tially the same as that for ablating the pericardial space, as reviewed by Buzaid and associates. Since the surfaces of the pericardial sac are many times smaller than those of the pleural space, one wonders whether or not too high a dose of tetracycline may be being proposed for ablating the pericardial space. To this point, it is interesting that Shepherd and colleagues recommend 500 mg of tetracycline in 20 ml of a saline solution rather than the 1-gram dose and base their conclusions on the fact that efficacy seems comparable but pain is increased in patients who receive 1 gram of tetracycline.[3] When our pharmacy tested the pH of 1 gram of tetracycline in 20 ml of a saline solution and compared it with that of 500 mg of tetracycline in 20 ml of a saline solution, it was found that the pH for both ranged between 2.5 and 3, which is the range that is thought to be required to induce pericardial sclerosis. Perhaps, therefore, the 500-mg dose is the preferred regimen for pericardial sclerosis.

The management of any chronic disease is a challenge to our profession. Buzaid and colleagues focus our attention on a rather common oncologic problem that frequently goes undiagnosed, particularly when not considered. In the process of reviewing this topic, they have given us some specific guidelines for management. Whether one agrees with me that the medical approach may be the better, or sides with the authors who suggest that the surgical approach is preferred, the real thrust of their article must be kept in focus. It challenges us to be aware of the potential of the problem and to plan immediate interventions to resolve this life-threatening complication.

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Lightning May Strike Twice

THE IDEA TAKES some getting used to at first. Patients with cancer may get into trouble once again, as the clinicopathologic conference in this issue of the JOURNAL so vividly illustrates. Only this time, the problem is not the initially treated tumor, a low-grade astrocytoma here, but a second, more malignant tumor, an osteogenic sarcoma, which arose as a direct result of radiation therapy. What are the risks? In which patients will it develop? What are the radiation doses? How long does it take for a second tumor to manifest itself? and, finally, What happens to the patients? These are some of the pertinent questions one should balance against the curative effects of irradiation on the primary cancer and the prolonged disease-free interval provided by the latent period.

Sarcomas secondary to irradiation constitute a rare albeit serious late effect of radiation therapy, but it is difficult to obtain a quantitative estimation of the risk. Unfortunately, only scattered reliable appraisals are available, but some reasonable calculations are on hand as more than 500 patients with postradiation sarcomas have been reported so far. Among more than 1,200 histologically verified osteogenic sarcomas of bones and soft tissues diagnosed and treated at Memorial Sloan-Kettering Cancer Center, 66 (5.5%) arose as a direct consequence of either external or internal ionizing irradiation.[1] Kim and associates from the same medical center estimate an incidence of 1.3% eight years after chemotherapy and irradiation for Hodgkin's disease.[2] The series reported, however, is small and the follow-up time brief. Mays and co-workers reported a long-term survey of 899 German patients, many of them children, who were treated for tuberculosis and ankylosing spondylitis by repeated injections of the short-lived radium isotope Ra 224: a bone cancer eventually developed in 53 (6%) of the patients.[3] This probably represents the uppermost limit of the estimate since the follow-up time is now at least 30 years.

The most recent large-scale, multi-institutional epidemiologic survey by Tucker and colleagues, which covers more than 9,000 patients treated for childhood cancer by irradiation, provides similar risk projections.[4] This study computes the cumulative mean probability of inducing a malignant bone tumor by therapeutic irradiation at 20 years after therapy to be $5.5\% \pm 2.1\%$. The absolute risk is calculated to be $9.4 \times 10^{-4} \times \text{year}^{-1}$. Naturally, the relative risk ranges widely, but it is the highest for patients with the hereditary form of retinoblastoma and for those with Ewing's sarcoma. The cumulative risk of a secondary sarcoma developing following irradiation for hereditary retinoblastoma at the age of 35 years was 19% (95% confidence interval, 11 to 29) in a series reported from Utrecht, the Netherlands.[5] There are many confounding factors that make interpolation of various radiation sources less than rewarding and not more than a rough approximation. During the first 35 years following exposure to the atomic bomb in Japan, there has been no increase in the incidence of primary malignant bone tumors among the more than 100,000 survivors.[6] These overall estimates by necessity do not quantitate the true risk of postradiation sarcoma, but at least they indicate its order of magnitude.

Most malignant bone tumors occur spontaneously, but on occasion they may develop from other benign tumors and they may follow as a direct consequence of previous radiation therapy. To wit, approximately 5.5% of all osteogenic sarcomas and 15.4% of all malignant fibrous histiocytomas of bone diagnosed and treated at Memorial Sloan-Kettering Cancer Center arose as a result of irradiation.[1,7,8] Postradiation bone sarcomas make up an infrequent but important segment of malignant bone tumors, particularly among adults.[9] These sarcomas represent, together with Paget's sarcomas, the most frequent secondary malignant tumors of bone.[10] It is also fair to say that the number of postradiation tumors will undoubtedly increase especially due to the expected rise in the number of patients who survive longer free of their primary disease but who have to confront this treatment-related disease, "the iatrogenic disease of success."[11]

Most successful treatment approaches in the management of various malignant tumors are multidisciplinary—a combination of radiation therapy, surgery, and adjuvant or even neoadjuvant multiple-drug chemotherapy. Although most patients undergoing such multimodal team management approaches undoubtedly benefit in terms of a prolonged disease-free survival, a shortening of the latent period for the appearance of a second cancer may have to be reckoned with. A heightened risk of postradiation sarcoma under such circumstances is not too farfetched a possibility since patients are likely to live longer.[12,13] There is also the possibility of a

synergistic or additive carcinogenic effect of two or more therapeutic agents.[14-18]

To estimate the relative risk of a second solid cancer following treatment of Hodgkin's disease, a survey emanating from McGill University in Montreal, Canada, pooled the data from seven studies for patients treated by radiotherapy, with or without chemotherapy, and those treated solely by chemotherapy.[19] For all patients with Hodgkin's disease, the relative risk of a second solid cancer developing was 2.1 (95% confidence limits: 1.8 to 2.4). The increased relative risk of a secondary sarcoma developing in bones and soft tissues was especially apparent in this study. Interestingly, those patients who had only chemotherapy for Hodgkin's disease showed no elevated relative risks for secondary cancers, which may be explained at least partly by the relatively shorter duration of follow-up information available for this group of patients. The study by Tucker and co-workers also attempted to evaluate the relative risks of sarcomas developing following chemotherapy alone or chemotherapy coupled with irradiation.[4] A close analysis of the epidemiologic data failed to find proof that chemotherapy using alkylating agents in this clinical setting appreciably enhanced the incidence of a second cancer. This lack of correlation was considered to be due to the relatively few cases under consideration and the limited follow-up time period.

The development of bone and soft tissue sarcoma in patients successfully treated by irradiation for a preexistent benign or malignant lesion is being reported with increasing frequency.[20-23] There are several plausible explanations offered for this. One major reason is the increasing awareness in identifying secondary cancers following successful therapy for another type of tumor—that is, to reach a specific and appropriate definition of what is meant by postradiation cancer. This was initially defined in 1948 by Cahan and associates: the patient received irradiation; the neoplasm occurred in the field of radiation; a latent period of years had elapsed; the original tumor was histologically identified; and the sarcoma is proved on microscopic examination.[24]

The number of sarcomas linked to radiotherapy is likely to increase because of the major successes achieved in the treatment of the primary tumors. That is, patients survive longer, thereby allowing more time for the development of a secondary cancer. Improving survival achieved by intensive therapy may result in side effects, one of the most feared of which is the occurrence of a second cancer. Illustrative of this is the increasing number of sarcomas following the treatment of Hodgkin's disease.[7,19]

Depending on the series of cases reported, the ages of the patients at the time of radiation therapy varied greatly, but at Memorial Sloan-Kettering Cancer Center they ranged from 6 months to 59 years with a mean age of 24 years. At the time of the diagnosis of the sarcoma, the ages of the patients ranged from 9 to 75 years with a mean of 38 and a median of 36 years. Postradiation osteogenic sarcomas developed in 27% of all patients during the sixth decade of life. Other series include more children.[4]

In most instances (64%) the sarcoma arises in patients whose skeleton had been normal at the time radiation commenced, and the osseous structures were only incidentally irradiated. In the others, radiation is aimed at an osseous tumor. The most common bone tumors treated by irradiation are giant cell tumors and Ewing's sarcomas. The reasons for the radiation directed against primary nonosseous conditions are Hodgkin's disease, carcinomas of breast and cervix, and the hereditary form of retinoblastoma.

Although any bone or extraosseous site can give rise to a postradiation sarcoma, the most common osseous sites are the femur and the humerus. The bones of the pelvic and shoulder girdles are involved less frequently, and the craniofacial bones are even rarer sites. Nearly half of all osteogenic sarcomas of the skull arise either in association with Paget's disease of bone or are secondary to irradiation.[10] Similarly to the case discussed in this issue's clinicopathologic conference, a postradiation osteogenic sarcoma developed in the frontal bone after a latency period of 36 years following surgical treatment and postoperative irradiation (48 Gy) for a brain tumor.[25] The most frequent postradiation soft tissue sarcomas are located in the nasal cavity, the neck, the shoulder, the chest wall, the upper arm, the back, and the groin.

The skeletal distribution pattern of postradiation sarcomas shows significant regional and site preferences. Whereas the spontaneously arising osteogenic sarcomas cluster in the knee region (50%), the bones of the pelvic and the shoulder girdles are the preferentially involved sites of the postradiation series. The distal end of the femur is the most common location in the naturally occurring lesions, in contrast to those associated with previous irradiation, where the upper end of the same bone is the preferred site. The relative frequency of the flat bones as sites of postradiation sarcoma, especially the craniofacial and the pelvic bones as well as the sternum, is of note.

Not only osteogenic sarcomas are seen following irradiation, but malignant fibrous histiocytomas, chondrosarcomas, and fibrosarcomas can arise as well.[8] A survey of bone sarcomas linked to radiotherapy in children reports an unusually high incidence (17%) of postradiation chondrosarcomas.[4] This is probably due to the inclusion of cartilage-producing osteogenic sarcomas into this group of tumors.

The mean radiation dose for postradiation bone sarcoma is 6,040 rads, the median dose is 5,700 rads, and the range is 2,500 to 15,000 rads. There is a direct relationship between rising radiation dose levels and the relative risk of postradiation bone cancer developing.[4] The risk clearly increases with increasing radiation dosages.[26] In osteogenic sarcoma the time interval between irradiation and the development of the soft tissue and bone sarcomas varies from 3.5 to 33 years, with a mean of 12.8 and a median of 10 years. This period of latency ranges from 6 to 24 years, with a mean of 11.3 years and a median of 9 years in patients in whom extraosseous sarcomas develop as compared with a range of 3.5 to 33 years, with a mean of 13 years and a median of 10 years of those with osseous osteogenic sarcomas.[1]

The latent period varies from a mean of 8.7 years in children and adolescents (16 years old or younger) to 13.5 years in adults with both osseous and extraosseous osteogenic sarcomas ($P = .02$). Excluding the nonosseous sarcomas, the mean latent period ranges from 8.3 years in children and adolescents (16 years or younger) to 13.8 years in adults ($P = .02$). In view of these figures, there are significantly shorter mean latent periods in patients 16 years or younger in contrast to those who are older than 16 years. The same conclusion is shared for both the osseous and the combination of osseous and soft tissue sarcomas.

True to expectations, the survival of patients in whom postradiation sarcomas develop is poor. The cumulative dis-

ease-free survival rate at five years is 17%, with an estimated median survival of one year. In the field of postradiation sarcomas, the past few decades turned out to be both good and bad. While scores of new cases have been recognized and added to the literature showing that treatment casts long shadows, in turn there was a definite improvement in the understanding of the causes, with a steady accumulation of knowledge of these rare malignant neoplasms. All of this should not arouse undue emotions and make us overly suspicious that the bugbear of a sarcoma lurks behind every irradiated patient. Instead, the occasional appearance of a secondary cancer arising in a field of irradiation should give one pause for thought and impose some restraint in the treatment planning that involves this therapeutic modality.

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Stress and Tension in Patient Care

PHYSICIANS TRADITIONALLY THINK of patient care as a relationship of trust and confidence between physician and patient. This has long been enshrined, in the minds of physicians at least, as the hallowed doctor-patient relationship. It extends, though sometimes to a lesser extent, to the relationship of other health care providers to their patients or clients. In any case, a physician, a patient, and whatever it is that takes place between them are at the true heart of patient care. There can be no doubt that this relationship of trust and confidence is being seriously eroded. There are new stresses on physicians, on patients, and on the relationships between them. Many new tensions are developing in this formerly trusting heartland of patient care, and one can readily suspect that there may be some adverse effects. So far this has received very little study or attention. But wherever there are stresses and tensions, the result is often uncertainty, anxiety, and tension, and these can erode trust and confidence.

The stresses on physicians are familiar, but they are increasing. There is always the stress of a difficult case, and there is the ever-increasing stress of trying to keep pace with the rapid progress in medical science and technology. There are growing tensions in relationships between physicians and the hospitals where they do much of their work, and, of course, there are stresses with third party payers of the care that physicians give, no matter what the system of practice. And perhaps physicians see the most anxiety producing of all to be the ever-present spectre of malpractice litigation, which makes their every action subject to review and criticism. This is at best unsettling; at worst, it makes every patient a potential adversary in a court of law.

There are also stresses—many of them relatively new—on patients. More of the responsibility for what is done or not done in patient care is being placed on patients. Some are eagerly assuming most of the responsibility for their own care. The legal doctrine of informed consent simplistically expects that every patient can be made so fully informed about his or her condition and the options for diagnosis and treatment that patient, not physician, theoretically becomes the one more competent to make the final decision as to what is to be done. While conceptually this may be ideal and desirable, in practice it can prove stressful for many patients, particularly when anxiety and fear of what they can never know and do not understand may already be present. For example, some states now require that all the options for diagnosing and treating cancer of the breast be explained to a patient, who must then decide herself what to do at a time when she is almost always under severe emotional stress and seeking help and advice. The media often contribute unwittingly to patient stress and anxiety. Horror stories of patient care gone wrong are vividly reported and frequently given repeated coverage, with little consideration for readers who may apply the horrific possibilities to their own situation, thus adding considerably to their perhaps already heavy burden of fear and anxiety.

The most stress producing of all for patients and their families may be the apparent lessening of the confidence of society as a whole in physicians and the medical profession. Rightly or wrongly, documented or not, and consciously or unconsciously, this lessening of confidence and trust is becoming very real, and it is beginning to produce new stresses and tensions in doctor-patient relationships. The traditional