A REPORT TO THE PHYSICIANS OF TEXAS

newsletter

THE UNIVERSITY OF TEXAS SYSTEM CANCER CENTER

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Progressive DNA Damage in Hepatic Nodules during Acetylaminofluorene Carcinogenesis

Daniel L. Stout, PhD, and Frederick L. Becker, MD*

Many lines of evidence suggest that the alteration of DNA that results from exposure to specific chemicals is an obligatory component of the carcinogenic process. The degree of binding to DNA and subsequent rate of removal of chemical agents, the specificity of their interaction with component bases, and the degree of DNA damage induced, especially in target cells, have been used to measure carcinogenic potential. DNA damage and repair following exposure to radiation or chemicals have been studied frequently by means of alkaline sucrose density gradients. More recently, alkaline elution, a highly sensitive technique for studying single-strand breaks in DNA, has been used to study carcinogen-DNA interaction in vivo. These results, like those obtained with gradients, often demonstrate a correlation between an agent's ability to cause DNA damage and its carcinogenic potential. While most of these studies have used acute exposure conditions, it has recently been reported that alkaline sucrose density gradient centrifugation demonstrates persistent, relatively constant DNA alteration of liver tissue through chronic exposure to known hepatocarcinogens.

We used the alkaline elution technique to assess DNA alteration during the hepatocarcinogenic sequence that resulted from exposure to a standard regimen: First, we were able to isolate and examine the DNA from a putative premalignant lesion, the neoplastic nodule (we use this term to provide morphologic and conceptual identification, rather than to imply a specific functional or biological characterization); second, we could examine DNA from these lesions after the cessation of carcinogen administration. Male CFE Sprague-Dawley rats were fed a diet containing 0.06% acetylaminofluorene (AAF) for 3 weeks, followed by 1 week of normal diet. Four cycles represented carcinogenic exposure. Age-matched rats maintained on the basal diet were used as controls throughout.

AAF-induced damage was monitored at the end of the first and fourth carcinogen periods (before normal diet) and 2 to 4 months after the fourth (last) AAF feeding cycle. After 3 weeks of the AAF regimen, sections of whole liver were taken for analysis because focal lesions were not available for dissection. However, at the end of the fourth feeding cycle and thereafter, hepatic nodules morphologically identical with previously

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Radiation Therapy with the Electron Beam

Norah duV. Tapley, MD*

The optimum irradiation program for the patient with malignant disease requires the careful selection of both treatment modality and dose-fractionation schemes. For any given situation, the technique used should be designed to provide the desired dose distribution with all possible protection of uninvolved structures. Current radiation equipment permits the delivery of high doses at the surface or at any selected depth with surface sparing. The high-energy electron beams now in use are invaluable in achieving dose distributions carefully tailored to the treatment situation.

The majority of electron beam units currently in clinical use in the United States are linear accelerators that have a peak electron energy of 18 MeV. In a few centers, accelerators and betatrons that provide 25- to 50-MeV electrons are available. The experience gained in the Department of Radiotherapy at MDAH with the 7- to 18-MeV Siemens betatron, installed 16 years ago, and with the 7- to 25-MeV sagittaire linear accelerator, installed 9 years ago, provides some insight into the significance of electron beam irradiation.

The features of the electron beam that make it a unique therapeutic tool are related to physical qualities and not to a different relative biological effectiveness (RBE). Laboratory studies have shown an RBE close to one when the electron beam is compared with megavoltage photon irradiation. Special treatment techniques have evolved using the 6- to 25-MeV electron beam for clinical situations in which satisfactory management may not be achieved with the photon beam alone.

The characteristics of the electron beam make it of distinct advantage in treatment of malignant lesions located at a limited depth. The desired dose of irradiation can be delivered to the tumor, while the total volume of tissue included in the high dose range is sharply limited. The characteristics of the electron beam that are of special significance in its clinical application are its rapid dose build-up and its sharp dose fall-off. Within the first millimeter of tissue, the dose approaches 90% of its maximum dose at full depth. High dosage close to the skin is

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DNA Damage . . .

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described putative premalignant lesions were dissected free from surrounding hepatic tissue and analyzed individually or in pools. No differences were detected among the elution patterns of individual nodules and pools.

Hepatic DNA from rats fed 0.06% AAF for 3 weeks eluted perceptibly faster than hepatic DNA from control rats. At the end of the fourth feeding, DNA from hepatic nodules demonstrated an even greater rate of elution. However, the most rapidly eluting DNA was found in hepatic nodules from rats that had not been exposed to AAF for 2 months or more.

When the percent of total DNA eluted in each 10-min interval was plotted, it was noted that hepatic DNA from AAF-treated rats contained a component or fraction that eluted abruptly as the pH of the eluting buffer approached 12.3, i.e., during the first 30 min of elution. The elution rates began to approach those of normal DNA by 80–90 min, after which time the DNA from all samples eluted at approximately the same rate. After 3 weeks of AAF exposure, the amount of DNA that eluted in 80 min was approximately 30% greater than that eluted from normal liver tissue. DNA from hepatic nodules obtained at the end of the final feeding of AAF was found to elute more rapidly; the amount eluted in 80 min was 71% greater than normal. Two months after the last exposure to AAF, the elution profile of DNA from persistent hepatic nodules was examined to determine if DNA repair had occurred During the first 80 min, the amount of DNA eluted was 108% greater than control values.

Because cell division in hepatic nodules is greater than in normal liver tissue, the presence of rapidly eluting DNA in nodules might have resulted from DNA synthesis. To determine what effect DNA synthesis would have on the elution profile, rats weighing 80g–200g were subjected to 70% partial hepatectomies. Rats at different ages were used to provide tissues with varying rates of DNA synthesis. Hepatic nuclei from these rats were prepared 22 hr–24 hr post-hepatectomy and the DNA eluted. DNA from the nodules of these rats eluted more rapidly than from normal liver tissue. However, the amount of DNA eluted in 80 min was less than the amount from hepatic nodules by about 30%. The rate of DNA synthesis in regenerating liver tissue of young rats may be as much as tenfold greater than that in hepatic nodules. Thus, it was concluded that the presence of rapidly eluting DNA in hepatic nodules was not mainly the result of DNA synthesis.

To examine the possible role of nuclease activity in the elution pattern of DNA derived from the nodules, hepatic nodules obtained 4 months after the last AAF feeding were bisected and two pools of halved nodules prepared. An equal amount (by weight) of normal liver tissue was added to one pool of nodular tissue. The combined tissues were then squashed in the usual manner to obtain nuclei, as were the separate aliquots of nodules and normal liver tissue. The rationale for this procedure was that if nuclease activity in the nodules was responsible for degradation of DNA during squashing and was in excess, then DNA from normal liver tissue would similarly be degraded and a disproportionate amount of rapidly eluting DNA would result. The elution profiles from this experiment reveal that DNA from the mixture of nodular and normal tissue behaved essentially in an additive manner. The percentages of abnormally eluting DNA in the nodules was 9.3% and 4.2% in the normal tissue. These results would make it unlikely that nuclease activity in nodular tissue degrades the DNA during preparation.

We believe our results indicate that the carcinogenic regimen of AAF led to a DNA alteration that increased during feeding. The presence of such damage in the DNA of a putative premalignant lesion, the neoplastic nodule, increases the probability that the damage is related to carcinogenic evolution. Another unique observation that resulted from this study was that this alteration of DNA persisted long after removal of the carcinogen and, indeed, became more severe with time.

It has been previously reported that AAF and dimethylnitrosamine (DMN) causes damage to liver DNA that is progressive up to 5 weeks, but that further feeding with DMN did not increase damage, even after 15 weeks. Another group of investigators reported similar results when DMN was fed to rats for 31 weeks, at which time tumors were present in the livers. A possible explanation for the differences between these results and our own may reside in our use of a focal cell population, the neoplastic nodule. This lesion is at higher risk for malignant evolution with time, a finding that parallels the increasing degree of DNA alteration demonstrated. The complex interactions between activation of carcinogens, repair of the resultant DNA damage, and the cell heterogeneity in the carcinogen-exposed liver may make it difficult to identify the source of altered DNA when bulk liver is used. Thus, in the study reported by the second group, the tumors that resulted originated in the vascular endothelium, while in our study the resultant tumors were primary hepatocellular carcinoma. These factors may also have been responsible for our finding of limited DNA alteration at the end of the first 3 weeks of AAF feeding, a time when previous experiments in our laboratory have demonstrated a two- to threefold increase in the ability of microsomes from bulk liver to activate to a mutagen.

Conversely, the nodules that result from a full carcinogenic regimen have been shown to be significantly defective in this activating ability, and it has been suggested that this defect is obligatory in the carcinogenic sequence. It was this severe defect in activating capacity that originally led us to examine the integrity of the DNA of nodules in the expectation that limited activation might be associated with unaltered DNA. However, despite our finding of a significant alteration in the DNA in these

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nodules at the end of four feeding cycles, we cannot conclude definitively that this resulted from damage induced by the generation of activated AAF metabolites within the nodule. The persistence of altered DNA long after cessation of exposure to carcinogen makes it difficult to identify the pathogenesis of the DNA alteration in nodules or its characteristics. Damage might result from the limited but detectable capacity of the cells of the nodule to activate AAF or from activated metabolites originating in neighboring cells, or it may have occurred much earlier in the exposure. Until we can isolate enough of the altered DNA fraction from nodules at the completion of feeding and those that persist unaltered, we cannot even suggest that they are similar. Examination of the relationship of DNA damage to carcinogenesis in other systems may help suggest the nature of the underlying defect in DNA.

*Department of Pathology, MDAH. (Physicians requiring further information should contact the authors—ED.)

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provided, but there is only modest skin sparing with the electron beam. A high dose level is maintained to a depth determined by the energy of the beam, with the doses falling off sharply beyond this depth. The sharp fall-off in dose beyond the 80% dose point offers protection to the structures deeper than the treatment target.

The selection of treatment techniques, the combination of electrons and photons of various energies, and the ratio of given doses of each beam depend upon the maximum depth of the lesion to be treated. A variation of combination treatment is that of additional, or "boost," therapy using reduced portals to raise the total dose to the initial gross disease to a high level. This practice is predicated on the hypothesis that microscopic disease can be permanently controlled with doses on the order of 5,000 rads in 5 weeks. By reducing the volume of tissue to be heavily irradiated, the risk of damage to normal tissue is diminished.

In the clinical applications of the electron beam, treatment aims and therapeutic principles are based on the fundamental parameters of radiotherapy that have been established for megavoltage photon irradiation. Alterations in the accepted time-dose relationships have been minimal. Treatment techniques have been modified only as dictated by the special characteristics of the electron beam.

The electron beam is particularly useful in the treatment of patients with head and neck cancers and breast cancer. It has proved ideal in the treatment of those lesions that present complex treatment problems or are critically located anatomically, involving such structures as the eyelids, nose, or ear. It is possible to design irregular treatment fields and to protect adjacent or underlying normal structures by using relatively thin and malleable lead masks and cut-outs (Figure 1). The lens is protected by an eye-shield placed under the eyelid.

Electron beam irradiation in treating skin lesions is preferable to kilovoltage irradiation, for which the dose at the skin surface is always higher than that at the target depth. The skin remains in good condition years after treatment with electron beam therapy, however, because the highest dose level is maintained to a depth determined by the energy of the beam.

In another context, electron beam is preferable to photon beam irradiation. Diffuse lesions of the scalp and skin of the head and neck are best treated with the electron beam because large areas of the skin need to be irradiated to prevent potential involvement. There is no way to cover the total area by using a photon beam, no matter how sophisticated the treatment planning.

Carcinomas of the nasal vestibule and columella present complex treatment situations, requiring irradiation of deeper structures over a wide area, since the deep limits of the lesion along the septum or floor of the nose cannot always be determined. These lesions may metastasize to either or both sides of the neck. Since "in transit" metastases are not uncommon, treatment should be given to the intervening lymphatics extending from the nose down the nasolabial fold and chin into the submental and submaxillary triangle areas.

A high local recurrence rate in patients with malignant parotid gland tumors has been reported in the surgical literature. The highest rates of recurrence have been associated with high-grade mucoepidermoid carcinoma and adenocarcinoma, malignant mixed carcinoma, and adenoid cystic carcinoma. In the effort to lower this recurrence rate, partial or complete sacrifice of the facial nerve has been commonly accepted as necessary for cure. Our own experience and that of others have shown that irradiation can be effective for local control when used alone or as an adjuvant to surgical excision. The proper selection of treatment, the radicalism of the surgery, the need for postoperative irradiation, and the irradiation technique used depend on the growth characteristics of the tumor (Figure 2).

The high-energy electron beam is ideal for the treatment of malignant tumors of the major salivary glands because of the relatively superficial location of these structures. The entire ipsilateral side of the neck is irradiated when the primary tumor is of high-grade malignancy, when tumor is found in connective

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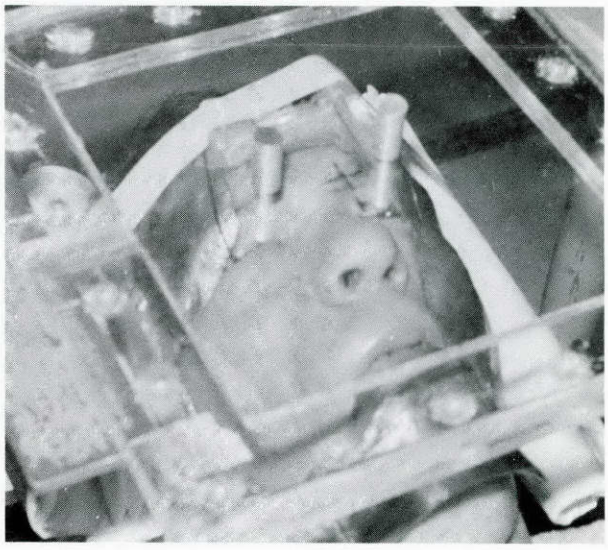

Fig. 1: Treatment field defined by a cut-out in a lead mask. Tungsten plugs protect cornea and lens. (Figure by permission from Tapley, Norah duV.: Clinical Applications of the Electron Beam. New York, John Wiley and Sons Publishers, 1976.)

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tissue, when there is extensive invasion of the perineural lymphatics, and when positive nodes are demonstrated in the operative specimens.

An example of the fitting of the beam characteristics to the clinical situation is seen with carcinomas of the retromolar trigone and of the anterior tonsillar pillar (T_1-T_3, N_0-N_1) with minimal extension into the soft palate or tongue. These lesions receive treatment with electrons 16 to 20 MeV combined with 18- to 25-MeV photon irradiation because a greater depth dose is necessary and because interposed bone may further decrease the depth dose. Electron and photon beams in equal dose delivery ratios provide the 80% tumor dose at a depth of approximately 6 to 8 cm unless it is shifted toward the surface by heavy cortical bone in the mandible. The subdigastric node area is included in the treatment field of the primary lesion. Mucositis is sharply limited to the affected side, with essentially no mucosal reaction on the opposite side. Acute radiation morbidity is decreased and late dryness is negligible. When there is a clinically positive subdigastric node, treatment is given to the entire ipsilateral side of the neck with the electron beam. A neck dissection must be done if the dose to the nodes is not higher than 5,000 rads.

Although it is tempting to use the electron beam alone to treat carcinoma of the buccal mucosa because these lesions are so well lateralized, previous experience demonstrated an undesirable degree and duration of acute reactions as well as sequelae of severe skin changes and fibrosis with trismus. The current technique for buccal mucosa lesions combines the electron beam with interstitial gamma-ray therapy. The tongue is protected by an intraoral stent containing lead.

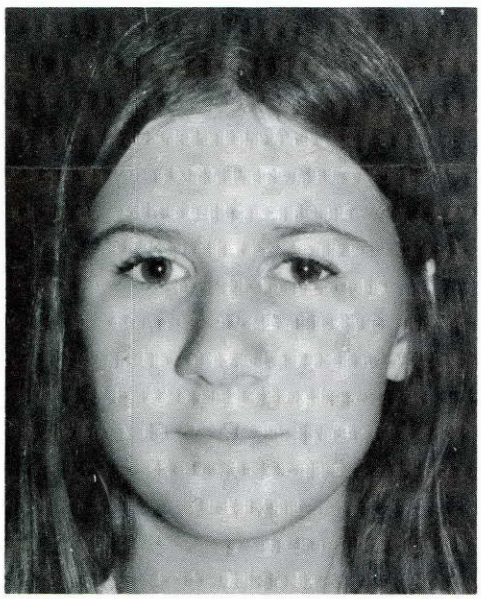

Fig. 2: Patient 6 years following left parotidectomy and therapy with combined 18-MeV electrons and photons. The patient shows no evidence of disease, has minimal facial nerve weakness, and the cosmetic result is excellent. (Figure by permission from Tapley, Norah duV.: Irradiation Treatment of Malignant Tumors of the Salivary Glands. Ear, Nose, and Throat 56:110–114, 1977.)

Prevention of disease in initially uninvolved areas and prevention of recurrences in the dissected neck can frequently be achieved because of the effectiveness of moderate doses of irradiation in eradicating subclinical disease, i.e., either microscopic disease or aggregates of cancer cells too small to palpate. Elective irradiation is given to the ipsilateral side of the neck only when the opposite side of the neck is not at a high risk of lymphatic involvement. This is ideally done with the electron beam. Suitable clinical situations include well-lateralized tumors of the oral cavity, anterior tonsillar pillar and trigone, maxillary antrum, skin (excluding the midline area), and major salivary gland. After radical neck dissection, indications for treatment of one entire side of the neck include many positive nodes in the surgical specimen, total replacement of a node by tumor or rupture of a cystic node, tumor found in connective tissue, or tumor found in the perineural lymphatics.

The electron beam has been of particular value in irradiation for breast cancer. Its special application has been in the treatment of subclinical disease in patients who have had radical removal of the primary breast lesion and the lymphatics of the axilla. The routes of spread of breast cancer have dictated the areas to be included in the treatment fields.

Patients who have a small lesion (less than 2 cm) located in the central or medial portions of the breast and who do not have positive axillary nodes receive irradiation to the first three intercostal spaces, the only lymphatic areas that have significant risk of involvement. Patients who have a lesion 2 to 5 cm in diameter located in the central or inner quadrants or who have one to three positive axillary nodes recovered at operation and who exhibit no grave signs receive irradiation only to the ipsilateral lymph nodes in the supraclavicular fossa, the apex of the axilla, and the internal mammary chain. Irradiation is given to the entire chest wall as well as to the peripheral lymphatics when there are more than three positive nodes in the operative specimen, when the breast mass measures more than 5 cm in diameter, or when there is skin or pectoral fascia fixation.

Peripheral lymphatic irradiation with moderate doses controls subclinical disease without producing complications or even detectable sequelae. The amount of irradiation delivered to the mediastinum is significantly lower when the electron beam is used alone or is combined with Cobalt 60 in treating the internal mammary chain nodes. This is of particular value in patients who have received or will receive Adriamycin in view of the reported incidence of cardiotoxicity with Adriamycin therapy. For patients who received peripheral lymphatic and chest wall irradiation with the electron beam after radical mastectomy and who had had heavily involved axillary nodes or grave signs of breast tumor or both, chest wall recurrence was 10%. This is a significant improvement compared with the 40% or higher local recurrence rates previously reported. Very few patients have significant sequelae following treatment of the chest wall and adjacent lymphatic areas with the electron beam. The skin reaction, a brisk erythema and superficial desquamation, disappears rapidly. Serial chest x-ray examinations show increased pulmonary markings in the lung apex and perihilar areas, indicative of radiation fibrosis, but less than 1% of the patients have symptomatic radiation pneumonitis.

Finally, electron beam irradiation can be utilized as a "boost" modality. Added irradiation can be given with photons through

glancing fields, but the electron beam, at low energies to spare the deeper structures and reduce the possibility of radiation-related sequelae, provides a simple approach, often through an apositional portal. For example, after resection for malignant salivary gland tumors, the electron beam combined with the photon beam provides an excellent dose distribution to relatively limited tissue volume. After mastectomy, the electron beam provides treatment to the dermal lymphatics over a wide area and limits dosage to deeper structures.

The electron beam is used in a number of situations to provide additional treatment to a limited tissue volume after Cobalt 60 therapy. In the intact breast treated with irradiation after wedge resection or excisional biopsy, the electron beam is used to treat the area of the primary lesion, the field encompassing the breast quadrant where the tumor was located. Local and regional control has been excellent. In the intact breast treated for extensive disease, the electron beam may be used to deliver a boost to the mass if it is located in the axillary tail of the breast, the inframammary sulcus, or the inner quadrant of the breast.

The electron beam is used to deliver a boost to a strip along the chest wall scar in patients who have had treatment with tangential Cobalt 60 fields after simple mastectomy. It is used to increase the dose to 5,000 rads to the first three internal mammary nodes in patients with central and inner quadrant lesions and heavy involvement of axillary nodes. After Cobalt 60 treatment, boosts to residual nodes in the supraclavicular area and axilla may be given with the electron beam. In each of these situations, additional dosage is delivered to the original area of gross disease without excessive dosage to underlying normal structures.

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Thoracic Oncology Clinic

A Thoracic Oncology Clinic, designed to expedite the care of patients with the type of cancer that accounts for one fourth of Texas cancer deaths, is opening at MDAH. The clinic, headed by David T. Carr, MD, Department of Medicine, MDAH, breaks away from traditional test routing of lung cancer patients by bringing specialists from throughout the hospital to one area in an attempt to cut the time from initial examination to the formation of a treatment plan to 5 days.

"The sheer magnitude of the problem is sufficient reason for our new program," says Clifton F. Mountain, MD, chief of thoracic surgery, Department of Surgery, MDAH. "But we firmly believe that with the early, aggressive use of new treatments we will be able to increase significantly the number of cures." Deaths from lung cancer increased by 53% from 1969 to 1976, and 6,300 of the 39,000 newly diagnosed cases of cancer in Texas this year will be lung cancer.

As part of a new Thoracic Oncology Program initiated in July and cochaired by Drs Carr and Mountain, the clinic will be

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History of Human Cytogenetics Published

T. C. Hsu, PhD, chief, section of cell biology, Department of Biology, MDAH, has written a new book that was published by Springer-Verlag.* *Human and Mammalian Cytogenetics: A Historical Perspective* attempts to portray background stories about some research events that were not reported in scientific papers. "The book does contain some serious discussions at times, but overall it is not designed to be scholastic. I had fun writing it, and I hope readers will have fun reading it," Dr Hsu says. The 186-page book is available from the publishers at $11.80.

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For registration information, contact Jan van Eys, MD, PhD, Department of Pediatrics, M. D. Anderson Hospital and Tumor Institute, 6723 Bertner Ave., Houston, Texas 77030.

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Thyroid-Stimulating Hormone and Prolactin Levels in Breast Cancer

Keith A. Aldinger, MD, Pamela N. Schultz, George R. Blumenschein, MD, and Naguib A. Samaan, MD, PhD*

Througout the years there has been some controversy in regard to the association between breast cancer and thyroid disease. Epidemiologic studies have suggested a greater prevalence of and mortality from breast cancer in endemic goiter areas. There have been reports of an increased prevalence of breast cancer in patients with hypothyroid states, and an association between breast cancer and decreased thyroid function has been suggested. In addition, it has been proposed that decreased thyroid function is more prevalent in patients with advanced as compared to local breast cancer. Numerous studies exist refuting most of the preceding contentions. This controversy has recently achieved renewed clinical attention due to a publication implying that thyroid hormone administration may play a causal role in breast cancer. We have studied the hypothalamic-pituitary-thyroid axis and prolactin secretion in a large group of breast cancer patients at MDAH in an attempt to shed some light on this association.

The study included 148 patients with a histologic diagnosis of breast carcinoma. Cases were accumulated during a 5-year period from two main sources: patients who had undergone a primary breast cancer operation and patients with metastatic breast carcinoma who were about to receive either chemotherapy or endocrine treatment. Serum thyroid-stimulating hormone (TSH) and prolactin (PRL) levels were measured after intravenous administration of protirelin to the cancer patients before any medical management. For the purposes of our study, the patients were divided into two groups: those with primary breast cancer and those with metastatic breast disease. Forty-two of these patients were premenopausal and had a mean age of 42.5 years, while the other 106 patients were postmenopausal and had a mean age of 60.3 years.

Forty-five normal women who were age-matched with the breast cancer patients were studied in a similar manner. Sixteen of these controls were premenopausal (mean age 42.5) and the other 29 controls were postmenopausal (mean age 60.0). In our study, basal and peak TSH and PRL levels were considered elevated only if they were above the upper limits of the range defined by these 45 normal women.

Among breast cancer patients, we found a high prevalence (36%) of elevated basal TSH levels. Prolactin levels were less often elevated, with only 22% of the patients demonstrating elevated basal levels. The differences in the mean serum TSH and PRL levels between the breast cancer patients and normal controls were statistically significant. The basal TSH levels were plotted against the basal PRL value for each patient, but there was no correlation between these two values. The mean values for the basal and peak serum TSH and PRL ($\pm$ SD) are shown in the table.

The TSH results were also compared for those patients with and without a history of irradiation to the upper chest area, but there was no statistically significant difference between these values. An attempt was made to compare the survival and the disease-free interval of those patients having elevated PRL or TSH levels with those having normal levels. In those patients with elevated basal TSH values, both the disease-free interval and survival were shorter, but in neither case was the difference to people with normal levels statistically significant (33 and 21 vs. 42 and 18 months). Likewise, with elevated PRL values, both the disease-free interval and the survival were shorter, but again, with no statistically significant difference (15 and 9 vs. 69 and 35 months).

Prolactin levels have been measured previously in patients with breast carcinoma. Early reports of PRL levels suggested a significant increase in breast cancer patients versus normal controls; however, more recent reports have shown little difference in the basal levels between breast cancer patients and controls. In spite of these findings, there is convincing evidence in experimental animal models that PRL plays a role in the development of mammary tumors.

In humans, PRL has been demonstrated in vitro to stimulate breast cancer. In addition, malignant human breast tissue has shown increased PRL binding when compared with benign mammary tumors. At the present time, the role of PRL in human breast cancer remains undetermined, and therapeutic attempts at suppressing PRL levels in breast cancer patients have produced controversial results.

Prolactin levels have been reported as elevated in primary hypothyroidism, sometimes in association with galactorrhea. One team of investigators demonstrated a strong positive correlation between the TSH and PRL levels of 16 women with primary hypothyroidism. Among our breast cancer patients with elevated TSH levels, we could find no correlation between TSH and PRL. It should be remarked that our patients differed in two ways from the group described by the others. In spite of elevated TSH levels, only two of our patients had a decreased thyroxine and T resin uptake. In addition, the mean TSH among our patients with elevated TSH was 13.2 μU/ml, as compared with a mean TSH of 372 μU/ml in the 16 patients described by others. It would appear from other reports that the PRL level is infrequently elevated in hypothyroidism. In one of these studies, only two of eight patients demonstrated increased PRL levels, and the mean TSH for the entire group was 120 μU/ml. In the first study, ten of 16 patients had elevated PRL levels, but no patient with a TSH level of 100 μU/ml or less had an elevated PRL level. In another study of breast cancer patients receiving aminoglutethimide, a threefold increase in the mean TSH level to 14.5 μU/ml was unaccompanied by any significant change in mean PRL. It would appear the elevated PRL levels may occur with increased frequency only in myxedematous patients with markedly elevated TSH levels.

In conclusion, we have demonstrated a high prevalence of TSH elevation in breast cancer patients. This occurs most often

in the presence of normal serum thyroxine levels and normal T resin uptake. This increased prevalence cannot be attributed to prior chest irradiation. In addition, serum PRL levels were elevated in 22% of the patients we studied. The mean PRL was significantly elevated over that in a control population; however, there was no correlation between PRL and TSH. If a state of thyroid dysfunction resulting in TSH elevation predisposes to breast cancer or worsens its course, as previously reported by others, our data would suggest that PRL elevation does not mediate this effect.

*Department of Medicine, MDAH. (Physicians requiring further information should contact Dr Samaan. This article is a summary of a paper that first appeared in *Archives of Internal Medicine* 138:1638–1641, 1978.—ED.)

Thoracic Clinic . . .

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staffed by about 40 persons, including 17 senior staff members, 6 fellows and residents, and 10 students. It will bring together professionals from radiotherapy, chemotherapy, surgery, immunotherapy, nursing, pulmonary medicine, social service, and cardiology.

According to Dr Carr, creation of the clinic means the patient will not have to spend as much time rotating through the different specialty clinics. For family members accompanying patients to Houston, that time savings means less anxiety and less money spent on lodging, transportation, and food.

"For us, the clinic will mean a chance for all the specialists to see the patient at one time and discuss the case rather than see the patient at various times and get together later," says Dr Carr. "It will give us the opportunity to exchange ideas and identify any weaknesses in our treatment areas so that we can strengthen them." Ultimately, Dr Carr adds, this benefits patient and physician.

Although each staff member will retain his position in his own department, Dr Mountain says each has a special interest in thoracic oncology and will devote a majority of his time to the new program.

Over 10,000 patient visits are expected at the clinic during the first year of operation, and Drs Mountain and Carr expect that number to double after an initial phase of 2 years. In the second phase, related basic science and clinical research programs will be coordinated and expanded, with special emphasis on epidemiologic studies and early diagnosis.

"If a multidisciplinary approach works as well as we expect it to work in the clinic, we think we will be able to apply it to research," says Dr Mountain. "Almost every specialist on the clinic staff will normally be working on a research project. If the group decides that we need the answers to certain questions first, we can cooperate on those projects and get the answers in perhaps 6 months rather than the much longer time it might take a single researcher."

According to Dr Charles A. LeMaistre, president of the Cancer Center, MDAH pioneered the development of the team approach to patient care, and Dr Mountain believes that treatment and patient care must continue to move to this multidisciplinary approach. "Such a partnership of experts concerned with a single problem," he says, "provides obvious advantages for patient, physician, and researcher."

Lung cancer is the program's major concern, but the clinic's purpose is to study and treat all forms of cancer that occur in the chest. The clinic's staff will be expanded after the 2-year initial phase to include members from many related areas. Dr Mountain says that understanding the scope of thoracic cancer means pulling specialists from a range of disciplines—cell biology to epidemiology to public health—if researchers are to understand the changes carcinogens cause at the cellular level or if they are to have any impact on prevention.

The chest clinic will be located on the first floor of the Clinic Building.

New Books on Nutrition Published

Nutritional support of the cancer patient is rapidly becoming the frontier of supportive therapy research. Physicians, nurses, dietitians, oncologists, and others concerned with nutrition for cancer patients will be interested in two new books recently published.

Nutrition and Cancer, edited by Jan van Eys, MD, PhD, MDAH, head, Department of Pediatrics, Buford L. Nichols, Jr., MD, Baylor College of Medicine, and Mildred S. Seeling, MD, MPH, NYU Medical Center, was published by SP Medical and Scientific Books, 175-20 Wexford Terrace, Jamaica, NY 11432. In the 270-page volume, the authors promote nutritional rehabilitation and support as a critical part of the treatment regimen for all cancer patients. The volume includes chapters on the use of elemental diets for the cancer patient; metabolism; nutritional concepts of neoplastic disease; psychophysiological aspects of cancer anorexia; vitamins and cancer; serum selenium, magnesium, zinc, and copper levels; and nutrition and immunity. It also examines nutritional concerns for patients with specific types of cancer, such as carcinoma of the breast and small bowel, solid tumors, and pediatric cancer patients.

Nutritional Management of the Cancer Patient, edited by Joy J. Wollard, RD, MDAH, Department of Nutrition and Food Service, provides a comprehensive guide to care of the cancer patient. The 220-page volume was published by Raven Press, 1140 Avenue of the Americas, New York, NY 10036. Its authors concentrate on the metabolic stress of cancer and the interactions between food and drugs given to cancer victims. Significant aspects of the nutritional care of the cancer patient are discussed; these include initial nutritional assessments; nutritional support during chemotherapy, radiotherapy, and surgical treatments; and nutritional needs during remissions or extended care. Complications such as anorexia, undernutrition, and lactose malabsorption are covered, as well as more specific concerns like dietary treatment of colostomy/ileostomy patients, pediatric patients, leukemia patients, and patients with head and neck cancers.

newsletter

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Regents Appoint New Chair and Professorship

The University of Texas System Board of Regents has approved appointments to the Charles B. Barker Chair in Surgery and the Mosbacher Pediatric Professorship at MDAH. The Barker Chair will be held by Richard A. Martin, MD, head, Department of Surgery. The chair was made possible by a bequest from the late Charles B. Barker, an attorney from Hollywood, Florida, whose 20-year association with MDAH particularly involved the area of cancer surgery. Dr Martin joined the MDAH staff in 1951, after earning his medical degree from Temple University in 1944. He was named chief of general surgery in 1967 and head of the department in 1977. His primary research interests lie in the fields of cancer of the gastrointestinal tract, soft tissue sarcomas, and bone tumors.

The Mosbacher Pediatric Professorship will be held by Jan van Eys, PhD, MD, head of the Department of Pediatrics since 1973. The Professorship was funded by Mr and Mrs Robert Mosbacher of Houston who presently serve on MDAH's Board of Visitors. The gift will be used to explore the mental health aspects of pediatric cancer care in addition to medical treatment. Dr van Eys received his early education in The Netherlands, and earned his PhD from Vanderbilt University School of Medicine in 1955 and his medical degree from the University of Washington School of Medicine in 1966. He is the author or co-author of more than 120 published articles, primarily in the field of mental health aspects of childhood cancer.

Charles A. LeMaistre, MD, MDAH president, said, "The Cancer Center is extremely fortunate to have these two new appointments filled by such outstanding leaders and physicians as Dr Martin and Dr van Eys. The importance of this type of private philanthropy is crucial in establishing and maintaining the margin of professional excellence necessary for the best cancer research and patient care."

Richard A. Martin

Jan van Eys