Thermobiological assessment of benign and malignant breast diseases

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The recent technical and clinical advances in breast thermography are reviewed in this article. Emphasis is placed upon liquid crystal thermal imaging and computer-assisted analysis of breast thermograms. New data are presented concerning the value of thermography for the early detection of mammary carcinomas, the identification of women at high risk of developing breast cancer, and the detection of cancer in fibrocystic breasts. (AM. J. OBSTET. GYNECOL. 147:861, 1983.)

Body temperature is one of the most important parameters of health or illness in man. Thermoregulatory processes are essential to the maintenance of well-being and life. Although physicians as remote as Hippocrates regarded heat as the chief diagnostic sign of acute disease, the history of thermometry[17] reveals how difficult it has been for clinicians to accept the value of temperature as a guide for diagnosis, prognosis, and treatment.

Galileo (1564-1642) invented the thermometer and designed various prototypes of this instrument. During the next 250 years, the thermometer faded in and out of prominence in medicine without achieving a permanent niche in practice in spite of its being fostered by illustrious clinicians. Far the most illustrious was Boerhaave (1668-1738), who examined the role of the thermometer among patients at the University of Leiden, The Netherlands.

Beginning in 1851, Wunderlich (1815-1870) of Leipzig introduced the intensive use of the self-registering mercury thermometer in the hospital bedside. Because of his forceful efforts and uncommon sway over other men of ability he was assisted by a score of faithful associates in establishing the laws of medical thermometry based on more than one million observations. His treatise, "On the Temperature in Diseases" (1871), elevated thermometry to a highly regarded diagnostic technique. Despite continuing opposition by some practitioners during the 1870s and 1880s, the universal use of the thermometer in medicine soon ensued.

Almost a century later, Lawson introduced infrared thermography for the evaluation of breast lesions in 1956.[23] Since that time, the science of medical thermography has developed continuously in many centers throughout the world and a vast number of scientific publications have appeared. In the last 5 years, the development of systems in which thermosensitive liquid crystal films are used has resulted in a renewed interest in this modality. Nonetheless, in spite of significant efforts to study the relationship between heat and disease, more especially in breast cancer, this area of biomedical investigation is in its infancy in comparison to our understanding of the thermal processes in healthy conditions.

The purpose of this presentation is to show how the primary care physician, in particular, the gynecologist, and his patients can benefit from the routine use of liquid crystal thermography as an adjunct to the physical examination. Special emphasis will be placed upon the study of fibrocystic diseases, the early detection of cancer, especially the nonpalpable carcinomas, and the identification of women at high risk of breast cancer. Other questions, like the pretherapy prognosis or follow-up after operation or radiotherapy, for which thermography has also proved to be effective[6, 10] will not be considered here.

From the Laboratory of Thermobiology, University Louis Pasteur School of Medicine, Strasbourg, and the National Institute for Health and Medical Research (INSERM), Paris.
Holmes Lecture, presented at the meeting of the Chicago Gynecological Society, April 15, 1983.
Received for publication May 18, 1983.
Accepted August 11, 1983.
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**Holmes Lecture, presented at the meeting of the Chicago Gynecological Society, April 15, 1983.*

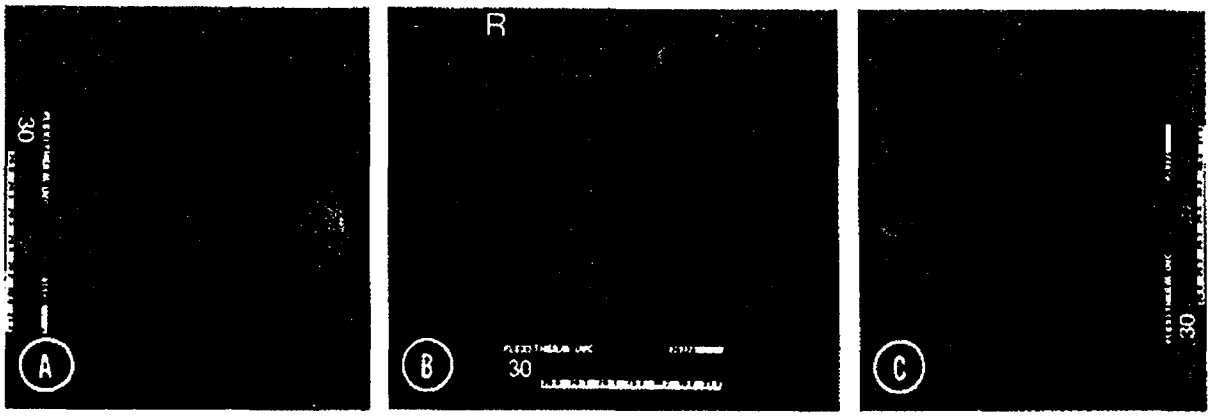

Fig. 1. Nonpalpable, minimal breast cancer (T0 N0, Stage I) found on follow-up of isolated thermographic abnormalities in a 52-year-old woman with no family history of breast cancer. At the first visit in June, 1982, severe bilateral mastodynia, more marked in the left breast, was present. There were no physical or mammographic findings of cancer. Abnormal vascular hyperthermia was demonstrated on the left breast (thermogram of Class Th III). At the first follow-up examination in September, 1982, there were no significant physical or mammographic changes. There were discrete changes in the thermovascular pattern of the left breast. At the second follow-up examination in February, 1983, there were no palpable findings. Further changes in the thermovascular pattern of the left breast and a clear increase of the intensity of the vascular hyperthermia were demonstrated; there was minimal dense opacity of 6 mm on a spot mammogram of the thermographically abnormal area. Cytology: type V (Papanicolaou's classification). Histology: undifferentiated, invasive ductal carcinoma. The liquid crystal thermograms were recorded with Quantum plates (Vectra International Corp.); see detailed thermographic analysis on Fig. 4.

Thermographic techniques

Two methods of thermal imaging are presently available for routine thermographic assessment of breast health: infrared thermography and liquid crystal thermography. Although both are noninvasive, they are totally different in their underlying physical principles and technology.[5]

Infrared thermography is performed with the use of remote-sensing scanners which analyze thermal radiation from the skin in the infrared range of the electromagnetic spectrum.[15] Electronic devices coupled to the scanner and fitted with microprocessors allow real-time display of images which represent the temperature distribution over a large part of the body. These machines are accurate, reliable, and can be used for thermographic studies in a variety of pathologic circumstances. However, their relative high cost has limited their utility to specialized imaging departments, mostly in hospitals.

In liquid crystal thermography, thermosensitive cholesteric liquid crystals deposited on special films are used. Plates containing these films are brought into contact with the skin and provide direct observation of the cutaneous thermal pattern as a colored map.[16] Most of the liquid crystal systems have been designed specifically for breast investigations. Dramatic improvements in this technology have occurred during the past 5 years, particularly in the areas of thermal and spatial resolution. These changes permit the clinician to obtain images close to those obtained with infrared thermographs. In this regard, the following recent developments assume extreme importance: (1) special plates exhibiting a richer palette of colors and a linear temperature-color relationship (Quantum plates, Vectra International Corp.) (Fig. 1) and (2) systems made of flexible films which permit a thorough exploration of all mammary areas, including the axillary extension of the breast (Thermoflex, Flexitherm Inc.) (Fig. 2). In contrast to the infrared technique, the low cost of the liquid crystal systems should result in their widespread use in private practice.

The Strasbourg breast research group started using infrared scanners in 1965 and doing research on liquid crystal in 1966. On the basis of our experience with most of the available infrared and liquid crystal equipments, we believe that liquid crystal thermography is more easily adaptable to the conditions which exist in the primary care physician's office.

Thermobiology and tumor growth rate

Starting with infrared observations of local temperature changes and thermovascular disorders in patients with breast cancer, in 1970, we initiated a series of measurements in humans which directly evaluated the heat of cancerous breast tissue compared with that of healthy breast tissue.[9] These studies were designed to

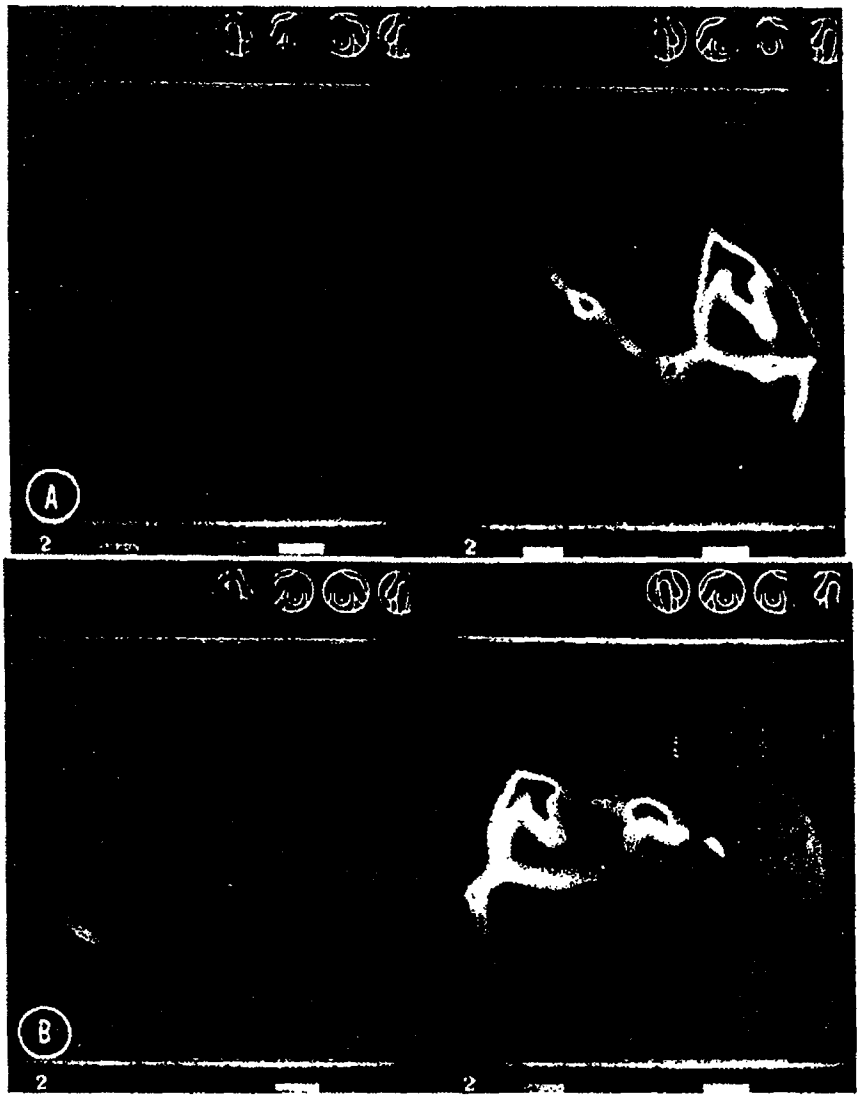

Fig. 2. In situ carcinoma found on initial thermal assessment and subsequent workup in a 34-year-old woman, with no family history of breast cancer. Routine examination by the gynecologist (private practice) in December, 1982, revealed no palpable findings, but there was irregular vascular hyperthermia in the upper inner quadrant of the right breast (thermogram of Class Th III). Upon referral to the Breast Center (University Hospital) for mammographic consultation 8 days later, groups of typically malignant microcalcifications (variable densities, irregular outlines) in the upper inner quadrant of the right breast were shown, together with confirmation of distorted intense vascular hyperthermia over the right breast (thermogram of Class Th IV). Histology: intraductal, in situ carcinoma. Liquid crystal thermogram recorded with Thermoflex pillows (Flexitherm Inc.).

find the origin of the heat observed on the thermogram: Did it derive from the tumor itself or from an increased blood supply? Our measurements confirmed the prior findings by Lawson and Gaston[24] which had indicated that tumor temperature was always higher than blood temperature. We concluded that the increase in tumor heat resulted from an increased metabolism.

Subsequent to these metabolic changes, two phenomena occur: (1) Tumor heat is transported within the surrounding breast tissue, principally by blood convection through the veins; this results in local or diffuse increases in the skin temperatures. (2) Vascular changes are elicited in the tumor area and further in the subcutaneous breast tissue as a result of the release of different vasoactive substances, such as bradykinin.

Thermographic observations reflect both metabolic and vascular changes. Generally, these changes cannot

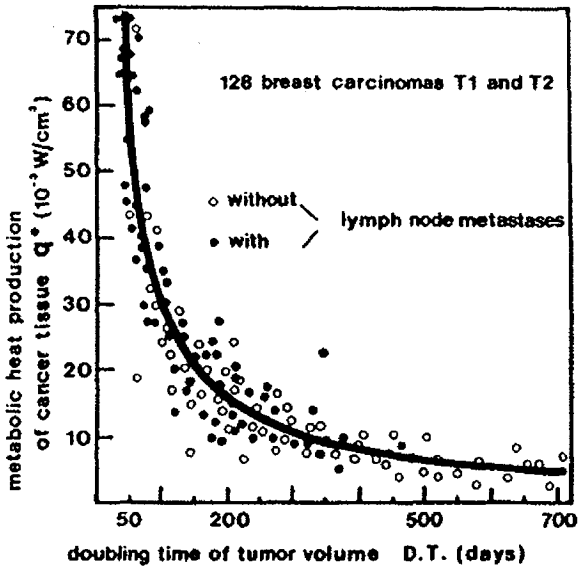

Fig. 3. Growth rate and specific heat production of breast cancer. The unequivocal relationship between specific heat production of cancer tissue and doubling time of tumor volume is shown in a group of 128 mammary carcinomas. All of these carcinomas were diagnosed at a relatively early stage (tumor size between 0.6 and 4.1 cm) and evaluated over a span of natural evolution (patients temporarily refused any treatment but were operated on later). (From Gautherie, M.: Thermopathology of breast cancer: measurement and analysis of in vivo temperature and blood flow, Ann. N. Y. Acad. Sci. 365:383, 1980.)

be identified separately because of the highly complex nature of the heat transfer processes and the vascular changes. Under such circumstances, the analysis of the thermal breast images in malignant conditions remains difficult.

In order to understand better the nature of the thermograms observed in the most frequent types of breast carcinomas, intra-mammary temperature and blood flow measurements were conducted with fine-needle thermoelectric probes. These studies demonstrated both hyperthermia and hypervascularization in the tumor and at its periphery in comparison to the temperature and blood flow of healthy tissue in the contralateral breast. From these investigations, we developed an improved understanding of the thermograms of breast carcinomas.

Our research on thermobiology of breast cancer culminated with experiments which serially measured the production of tumor heat and the increase in tumor size during the natural growth of malignant disease in a select group of patients who temporarily refused any treatment. An unequivocal relationship was demonstrated between the metabolic heat production of cancer tissue and the doubling time of tumor volume: The faster the tumor grows, the more heat it generates. Moreover, in most of the fast-growing, hot cancers, lymph node metastasis was established after subsequent surgical treatment and axillary dissection[6] (Fig. 3).

These observations strongly suggest that thermography has the ability to depict most of the fast-growing carcinomas, i.e., those with the worst prognosis, at a very early stage before there is any palpable abnormality or suspicious opacity on the mammogram. In contrast, slow-growing cancers with a relatively good prognosis generally either are cold or only generate moderate degrees of hyperthermia, even if the tumor size is large.

Interpretation of thermograms

In the normal breast, the basic thermal pattern is one of symmetry between both breasts. This symmetry can be demonstrated over long periods of time. Thermal variations associated with the times of the day,[11] the menstrual cycle, and possibly pregnancy can be observed with thermography. In most women, these physiologic changes affect both breasts in the same manner.

In the diseased breast, however, symmetry is generally lost, and changes in temperature levels as well as in thermovascular patterns occur. Because of these changes, the thermographic image obtained in most diseased breasts is of such a complexity that its evaluation requires an objective and accurate protocol.

Over the years, several systems have been designed stressing one or another aspect of these thermal changes. Some of these systems were useful since they considered the totality of the changes involved; others were deficient because they focused only on specific parts of the picture.

Without a doubt, the accuracy of interpretation of a breast thermogram is of unparalleled importance. Thus, it is possible that some of the programs which in the past have failed to demonstrate effectiveness of thermography, such as the Breast Cancer Detection Demonstration Project (BCDDP), did not require systematic training of those individuals who were requested to evaluate the thermograms and a common and appropriate protocol of evaluation. Since our first publications on this matter,[19, 20] we have insisted upon standardized examination conditions and standardized protocols of evaluation. Our original system of evaluation has undergone numerous modifications,[10] most of which take into consideration both absolute temperature differences between both breasts and changes in the thermovascular patterns.[7] Numerical scores can now be assigned to each abnormality and the sum of these single scores can be related to the ultimate thermal class assigned. A particular feature of our new scoring system is that it is designed to maximize the reproducibility of interpretation by different readers.

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***** BREAST THERMOGRAPHY ANALYSIS *****
computerized system by M.Gautherie ( Strasbourg - France )

Doctor J.P. WALTER
HOSPITAL OF HAUTEPIERRE - STRASBOURG FRANCE
Patient:x
Date: 01/20/83

REPORT OF THERMOGRAPHIC FINDINGS

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PATIENT:

-Name.............................. x
-Maiden name....................... x
-First name........................ x
-Sex (f/m)......................... f
-Address........................... xxx
-Birth date........................ 05/09/09
-Dossier No........................ 112/83

CONDITIONS OF EXAMINATION:

-Examination N:.................... 1
-Phase of menstrual cycle:......... 9th day
-Equipment:........................ VECTRA liquid crystals QUANTUM plate
-Ambiant temperature (°F):......... 70
-Patient's Posture:................ sitting
-Duration of Physiological cooling:. 10 min.

REPORT:

RIGHT BREAST:
Score: 15       Thermal Signs: P1  P9
P1:     Uniform thermal Pattern
P9:     Asymmetrical thermovascular Pattern between right and left Breast

LEFT BREAST:
Score: 105      Thermal Signs: P5-H1  P7-H5  H7  P9
P5-H1: Distorted thermovascular Pattern (upper-medial).with Convolutions and
        Ramifications.intense (ΔT max/opposite Breast = 4.8 °C.Δ
        T max/same Breast = 3.2 °C)
P7-H5: Intense Hyperthermia of the Nipple (ΔT /opposite Nipple = 2.4 °C.Δ
        T /same Breast = 0.8 °C)
H7:     Intense total Hyperthermia (ΔT /opposite Breast = 2.4 °C)
P9:     Asymmetrical thermovascular Pattern between right and left Breast

CONCLUSIONS:

RIGHT BREAST:     TH 1  -  NORMAL
LEFT BREAST:      TH 5  -  ABNORMAL
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Fig. 4. Computer-assisted analysis of breast thermograms (interpretation system and computerized protocol by Gautherie[7, 8]). Copy of the computer printout of the thermographic findings and conclusions on the analysis of the thermograms shown in Fig. 1.

The system has been computerized with a view to force the human interpreter to answer thoroughly a series of specific questions about the thermogram which are always asked by the computer in the same order. Recent double-blind studies performed in our department and other breast centers have proved that accuracy and objectivity of the interpretation are greatly improved with the use of such a computer-assisted protocol.[8] Moreover, the computer system produces automatic printouts of the thermographic findings and conclusions (Fig. 4).

Thermography of fibrocystic diseases

The diagnosis and long-term follow-up of patients with moderate or extensive fibrocystic disease in one or both breasts is difficult. To be more precise, experienced clinicians as well as experienced radiologists and pathologists acknowledge difficulty in assessing the evolution of a cancer in patients with a fibrocystic disease. To complicate matters further, some pathologists are even of the opinion that specific types of fibrocystic disease represent precancerous lesions. However, there is no unanimity in the existing information.[21]

In many circumstances, mammography cannot distinguish between benign and precancerous conditions, as the presence of a large amount of high-density fibrotic tissue and many lumps may diminish the ability of the radiologist to identify an early cancer, especially if no microcalcifications are present. For these reasons, numerous investigators have begun to use thermography to assess serially the natural changes occurring in fibrocystic breasts.

Evaluation of our data shows that approximately 40% of women with fibrocystic disease and an abnormal thermogram develop cancer within 5 years (Fig. 5). This high rate of cancer stands in stark contrast to the rate of less than 3% which prevails among those women with fibrocystic disease who did not exhibit thermographic abnormalities.[12, 13] Similar findings have been reported by other European authors.[2] Similar data have not yet been published from the United States because long-term follow-up of benign breast disease is not universally practiced by many American primary care physicians.

In some centers in the United States, however, patients with fibrocystic disease receive hormonal therapy, i.e., with bromocriptine or danazol, in an effort to produce regression of the lesions. In at least one

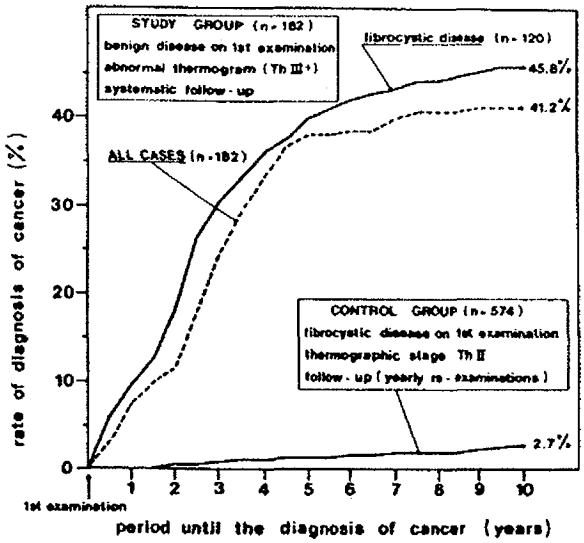

Fig. 5. Evolution of cancer in patients with a fibrocystic disease (long-term follow-up, up to 10 years). In the study group, 45.8% of the 120 patients who had a fibrocystic disease and an abnormal thermogram (Th III) at the time of their first examination developed cancer. The rate of cancer was only 2.7% in the control group which incorporated 574 patients also with a fibrocystic disease but stable, moderate thermal abnormalities (thermogram of Class Th II). (Data from Gautherie and associates.[13])

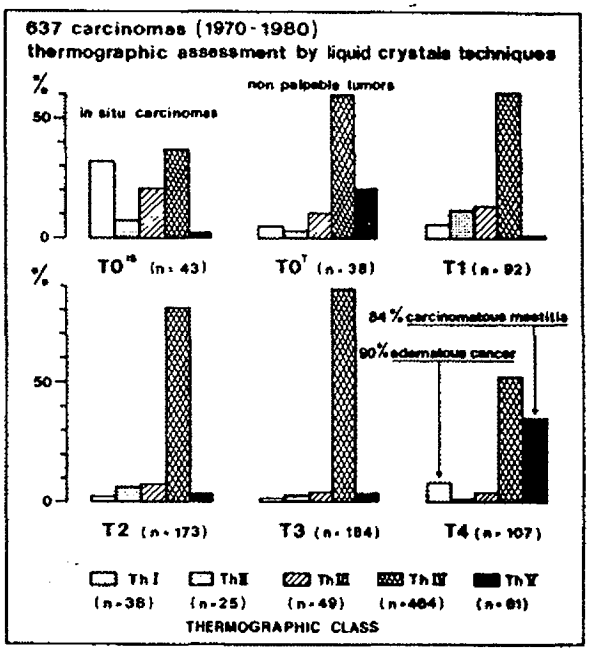

Fig. 6. Distribution of 637 breast carcinomas by physical staging (TNM classification) versus thermographic staging (Gautherie and Gros' classification). Within the group of nonpalpable cancers (T0), the subgroup $T0^{is}$ includes the in situ carcinomas (intraductal and intralobular), and the subgroup $T0^{T}$ includes deep-seated or soft tumors with a well-circumscribed mammographic opacity ranging in size between 0.5 and 4 cm. A total of 61% of the patients with a nonpalpable in situ carcinoma exhibited clear thermal abnormalities (thermogram of Class Th III, IV, or V). (From Gautherie, M., Haehnel, P., Walter, J. M., and Keith, L.: Long-term assessment of breast cancer risk by liquid crystal thermal imaging, *in* Gautherie, M., and Albert, E., editors: Biomedical Thermology, New York, 1982, Alan R. Liss, Inc., pp. 279-301.)

American center, thermography has proved to be effective in the assessment of the effects of such hormonal therapy.[18] It is particularly useful in that many examinations can be performed with no excess of exposure to radiation.

Thermography of nonpalpable cancers

Short of removal of the entire breast and complete sectioning of all tissue, there is no 100% accurate way of detecting all nonpalpable carcinomas of the breast, including in situ (intralobular and intraductal) lesions and minimal (albeit invasive) cancers.[4] On the basis of the presence of microcalcifications or minimal opacities, mammography detects many but not all of these lesions.

On the other hand, thermography has been shown to detect approximately 60% of such nonpalpable lesions (Fig. 6); most of these generate localized vascular hyperthermia of moderate intensity in association with a distorted vascular pattern (Fig. 2).[13, 22, 27] In these cases, it is reasonable to speculate that the tumors are growing more rapidly, thus producing more heat and more marked vascular changes along with a worse prognosis. While the critics of thermography have pointed to its inability to pinpoint 40% of very early tumors, the proponents of the technique point out that the 60% of cancers found would have been totally missed by the primary care physician simply because the minute lesions are not palpable.

Since the woman is essentially well at this point, it is axiomatic that neither the most accurate and repeated self-examinations nor accurate palpations by the clinician will find these nonpalpable abnormalities which require further follow-up. However, the observation of an abnormal thermogram will demand mammographic examination and additional appropriate workup (Fig. 2).

Thermography and early detection of cancer

There is no question that early detection of breast cancer is associated with improved rates of survival.[28] Specifically, in published studies, the survival rates associated with minimal breast carcinomas approximate 95%.[26] It is also recognized that survival rates decline progressively with increasing stages of the disease no matter what type of therapy is offered.

The recent quotation of Moskowitz and Gratside[25] is

typical of present thinking on this subject. These authors say their data "suggest that aggressively screening younger women, finding and treating breast lesions while they are in situ or five millimeter microinvasive, is highly likely to reduce mortality . . .," and "argue strongly to try to detect breast cancer at the earliest possible stage by the most effective means available."

Given the above-mentioned statistics and quotations, it is reasonable to ask where thermography fits into programs designed to detect breast cancer at the earliest possible moment. On the basis of our work, an abnormal thermogram is the single most important marker of high risk for breast cancer, far more significant than family history.[11] We can make this statement on the basis of our findings that approximately 35% of women with healthy breasts and an abnormal thermogram develop cancer within 5 years. Once again, this high rate is in stark contrast to the rate of less than 4% among those women with healthy breasts and a normal thermogram who were observed with repeat studies because they had a family history of breast cancer (Fig. 7). It should be emphasized that all of these patients, i.e., those with and those without cancer, initially had no abnormal physical or mammographic findings. These observations held true in the early years of our studies with infrared technology,[12] as well as in the last years with liquid crystal technology.[13]

Other authors have confirmed these observations, namely, the value of thermography is greatest in detecting early cancer of the breast if the patient is evaluated longitudinally over time.[1] This longitudinal follow-up methodology is the most realistic use of thermography. The worst possible use of thermography would be to demand from it a "yes or no" answer on the presence or absence of a breast carcinoma at the time of the patient's first visit without considering the need to evaluate the patient over time. It is imperative that we accept the concept that, even with negative findings on physical examination and mammography, an "isolated" abnormal thermogram may be the first sign of a rapidly developing cancer (Fig. 1).

Effectiveness of thermography in terms of survival benefit

One of the most frequently posed questions during my numerous lecture tours in the United States was whether the survival rate was improved in those patients whose diagnosis had been initiated by the finding of an abnormal thermogram. If, indeed, survival were not affected by an earlier diagnosis, then it could be argued that all earlier detection had accomplished was a prolongation of the knowledge of the existence of a serious disease along with its disturbing physical, psychological, and social consequences.

We recently analyzed survival rates of 106 patients in whom the diagnosis of breast cancer was established as a result of the follow-up of thermographic abnormalities found at a first visit when the breasts were apparently healthy (negative physical and mammographic findings). The survival rates of these women were compared with those of a group of 372 patients whose diagnosis of breast cancer was established at the time of their first visit to the medical facility.[14] Patients in the study group and the control group were subdivided by method of therapy (radiotherapy or operation). Length of posttherapy follow-up was equal for matched groups of patients and control subjects.

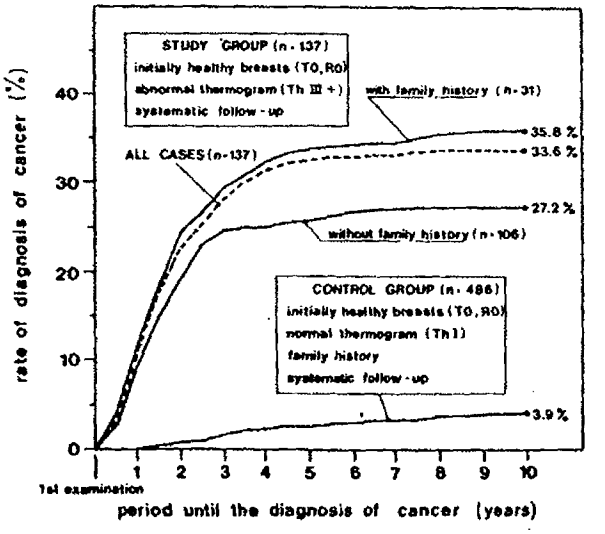

Fig. 7. Evolution of cancer in patients with physically and mammographically healthy breasts and a family history of breast cancer (long-term follow-up, up to 10 years). In the study group, 35.8% of the 31 patients who had healthy breasts and an abnormal thermogram (Th III) at the time of their first examination developed cancer. The rate of cancer was only 3.9% in the control group which incorporated patients with healthy breasts and a normal thermogram (Th I). (Data from Gautherie and associates.[13])

In the women treated by radiotherapy and followed up over 10 years, there was a very significant augmentation in survival among those women whose tumors were detected as a result of the follow-up of isolated thermographic abnormalities as compared to that in those women whose tumor was detected at first visit (Fig. 8, *A*). A similar augmentation in survival rate was found for patients treated by operation and followed up over 5 years (Fig. 8, *B*). These findings clearly establish that the early identification of women at high risk of breast cancer based on the objective thermal assessment of breast health results in a dramatic survival benefit.

Impact for gynecologists

Following the accumulation of the data cited above, it becomes important to answer the question of whether

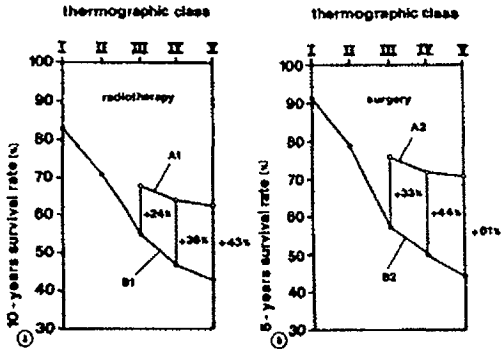

Fig. 8. Survival rate of breast cancer patients by thermographic class at the time of cancer diagnosis. *A:* Initial thermal assessment by infrared thermography, treatment by radiotherapy, follow-up over 10 years. *A1* (65 patients): Diagnosis of cancer established on follow-up of isolated thermal abnormalities (initial thermogram of Class Th III in all cases and progression to Th IV or Th V in about two thirds of the cases). *B1* (169 patients): Diagnosis of cancer promptly established on first visit, variable thermographic class from Th I through Th V. *B:* Initial thermal assessment by liquid crystal thermography, treatment by operation, follow-up over 5 years. *A2* (42 patients) and *B2* (203 patients): Groups similar to *A1* and *B1*. The improved survival in the upper line (*A1* on Fig. 8, *A* and *A2* on Fig. 8, *B*) is noted among patients whose cancer was found as a result of the follow-up of isolated thermographic abnormalities. (From Gautherie, M., Haehnel, P., Walter, J. M., and Keith, L.: Long-term assessment of breast cancer risk by liquid crystal thermal imaging, *in* Gautherie, M., and Albert, E., editors: Biomedical Thermology, New York, 1982, Alan R. Liss, Inc., pp. 279-301.)

the average gynecologist or, for that matter, the family practitioner should make more frequent use of thermography as a routine office procedure. My colleagues and I believe the answer is yes for several reasons. Simply stated, thermography permits the primary care physician: (1) to be more accurate in requesting mammography and other diagnostic procedures (as a result, referrals for radiographic and surgical consultation will increase as additional attention is given to a selected group of women at higher risk of developing breast cancer); (2) to become aware of the presence of a nonpalpable in situ or minimal carcinoma (this applies particularly to those carcinomas with increased heat production and associated thermovascular disorders which show a greater likelihood of an earlier tendency toward invasiveness); (3) to evaluate women with thermal abnormalities in the presence of negative physical and mammographic findings over prolonged periods of time (this is based upon the ample demonstration that finding of persistent asymmetry or progressive change on the thermogram have a strong association with future development of a cancer); (4) to evaluate patients who have undergone surgical operations for therapeutic or esthetic reasons, in particular, after excision of benign growths, prosthesis insertion, or subcutaneous mastectomy; (5) to delineate the evolution of benign breast diseases, especially those to which there is attached an increased risk of cancer, i.e., the fibrocystic diseases; (6) to evaluate the effects of hormonal medications given for the treatment of benign mastopathies, including dysplasia and tumors.

Comment

It is fortunate that more and more gynecologists are becoming concerned with a wide variety of the different aspects of breast health. We applaud these efforts and hope they will be reinforced in the future. It would be unfortunate if the gynecologists were to continue to rely solely on self-examinations and physical examinations, because these methods simply cannot lead to earlier diagnosis in large numbers of patients. The gynecologist is in a particularly favorable position to effect earlier diagnosis by the use of presently available modalities, such as thermography and diaphanography. In this regard, simple and cost-effective procedures, such as liquid crystal thermography, certainly merit widespread use.[3]

It must also be recognized that further research on the subject of thermobiology of tumors should be undertaken and sponsored by governmental agencies and insurance companies, both of which must bear the staggering financial impact of breast cancer.

I wish to express my gratitude to Professor Louis G. Keith, M.D., Department of Obstetrics and Gynecology, Northwestern University School of Medicine, Chicago, Illinois, for his critical suggestions and his invaluable help in the preparation of the manuscript.

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