frequency of 1.7 MHz and an azimuthal resolution of 0.9 mm, (2) a lead metaniobate (LM 302- a ferroelectric ceramic with a low mechanical Q) unit of 5.0 cm diameter with an attached epoxy resin plano-concave lens providing a focal length of 10.2 cm; this unit has a mid-band frequency of 2.2 MHz, and an azimuthal resolution of 0.6 mm. Both transceivers were highly damped with an epoxy resin backing allowing short (less than 1 μsec) energizing pulses and yielding range resolution equal or better than the azimuthal resolution. The system has been designed in such a manner that it is very simple to accommodate to different acoustic transducers, since the primary method of investigation is a continuous evolvement of transducer designs. The translational and angular motions of the transducers are under the control of the computer, thus allowing considerable accuracy of scanning. The output signals of the transducer are fed into an attenuator, calibrated in decibels from 0 to 80 db. In addition to the transducer motion control feature, the computer has another essential function; it allows reception of acoustic signals from specified depths of tissue, in the region of the focus of the transducer, with (if so desired) complete rejection of signals from adjacent areas (the so-called banding technique).[37,38,49] Under the control of the computer, each of these "bands" or selected tissue depths in the region of focus of the transducer, can be displayed on a single echogram. Therefore, the computer and associated electronic instrumentation can act as an integral part of the biological experiment by assuming the functions of a variable gain control. Echograms can be produced which have the advantage of a multiple focus combined with a variable gain. The computer control, in combination with the wide aperture, focused transducers, allows wide dynamic range combined with good azimuthal and axial resolution.

A non-computerized, portable, B-mode scan visualization system was also used.[48]

Experimental Design

The two distinct approaches to early detection of breast pathologies, outlined in the introduction, were not pursued as completely separate problems. Attempts were made to fulfill the requirements of both goals in the experimental designs. In that regard emphasis was placed on detailed visualization experiments on subjects with normal breasts over the age ranges of young, middle aged and old, followed by study of patients with benign pathologies, prior to the consideration of patients with malignant growths. Studies of the variation of normal subjects is critical to quantitative interpretation of breast visualization echogram data. Each subject was examined by a physician prior to ultrasonic scanning and a clinical history obtained. For those subjects for whom mammograms were available, the radiologist was requested to interpret (in addition to the usual interpretation of the possible presence of any abnormality) the mammogram in respect to the relative amounts of fat, glandular and connective tissue in the breast. Subject selection was designed to fulfill specific experimental goals: the subjects' ages

ranged from 19 to 74 and included subjects with small, medium and large breasts. Whenever such tissue could be obtained, the excised benign tumors were scanned and the results correlated with that of the in vivo breast.

In addition to the physiological and biological aspects briefly outlined above, a number of other features were critical to the experimental design. Of first importance was a quantitative approach to study of the echogram data. For every series of experiments, the system was calibrated,in order to detect any change in sensitivity or resolution characteristics of the system. All experiments were carried out under controlled conditions of instrumentation parameters in order to make precise comparisons of the results of studies of the various types of subjects, such as comparison of the echograms of the young subject with that of the middle aged individual, or comparison of the echogram of a normal subject with that of a subject with a benign or malignant pathology.

It is important to understand that most scans were carried out under conditions of single focus rather than the multiple focus technique described under Materials and Methods. Early in this study (see Results) it was determined that the single focus was adequate, at the present stage of knowledge, for defining breast characteristics and for locating tissue abnormalities. A "search technique" was evolved in which both breasts could be completely scanned in a comparatively short time with the aid of the computer controlled motion system. In this technique, the attenuator gain was used as a variable while a single focus technique was maintained. If an area of interest was found, then, for that specific area, the technique of multiple focus, multiple gain was applied.

Breast characterization studies included experimental determination of the acoustic velocity of the in vivo breast over the age ranges 19 to 74.[47,48](This initial velocity data and subsequent data obtained at the Commonwealth Acoustic Laboratories in Australia is reported in reference 50.) Interpretation of the echogram images of breasts of various types and ages included consideration of the values obtained for tissue velocity, correlated with the data provided by the radiologist regarding the tissue content of the specific breast.

Early in this study, a technique was evolved which allowed visualization of the breasts (with the subject lying on her back) without any intervening covering other than the 37°C water bath.[45,47] This technique has also been used by other investigators.[35,36] The purpose of this approach was to determine the echogram characteristics of the breast without any physical distortion of the breast tissue by use of a plastic water bag as a coupling medium between breast and transducer (water bag coupling is a standard technique in tissue visualization). A series of experiments were carried out, on the same subject, in which comparisons were made of the echograms obtained with freely floating breasts and echograms obtained with the breast covered by various types, size and thicknesses of plastic water bags.

Results

Space considerations preclude presentation of sufficient number of echograms to demonstrate and to adequately discuss all the results obtained. Earlier reports include some aspects not detailed here.[45-48] The following is a brief summary of some of the findings: (1) success was obtained in acoustically characterizing the breast tissue of a variety of types of subjects. One of the most significant findings in that regard is the characterization of the young breast containing a normal content of glandular tissue. Figure 2a,b shows a scan taken over the nipple region of a 19 year old subject at two different instrumentation sensitivities. The echogram shown in 2a with the higher db number (in the system discussed here, meaning higher attenuation of the signal leaving the transducer, therefore, essentially, less sensitivity than the lower db numbers) is characteristic for the young subject.The area of decreased reflections below the nipple region is the region of glandular tissue. This conclusion regarding the typical echogram pattern is based on detailed studies of twenty one young subjects, using different transducers and correlating the findings with acoustic velocity and mammogram data. The echogram on the right is shown to indicate that if sufficient instrumentation sensitivity is available, reflections from the glandular tissue region can be obtained. This reflection pattern, however, is different from that of a postmenopausal woman.

Postmenopausal breasts normally have greatly decreased glandular tissue and increased deposits of fat, interlaced with connective tissue. Figure 3a shows a typical echogram of a scan over the nipple area of a postmenopausal breast; for comparison, Figure 3b shows an echogram of a scan over the nipple area of a young subject (same transducer). The differences are obvious. Interpretation of the echogram images of the postmenopausal subject were also correlated with the acoustic velocity data and the mammogram findings. It has also been found that in the case of atypical young subjects, that is, subjects who despite their young age have breasts with large deposits of fat and small amounts of glandular tissue, that such breasts yield echograms which are very similar to those of postmenopausal subjects.

Echogram 4a,b demonstrates the ability of the visualization technique to detect a benign pathology by means of characterization of the breast echogram image. These two echograms were obtained under precisely the same experimental conditions. Therefore, if the breast tissue of these two young subjects were the same the echograms would be similar. Echogram 4b is not a normal echogram pattern; it is characteristic of that of an individual with fibrosing adenosis, a benign condition of the breast in which there is a proliferation of connective tissue. Apparently there would be no difficulty in distinguishing such cases by means of ultrasonic scanning.

The results illustrated in Figures 2 - 4, as well as other findings of this study not discussed in this paper, indicate that ultrasound visualization methods may have good potential for detecting malignant pathologies of the breast, prior to formation of clinically detectable tumors.

(2) Figures 5 and 6 demonstrate the ability of ultrasound visualization techniques to locate confined pathologies such as cysts or solid benign tumors. A large, fluid filled cyst in the breast of a middle aged subject appears in this echogram as a circumscribed "hole" with a piece of intervening tissue strung along its lower border. There is no difficulty in detecting cysts, even those of quite small dimensions. Normally the borders of cysts are sharply defined on the echogram; no reflections appeared in the liquid filled cysts at the maximum sensitivity settings available for this study. Figure 5 is of additional interest because it demonstrates the ability of the system used in this study to differentiate nipple structure.

Figure 6 (same patient as that shown in Fig. 5)also demonstrates a cyst and, in addition, a solid benign tumor, a fibroadenoma, on the wall of the cyst. This fibroadenoma shows internal reflections in contrast to the cyst. Studies on excised fibroadenomas clearly demonstrated reflection from the internal structure of the tumor.

(3) Figure 7 is an echogram of a young, normal subject who was scanned with a water filled plastic bag as the coupling medium between breast and transducer. Scans of this same subject, taken with the breast freely floating in water, were similar to that shown in 2a so that this scan should be compared to that figure. Consid-

erable tissue structure information is lost by use of such coupling techniques. It is not possible to define nipple structure when such coupling techniques are used and the breast tissue is sufficiently distorted to make tissue characterization difficult. The effects of the use of a water bag are clearly evidenced in the Japanese studies.[30]

(4)Figure 8 is an echogram resulting from a scan of a middle aged subject with a clinically confirmed carcinoma located slightly below the surface of the skin. For a specified sensitivity setting, this carcinoma was evidenced on the echogram by a clearly defined shadow in the area below the tumor. This result may be significant because such "shadows" should be easily differentiated from the echogram patterns of solid benign tumors or liquid cysts. Unlike benign tumors which show posterior borders of the tumor outlined on the echogram, this malignant tumor apparently attenuates the sound,so that, for this particular instrument sensitivity, a shadow is cast below the tumor. (Studies carried out in Japan on breast carcinoma are of interest in regard to this finding.[30,51]) With increased sensitivity settings, it is possible to define structure within this shadow region but this structure is distinct from that of benign tumors. This result needs to be confirmed on a large number of subjects; further,since there is more than one category of types of malignant breast tumors, detailed studies are underway on the echogram characteristics of the various types of tumors.[52,53]

(5)Finally, it has been determined that essentially all of the results obtained above can be duplicated with a comparatively simple, noncomputerized system. Although multiple focus echograms are distinctly better than single focus echograms in regard to resolving power, it is possible, at the present stage of knowledge, to provide many seriously needed answers on breast pathologies, with wide aperture, single focus systems. The significance of this result, particularly in regard to what has been considered the inherent limitations of acoustic visualization systems for medical applications, can not be discussed here.[54,55] However, this finding, in association with the specific results found on breast carcinoma, is most encouraging in regard to the potential of a relatively simple ultrasonic visualization system for detecting breast pathologies. The design of such clinical apparatus should include a number of bioengineering aspects which are critical, including the method of coupling the breast to the transducer and considering the effect of the changing density and resiliancy of breast tissue with aging.[47]

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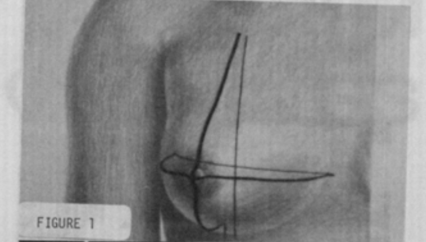
FIGURE 1

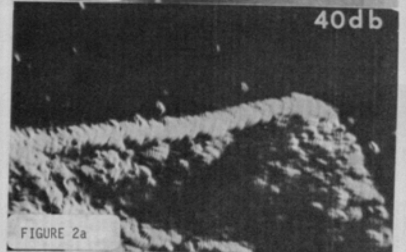

FIGURE 2a

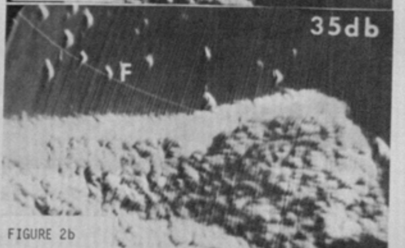

FIGURE 2b