From: ACOUSTICAL HOLOGRAPHY, Vol. 7
Edited by Lawrence W. Kessler
(Plenum Publishing Corporation, 1977)

THE USE OF ULTRASOUND METHODS TO DETECT CHANGES IN BREAST TISSUE WHICH PRECEDE THE FORMATION OF A MALIGNANT TUMOR*

E. Kelly Fry, Indiana University School of Medicine and Indianapolis Center for Advanced Research, Indianapolis, Indiana 46202 U.S.A.

INTRODUCTION

The approach taken, to date, by most investigators studying the use of ultrasound visualization for breast examination has been traditional, namely: scan the region of the palpable mass; compare the imaging pattern of the mass, as it appears on the echogram, to known features of benign and malignant tumors, such as wall contours; attempt to identify the physical character of the mass by its effect on reflection and transmission of the ultrasound beam; and finally, strive to detect smaller and smaller masses using this approach. In view of the fact that there is a large population of women presently harboring an undetected malignant mass within their breasts and in consideration of the statistical data on life span of the breast cancer patient in relation to size of the tumor within the breast at the time of initial treatment, this approach is valid.[1-3] However, in consideration of the known systemic nature of breast cancer, that removal of the breast is still the primary treatment even under the circumstances of identification of minimal malignant masses, and in view of the potential of ultrasound to detect pre-malignant changes in breast tissue, this limited approach is not sufficient.

Although earlier investigators recognized the continuing lethal effect of breast cancer over the lifetime of the patient, and thus the systemic nature of the disease, it is only recently that this systemic aspect has been emphasized.[2-5] The average patient who undergoes surgical treatment for a malignant mass within the breast, including the classical radical mastectomy procedure, will have a decreased life span as a result of recurrence of some aspect of the disease associated with the systemic factors.[3] The recurrence may

* Supported by Showalter Residuary Trust, Indianapolis, Indiana.

take place decades after the initial surgical procedure. Apparently, the disease is already systemic for most of the United States women who currently receive a diagnosis of breast carcinoma and undergo surgical treatment as a result of that diagnosis.[3] Clearly, there is a need for a diagnostic technique which will recognize the presence of breast carcinoma prior to the formation of an overt mass.

Before discussing possible approaches to this problem, it is important to emphasize here that recognition of the systemic nature of breast carcinoma should not, in any way, decrease efforts to increase the efficiency of detecting small malignant masses in the breast since both earlier and current clinical studies clearly indicate that there is a significant relation between the life span of the patient, the size of the tumor, and extent of nodal involvement at the time of initial treatment.[1-3,6-8] There are many factors involved in this data, (including the histological character of the malignant mass) which cannot be discussed here since the approach of detecting small masses in the breast is not the primary subject of this paper. However, it is clear from existing statistical data that efforts to identify small malignant breast masses prior to nodal metastasis should continue. At the present time, knowledge of the basic character of breast carcinoma is extremely limited. It is known, however, that (a) there is a large population of generally older women (well over the 90,000 United States women whose tumors will be detected in the coming year) who now harbor a malignant mass within their breast; and, (b) there is a population of younger women whose breasts are already undergoing the changes that precede the formation of a malignant mass. Therefore, two separate instrumentation approaches should be taken to the breast carcinoma detection of problem, namely: (1) improvement of all presently existing examination techniques with a goal of accomplishing reliable detection of malignant masses less than 0.5 cm in largest diameter and (2) development of instrumentation with the capability of detecting those breast tissue changes which precede the formation of a malignant mass.

Since a number of authors have found a relationship between breast carcinoma and ductal hyperplasia and some have suggested that detection of enlarged ducts by mammographic techniques can be used to increase the efficiency of breast carcinoma detection, ultrasonic detection of disturbed ductal structures may prove to be a valid approach to early detection of malignant changes within breast tissue.[9-17] This paper discusses the results of the present author's and associates' earlier investigations on detection, by ultrasound visualization techniques, of enlarged ductal structures in excised breasts. Also included are the preliminary findings of current studies on detection of ductal structures of _in vivo_ subjects by an ultrasound B-mode visualization system.

BACKGROUND

The normal procedure in the case of a patient undergoing a biopsy to determine whether neoplastic tissue is present in a breast mass is surgical excision of the mass, and frozen section examination of the excised tissue. If carcinoma is diagnosed, a mastectomy is carried out and both gross and microscopic examination of the breast and the tumor follow. Unfortunately, however, sectioning and histologic staining, in most cases, is confined to the tumor and selected areas within the breast. The major mass of breast tissue remains unexamined except for gross inspection. It is not possible, therefore, to correlate pre-operative diagnostic examination of the breast by mammography, xeromammography, or ultrasound with the possible overall tissue changes in the pathological breast or to a sufficient degree, with the tissue changes in the area surrounding the tumor and in the tumor itself. Adequate correlative information on the generalized changes in the breast and in the immediate region of the tumor requires whole breast sectioning and histologic staining.

Gallager and Martin's approach to the problem of devising a method for correlating pre-operative examination data with the tissue changes that are presumably present in breasts containing a malignant mass is to have a mastectomy performed without any surgical intervention in the area of the tumor and to study the breast tissues by whole breast sectioning and histologic staining.[9-12] Such a procedure is only carried out in the case of patients whose breast carcinoma can be diagnosed with certainty by x-ray and needle biopsy techniques. A partial summary of the early surgical specimen preparation technique used in the Gallager and Martin studies is provided in the following excerpt:[9]

> "To prepare a radical mastectomy specimen for whole organ sectioning, the axilla is removed, and the breast (with its attached pectoral muscles) is divided into 3 or 4 parallel blocks, each 6 to 8 cm thick. The plane of sectioning is selected by reference to the mammograms. Each block is molded into a shape conforming as nearly as possible to that shown in the mammogram and is fixed in this position, dehydrated, infiltrated and embedded in paraffin. Sections 12 to 20 microns thick are cut at intervals of 0.5 to 1.0 mm. Thus, a series of slides is prepared which represents the entire sectioned area 3-dimensionally. In the earliest specimens studied, the entire breast was sectioned. However, it was learned that in older patients the extreme lateral and medial parts of the breast are composed almost entirely of adipose tissue. Accordingly, in subsequent specimens only the center blocks have been cut, the outer ones being embedded and reserved for later sectioning if necessary".

> "Assembled sections and mammograms are examined by a radiologist and a pathologist working together. Immediate comparisons and correlations are made and recorded."

A number of experimental goals were included in these histopathologic/mammographic studies but the initial, primary aim was improvement in the detection of small, early breast tumors by mammographic techniques. The results obtained in these investigations on the histological structure of overt tumor masses are significant to the problem of detecting such masses by ultrasonic techniques. However, since detection of small breast masses is not the subject of this paper, these specific results will not be discussed in this paper.

In more than three quarters of the originally examined breast specimens containing invasive carcinoma, Gallager and Martin found areas of intraductal carcinoma or intraductal hyperplasia with epithelial atypism.[9] Such involved ducts are dilated or surrounded by increased amounts of hyalin connective tissue. The subsequent hyperplasia of the ductal structures is sufficient to allow detection by mammogram inspection. Although the affected ducts may be located close to the malignant mass, this is not necessarily the case. They may be widely distributed to remote sections of the breast.[9-10] The data of Gallager and Martin, as well as the findings of previously cited authors, seems to indicate that hyperplasia of ductal structures and carcinoma are causally related.

In an effort to correlate the echogram patterns of malignant breast tumors with the structural and histological features of such tumors, a cooperative ultrasound/histopathologic investigation was undertaken with the previously referenced H. S. Gallager and the present authors and associates.[18] The fundamental approach consisted of detailed ultrasound visualization of the previously described formalin-fixed breast specimens and comparison of the echograms with the histological sections. This early research was not directed at a specific study of the ductal structures. Rather, its primary aim was to determine the relationship between the structure of various classes of malignant tumors and the attenuating or non-attenuating character of such structures in respect to the applied ultrasonic beam. These aspects are not detailed in this paper. Only the observations made on enlarged ductal structures of one of the examined specimens is discussed and related to the subsequent attempts to detect ductal structures of normal subjects.

METHODS AND PROCEDURES

A. Ultrasound Visualization of Formalin-Fixed, Excised Breasts Containing an Intact Malignant Tumor

More than one type of ultrasound transducer was used to study the excised breast tissue but the data presented in this document was obtained with a computer-controlled, B-mode visualization system, used in conjunction with a 5 cm diameter, 10 cm focal length lead zirconate titanate transceiver with a frequency of 2.5 MHz. Earlier publications discuss the specific details of the acoustic, electronic aspects of the system.[19,20]

The transducer motion consisted of a sector sweep with the transducer pivoting about its axis for an angular motion of $\pm$ 15 degrees. After each single scan, the transducer was moved in appropriate linear steps (2 to 5 mm) and another scan was recorded. This method of operation was continued until, essentially, the complete specimen of tissue was scanned. For a sagittal (vertical) scan, the transducer was positioned so that it swept the tissue along the superior-inferior axis. For transverse (horizontal) scanning, the transducer was turned 90 degrees from the position set for sagittal scanning. Polaroid photographs of the information presented on a CRT were used to record the breast scan information.

Essentially a search technique for the purpose of (1) identifying on the echogram the normal components of the tissue under study, and (2) recognizing any pathological structures within the normal framework was used in the study of these excised breasts. In order to relate data recorded on the echograms to specific areas of the tissue, an anatomical landmark on the tissue (such as the center of the nipple or the center of a prominent skin discoloration over the area of pathology) was selected, and a highly reflective and attenuating acoustic target was placed in this landmark. A scan was made with the target in place and the two linear coordinates (X and Y) and the depth coordinate (Z) of the transducer position recorded. The echogram of the breast tissue with the target in place showed a distinct, easily identified reflection of the target. Therefore, subsequent scans of the tissue with target removed could be directly related to the chosen anatomical landmark. The data on the X, Y and Z coordinates was automatically printed on each echogram with the aid of the computer.

The response signals of the transducer were fed into an attenuator calibrated in decibels from 1 to 80 db. Prior to carrying out the search procedures, appropriate ranges of attenuator settings were determined, as well as the best location in the tissue for the focus of the ultrasound beam. In addition to the method outlined above for obtaining echograms with sufficient information for the identification of normal structures and the detection of pathological growths, another more complex method was used which can yield echograms with a multiple focus and with a variable db setting for each focal region. This was carried out with the aid of the computer and gating circuitry for the display system.[19] This multiple focus technique indicated that sufficient information could be obtained with the single focus to allow detailed scans by this method.

B. Ultrasound Visualization of Breasts of In Vivo Subjects

The instrumentation applied for the examination of breasts of in vivo subjects was a linear scan, B-mode visualization system designed to obtain information useful for clinical application but not to fulfill the function of a routine clinical instrument.[21] The general instrumentation system included: pulsers with PRF of 500 to 1000/sec. and rise times varying from 20 nsec. to 0.1μsec. (for echograms displayed in this paper, PRF 1000/sec., rise time of 0.1μsec.), a zero to 80 db attenuator preceding a logarithmic amplifier, a display system consisting of a PEP 400 scan converter, a 14" GBC monitor, a 9.5 × 7.5 cm dedicated monitor and a Polaroid camera. Various amplifiers have been designed and tested in an attempt to obtain adequate amplification, over a wide frequency spectrum, of the signals received from fine structures of the breast (present units under test have 10μv sensitivity and a bandwidth of 600 KHz to 13 MHz; for echograms displayed in this paper, the amplifier had a sensitivity of 40μv, frequency response of D.C. to 5 MHz, and a dynamic range of 80 db). A series of relatively small diameter (1.9 cm), concave disc-type transducers with center frequencies from 2.25 to 10 MHz were specifically designed for the breast visualization study. A lead metaniobate, 1.9 cm diameter, 7.5 cm focal length transducer with a midband frequency response of 4.4 MHz and a bandwidth of 3 MHz just above the noise and 1 MHz at the 3 db point was used to obtain the echograms displayed in this paper (for in vivo subjects with a direct water coupling between transducer and breast). For the two echograms shown in this paper for in vivo subjects with a water bag coupling between transducer and breast, a lead metaniobate, 5 cm diameter, 10 cm focal length with a 3.0 MHz frequency response and a bandwidth of 3 MHz just above the noise and 0.5 MHz at the 3 db point was used.

The overall instrumentation system, but in particular the transducers and amplifiers, were initially tested for probable adequacy of display of structures such as ductal structures by using fine grain natural sponges as test targets. In addition to using the fine grain of the sponges as breast phantoms, a variety of types of solid structures, varying in diameter from 0.25 mm to 5.0 mm, were either embedded in the sponges or used on the surface as test targets of known dimensions and locations. These structures included nylon threads, 1 mm plastic hollow tubing, steel wires and tungsten araldite attenuating spheres.

RESULTS

Prior to discussing the results obtained in these studies, it is of value to consider the primary features of the ductal structure of the female breast. In the lactating breast, milk is conducted to the nipple by means of excretory ducts. These ducts are part of the glandular system, which, on a macroscopic scale, consists of fifteen to twenty lobes arranged radially around the nipple, with each lobe having a single excretory duct. From the nipple surface, the ducts run dorsally and essentially parallel and at the base of the nipple diverge, first forming a wide reservoir (ampulla or sinus lactiferus) and then proceed in a complex pattern of fine sub-divisions to the peripheral regions of the breast. Each of the terminal branches of a duct lead into small structures called lobules, containing the basic secretory tissue (acini or alveoli). There is varying information on the size of the primary ducts. Martin and Gallager indicate diameters of 0.5 to 0.8 mm in the nipple and subareolar region.[12] Earlier authors have indicated diameters as large as 1.5 to 2.5 mm; for the ampulla region, generally located just below the areola, diameters as wide as 5 to 9 mm have been reported.[22,23] Figure 1 is an artist's view of the primary breast structures in the field of view of a single, transverse ultrasound scan across the nipple. The fine acini structures have been exaggerated in size in order to demonstrate the glandular terminations of the ducts.

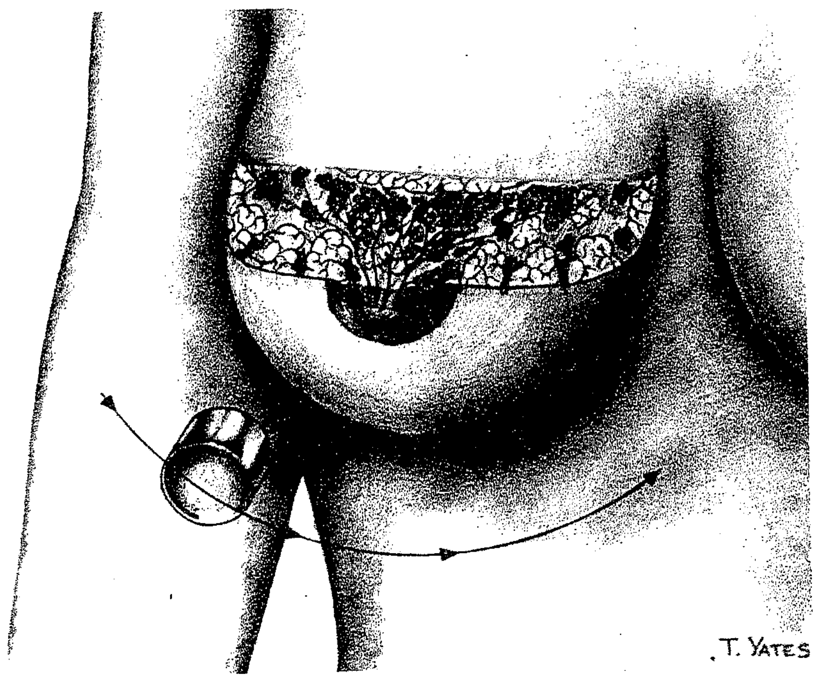

Figure 1

The echogram patterns obtained from scans of the formalin-fixed whole breast of a 39-year-old subject with a confirmed diagnosis of breast carcinoma indicated the presence of discrete, vertical, tract-like structures in the general area beneath the nipple and areola, with the tracts apparently traversing the areas from the deep regions of the breast to the nipple surface. These tissue tracts can be observed in the echograms shown in Figure 2, which resulted from a sagittal scan of the excised breast; i.e., a scan at right angles to the plane shown in Figure 1. Although the sagittal scans appeared to demonstrate the tract-like structures with greater clarity, they were also visible on transverse scans, as demonstrated in Figures 3a and 3b. (The echogram shown in Figure 3b was obtained by scanning the same tissue plane as that of Figure 3a, but at a 5 db less attenuator setting).

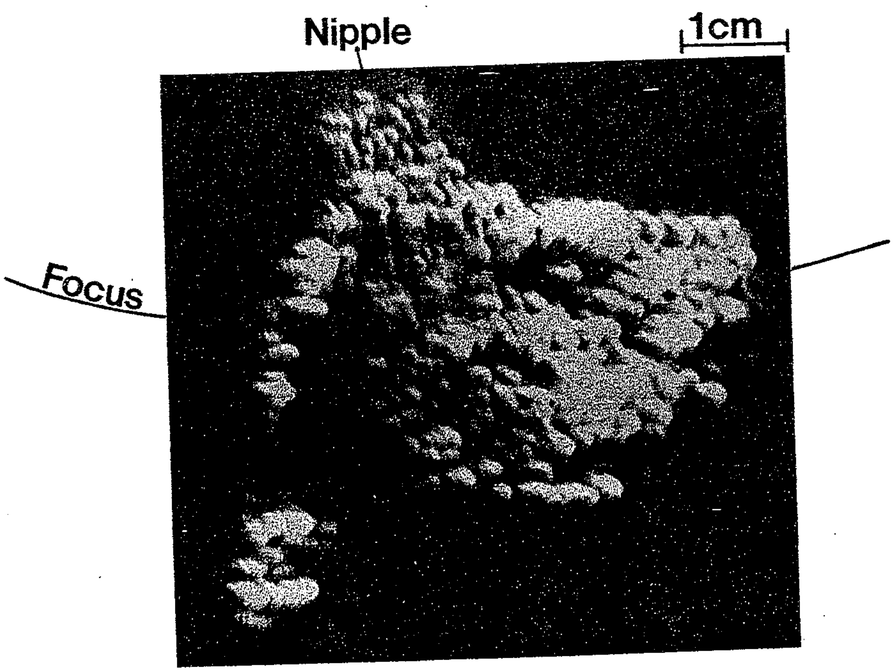

Figure 2

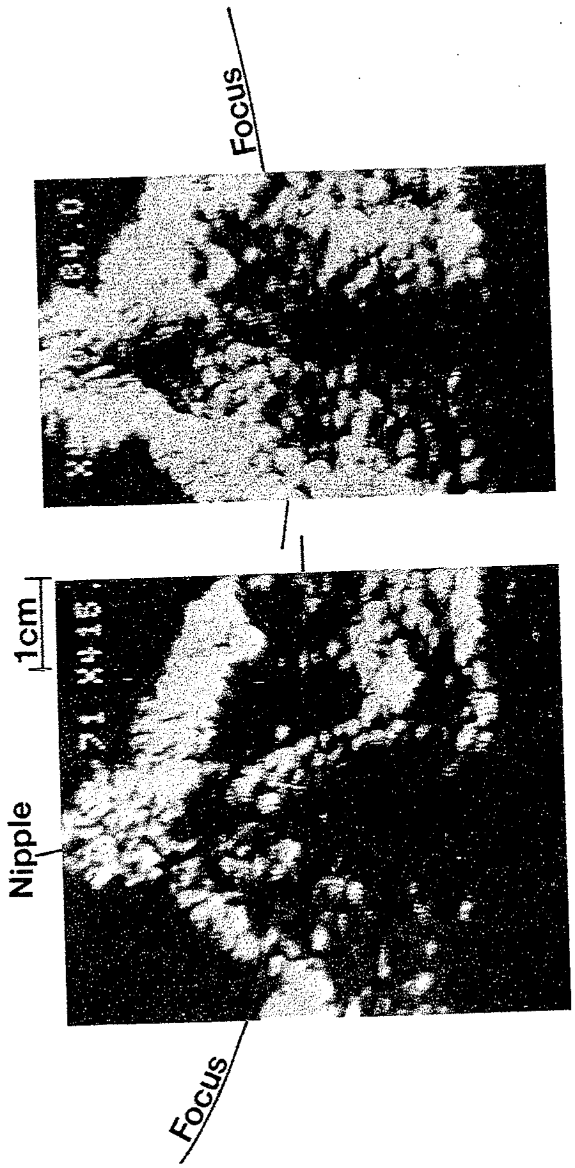

Figure 3a (left) and 3b (right)

The general character and location of the echoes located beneath the nipple in Figure 2 would lead to the tentative conclusion that ductal structures are being visualized. This assumption was confirmed by the histological sectioning and staining. Figure 4 is a duplication of just one of the histological sections for the region below the nipple. Some of the enlarged ductal structures are quite obvious in this cross-section.

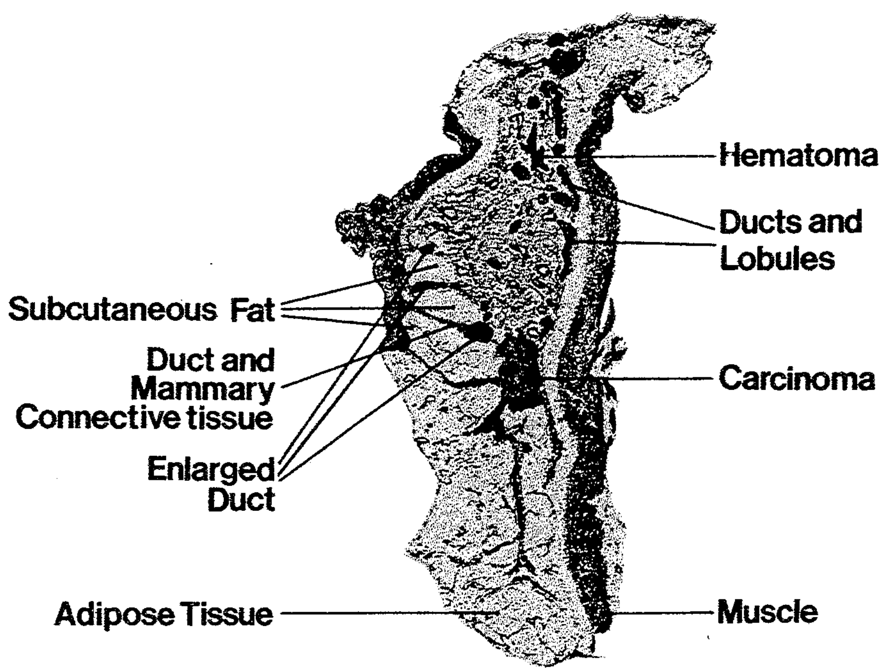

Figure 4

After considering the need for a non-ionizing radiation method for examination of the ductal structures of the breast, and after reviewing the earlier studies on excised breasts, investigations were recently initiated on application of ultrasound visualization techniques for detection of ductal structures of normal subjects. At the present time, this investigation is in a preliminary stage. One practical initial approach to the problem of ultrasonically detecting the fine tube-like ductal structures is to use relatively high frequency, focused transducers to obtain adequate resolution and to confine the search to the region directly beneath the nipple and areola, a region where the ducts have their largest diameter and are greatest in number per unit area. Until such time that the more advanced transducers (such as phased array or synthetic aperture) are readily available for ultrasound breast examination, simple focused transducers, either of the lens or disc type, can be used in clinical programs to obtain much-needed data on breast structure. Small diameter, concave disc units are particularly useful because the three basic design parameters of such transducers---1/2 diameter, wavelength and radius of curvature of the disc---can be formulated in varying combinations and test units can be fabricated with relative ease. Thus, the importance of factors which probably have a specific influence on successful detection of discrete structures in the breast (such as attenuation, beamwidth, transverse (D_t) and axial (D_a) focal region diameters, pressure amplitudes in regions on either side of the focus) can be experimentally determined.[24-27] Further, although small diameter transducers have decreased sensitivity in comparison to the larger diameter discs, they have distinct advantages in regard to designing relatively simple clinical instruments for examination of the breast. The units mentioned in this paper were originally designed for a hand-held, rapid scanner.

Earlier studies of the author and associates demonstrated the enhanced value of direct water coupling between breast and transducer in comparison to the more traditional water bag technique.[20,28] Nonetheless, in view of some of the practical aspects of the water bag coupling technique, a clinical-research study on the possible advantages and limitations of a modified water bag technique, when used in conjunction with wide aperture focused transducers, was undertaken.[21] Figures 5 and 6 (3 MHz transducer) resulted from this study rather than the present specific efforts to detect normal duct structures. They are shown here to illustrate that it is possible to detect fine structural features, including ducts, while using the water bag method but, in comparison to direct water coupling, this method is less effective. As can be clearly seen in Figure 5, some of the ductal structures below the nipple are evident but they cannot readily be traced to their exit point at the nipple. In detecting discrete breast structures, the placement of the focus of the transducer is significant. One aspect of this is illustrated in Figure 6, which represents the case of the focus just above the

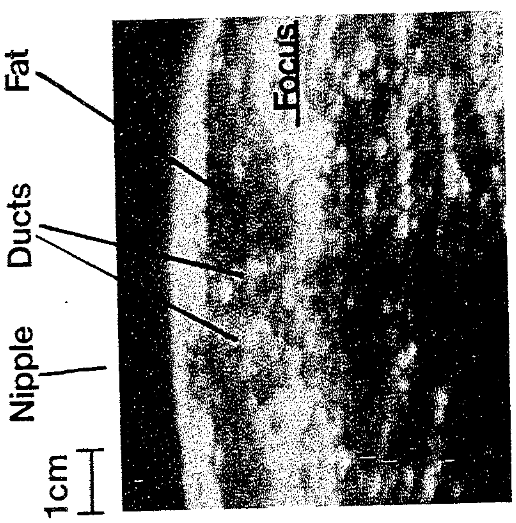

Figure 5

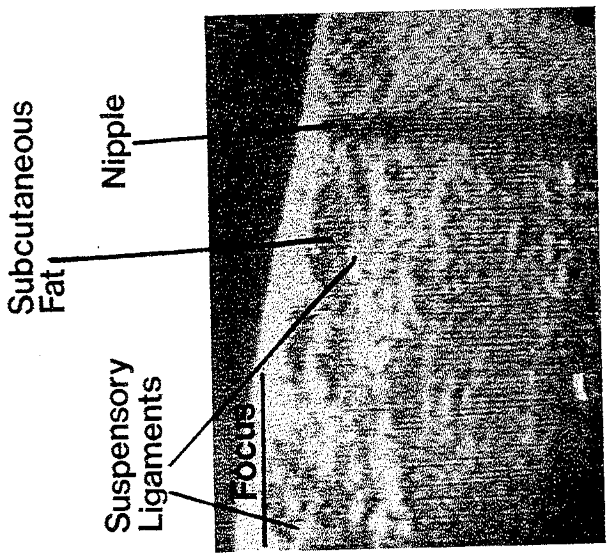

Figure 6

nipple surface. It is apparent that although the fine structures of the subcutaneous fat and suspensory ligaments are well visualized, no tissue structures can be viewed in the shadow resulting from the attenuation of the nipple. This effect was demonstrated with all ages of subjects. If, in fact, an attenuating target, which is approximately the same size as the nipple, is placed on any non-nipple/non-areola surface of the breast, a simulation of effect of nipple structure in relation to the placement of the focus can be clearly demonstrated.

Although the water bag coupling technique is not recommended, there is one application of this method which may prove of value in studying the ducts of the breast, namely, use of the water bag for regions other than nipple and areola. If the subject is lying partly on her side, so that the outer breast surface is essentially horizontal, the water bag compresses the tissues but does not cause the type of distortion observed in the nipple. The compression of the tissue is an advantage from the viewpoint of attenuation. It may be of value, therefore, to consider the water bag technique in attempting to locate the ducts in the outlying areas of the breast.

Figures 7a and 7b are echograms obtained under the circumstance of direct water coupling between transducer and skin surface. The coupling was accomplished by an adaptation of the water bags used for the previously mentioned study (the bags are designed to contour the top and side surfaces of the breast reasonably well). A circular opening (as large as 10 cm in diameter) was cut in the mylar bag and the bag then placed on the breast surface with the nipple in the center of the opening, and the cut edges carefully formed to the skin surface. If the cut edges of the bag are properly contoured to the skin surface, and care is taken in the initial pouring of the water, it will be found that the combined effect of the upward flotation of the breast and the downward pressure of the water forms a good seal without the aid of any oil or glue. This technique worked well on both young and older subjects with average and large size breasts.

Figures 7a and 7b are echograms of the same subject (different time periods) obtained while using this coupling technique and the 4.4 MHz transducer described under Methods and Procedures. Figure 7a was obtained by means of a sagittal scan mode, while 7b resulted from the more conventional transverse scan. The ductal structures are clearly apparent in both echograms but, as in the case of the excised breast previously described, the ducts are better visualized in the sagittal scan. However, further studies on a large number of subjects need to be carried out before any conclusion is made in this regard.

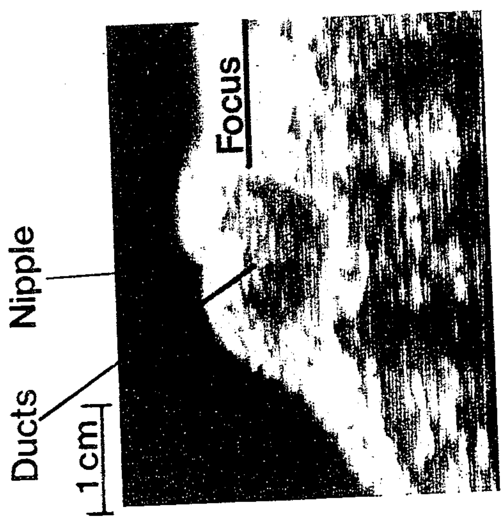

Figure 7a

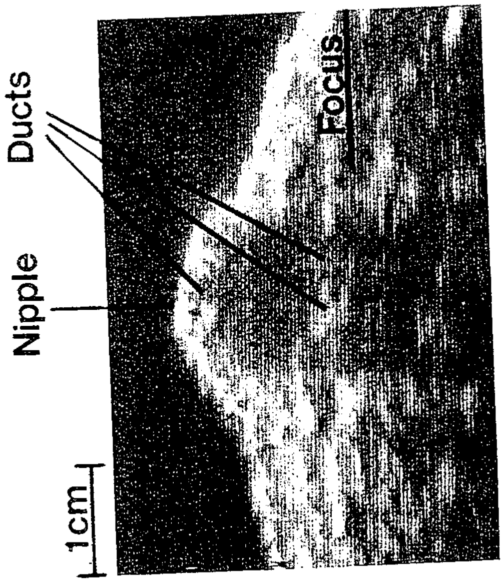

Figure 7b

It is clear from the results obtained in these preliminary studies that normal ductal structures can be visualized. Improvements in the quality of the imaging is dependent on further instrumentation development.

DISCUSSION

As pointed out in the Introduction, there is a serious need for methods that are capable of detecting breast tissue changes which may precede the formation of a malignant mass. The mammographic and histological data of the previously cited authors on ductal changes accompanying breast carcinoma are significant in this regard. However, at the present stage of knowledge, the presence of ductal epithelial hyperplasia is not a proof of malignancy. The exact nature of the causal relationship between ductal changes and breast carcinoma are not known. Gallager and Martin indicate that epithelial hyperplasia is premalignant in a nonobligate sense, that is, although epithelial hyperplasia is one of the changes that must take place during the carcinoma process, hyperplasia per se may be due to causes other than a malignancy.[9-10]

Although the histological and mammographic studies carried out, to date, on ductal changes detected in patients with breast cancer, are significant, they are limited by the nature of the examination technique. Obviously, histological studies can only be carried out on excised breasts. X-ray examination of the breast has usually been confined to special categories of subjects and may be further restricted in the future. If, however, sufficient improvements are made in ultrasound instrumentation, the ultrasound method could be used to examine large populations of women of all ages, both normal and those with a breast pathology. Thus a large amount of data, particularly on the younger women, could be collected which might, in conjunction with histological and mammogram information, lead to further understanding of the causal relationship between ductal changes and breast carcinoma.

The author would like to indicate that it is not being proposed in this paper that ductal structures be investigated without regard to the other tissues in the breast. Since this paper is concerned with the specific topic of detection of ductal structures by ultrasound, only the ductal changes which accompany a breast malignancy have been discussed. However, epithelial changes may also be found in the lobules. Further, there may be more generalized changes in breast tissue when a carcinoma is present. Gallager and Martin not only found changes in the supportive connective tissue and, in some breast carcinoma cases, an increased density of the breast due to proliferation of collagen in the mammary tissue, but consider these types of changes to be diagnostically significant.[9-10]. It is important to ultrasound detection that this change in the mammary tissue is not confined to the region of the tumor mass but may be a widespread density effect. Wolfe has proposed that the pattern of distributed breast tissues, as seen on xeromammography, can be used as a predictive diagnostic tool.[29] In that regard he has developed a classification system for xeromammographic images that is predictive in regard to women who have a high risk of breast cancer. The tissue characteristics that are significant to this classification are broad categories, such as fatty, dense, cystic, and prominent ducts. Myron Moscowitz's and associates' recent studies, correlating breast biopsy data, and Wolfe's classification scheme, is additional evidence of the value of this approach and also lends further credence to the concept that epithelial hyperplasia is a malignant precursor (the University of Cincinnati College of Medicine).[30]

The generalized tissue changes (such as increased density) or characteristics (such as fatty, cystic, etc.) briefly mentioned above can be detected ultrasonically. The present limitations on the extent to which such components of generalized tissue can be delineated and quantified cannot be discussed in adequate detail here because there are many factors involved in such a discussion including types of ultrasound instrumentation in relation to complexity of breast tissue structure. However, there is little doubt, in this author's opinion, that such identification and characterization can be accomplished if sufficient combined clinical and research studies are undertaken.[31-37] The primary aim of the earlier ultrasound investigations of the author and associates was echogram characterization of the tissues of the normal breast, over the age of young to old, with the purpose of providing a means for early breast cancer detection by recognition of slight deviations from such echogram pattern norms.[20,21,28,31,34,35] Even in these early studies it was shown that a breast with a clinical diagnosis of fibrosing adenosis (a dense breast usually with hyperplasia and a proliferation of connective tissue) could be ultrasonically identified by the echogram characterization approach.[20] It is also of interest to note the type of tissue detail in regard to fat lobules and suspensory ligaments that can be imaged by means of relatively simple ultrasound instrumentation, as shown in Figure 6 of this paper.

CONCLUSION

It has been shown that ductal structures located in the region inferior to the nipple and areola can be detected by relatively simple ultrasound visualization techniques. It is suggested that further ultrasound investigations be carried out to improve echogram resolution of these fine tissue structures and to increase accuracy of detection of ducts in other regions of the breast. This approach is recommended in order to provide a means of examining the ductal structures of a large population of women for the purpose of adding to present histological and x-ray data on the causal relationship between ductal hyperplasia and breast carcinoma.

REFERENCES

1. 75 Cancer Facts and Figures; American Cancer Society, Inc., New York, 1974, pp. 1-29.

2. J. W. Berg and G. F. Robbins: "Factors Influencing Short and Long Term Survival of Breast Cancer Patients," Surgery, Gynecology and Obstetrics, January-June, 1966, Vol. 122, pp. 1311-1316.

3. B. Fisher, N. Slack, D. Katrych and N. Wolmark: "Ten Year Follow-up Results of Patients with Carcinoma of the Breast in a Cooperative Clinical Trial Evaluating Surgical Adjuvant Chemotherapy," Surgery, Gynecology and Obstetrics, Vol. 140, 1975, pp. 528-534.

4. I. Macdonald: "The Breast," in, Management of the Patient With Cancer, ed., T. F. Nealon, Jr.; W. B. Saunders Co., Philadelphia/London, 1965, pp. 435-469.

5. D. C. Tormey: "Combined Chemotherapy and Surgery in Breast Cancer: A Review," Cancer, Vol. 36, 1975, pp. 881-892.

6. S. J. Cutler and R. R. Connelly: "Mammary Cancer Trends," Cancer, Vol. 23, No. 4, April, 1969, pp. 767-771.

7. J. A. Urban: "Biopsy of the Normal Breast in Treating Breast Cancer," Surgical Clinics of North America, Vol. 49, No. 2, April, 1969, pp. 291-301.

8. N. H. Slack, L. E. Blumenson and I. D. J. Bross: "Therapeutic Implications From a Mathematical Model Characterizing the Course of Breast Cancer," Cancer, Vol. 24, 1969, pp. 960-971.

9. H. S. Gallager and J. E. Martin: "The Study of Mammary Carcinoma By Mammography and Whole Organ Sectioning," Cancer, Vol. 23, No. 4, April, 1969, pp. 855-873.

10. H. S. Gallager and J. E. Martin: "Early Phases in the Development of Breast Cancer," Cancer, Vol. 24, No. 6, Dec., 1969, pp. 1170-1178.

11. H. S. Gallager and J. E. Martin: "The Pathology of Early Breast Cancer," in, Breast Cancer: Early and Late, Year Book Medical Publishers, Inc., Chicago, 1968, pp. 37-50.

12. J. E. Martin and H. S. Gallager: "Reflections on Benign Disease: A Radiographic-Histologic Correlation," in, Early Breast Cancer, Detection and Treatment, ed. H. S. Gallager; John Wiley & Sons, New York, 1976, pp. 177-181.

37. J. Jellins, G. Kossoff, T. S. Reeve and B. H. Barraclough: "Ultrasonic Grey Scale Visualization of Breast Disease," Ultrasound in Med. Biol., Vol. 1, No. 4, March 1975, pp. 393-404.