REPORT AND COMMENTARY
The Carcinogenic Hazard of Radiation to the Breasts

Recently, articles have been appearing in medical journals implicating diagnostic X-ray examinations and other forms of radiation as a cause of breast cancer. Among them was an editorial, and a paper by C. K. Wanebo et al., in The New England Journal of Medicine. Wanebo reported that among survivors of the atomic bombings in Japan women exposed to 90 rads or more developed breast cancer at a rate two to four times the rate in comparable control groups. The editorial (reprinted on pages 25 and 26) referred to a paper by MacKenzie reporting that the incidence of mammary tumors was increased by extensive diagnostic chest fluoroscopy, and to a paper by Mettler, who reported a higher incidence of tumors in the irradiated breasts than in the nonirradiated breasts of women who had in the past received radiotherapy for mastitis.

Studies by Myrden and Hiltz, reported in the Canadian Medical Association Journal and Medical World News, revealed that 22 percent of 300 women exposed to multiple fluoroscopic examinations of the chest during pneumothorax therapy for tuberculosis had developed breast cancer, a rate of 7.3 percent, while only 4 cancers were found among 483 women who did not receive pneumothorax therapy, a rate of 0.83 percent.

Because breast cancer is the leading cause of death from cancer in American women (69,000 cases will be diagnosed in 1970), these reported effects are of major interest. Therefore, the editor invited the following distinguished authorities in radiology to comment on these reports:

RICHARD H. CHAMBERLAIN, M.D.
Director
Department of Radiology
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania

ROBERT L. EGAN, M.D.
Professor of Radiology
and Chief, Mammography Section
Emory University School of Medicine
Atlanta, Georgia

ROGER A. HARVEY, M.D.
Head, Department of Medical Radiology
University of Illinois
Medical Center
Chicago, Illinois

LOUIS H. HEMPELMANN, M.D.
Professor and Chairman
Department of Radiology
University of Rochester
School of Medicine and Dentistry
and Strong Memorial Hospital
Rochester, New York

JUSTIN J. STEIN, M.D.
Professor of Radiology and Chief, Radiation Therapy Division
Department of Radiology
The Center for Health Sciences
Los Angeles, California

References
1. Cronkite, E. P.: More hazards of radiation. New England J. Med. 279: 714-715, 1968.
2. Wanebo, C. K., et al.: Breast cancer after exposure to the atomic bombings of Hiroshima and Nagasaki. New England J. Med. 279: 667-671, 1968.
3. Myrden, J. A., and Hiltz, J. E.: Breast cancer following multiple fluoroscopies during artificial pneumothorax treatment of pulmonary tuberculosis. Canad. M.A.J. 100: 1025-1028, 1969.
4. "When fluoroscopy causes cancer," Medical World News, August 8, 1969, p. 14a.
—Editorial by Eugene P. Cronkite, M.D., In the New England Journal of Medicine 279: 714-715, 1968.

More Hazards of Radiation

Radiation must be accepted as a tumorigenic agent in man. Skin cancer, which followed radiation-induced dermatitis and ulceration, made martyrs of early roentgenologists. Osteosarcomas and carcinoma of the paranasal sinuses resulted from ingestion of orthorium by many radium watch-dial painters. Hundreds of these workers are still being studied to ascertain other late effects from this unique radiation exposure. Thyroid tumors, including cancer, have been found in people exposed to fallout and atomic bomb radiation. Furth and Furth, in 1936, demonstrated a high incidence of leukemia in mice after exposure to radiation. Accordingly, a systematic search was made for leukemia in the Japanese atomic bomb victims, and indeed it was found—the incidence being proportional to the dose of radiation above 100 rads.

Several studies in mice and rats have shown that radiation produces diverse mammary tumors after single doses and protracted exposure. The response in rats is linear between 25 and 400 rads. The yield of tumors was suppressed by ovariectomy. Irradiation of mammary tissue alone or in vitro with autotransplantation was sufficient to induce tumors.

MacKenzie suggested that the incidence of mammary tumor was increased by extensive fluoroscopy. Mettler et al. have retrospectively followed women who had received radiotherapy to a single breast for mastitis. Tumors appeared in higher incidence in the irradiated than in the nonirradiated breast. Now, in this issue of the Journal, Wanebo et al. report that the incidence of tumors in the breasts of the females exposed to atomic bomb radiation at Hiroshima and Nagasaki is increased and, in contrast to nonexposed women, occurs in the premenopausal period. The association between radiation exposure and breast tumors in women has now been suggested in three studies. Though still tenuous, this association demands continuing critical study. Where do we go from here? How can such an association be confirmed or refuted? If it is confirmed, how can the association be quantified with delineation of factors that impede or accelerate the development of tumors in the irradiated target tissue? Animal studies can be helpful—particularly in revealing mechanisms—but only if the proper strain of rat is chosen. Since some strains of rats are much more sensitive than others, animal studies will not answer quantitative questions for man. The solution is simple: to find out what has happened in man, man must be studied; and to find out what will happen in man, man must be studied. Animal studies can only point the way in the most general terms. In fact, the rat mammary studies might have allowed one to predict the current findings of an apparent increase in tumor incidence over 50 rads exposure.

Funding agencies, it is hoped, will have the wisdom to support prospective as well as retrospective studies on all irradiated human populations. Certain-
ly, physicians are armed with the knowledge of potential hazards of radiation so as to avoid unnecessary exposure of patients. One also hopes that political leaders will consider long-term effects of radiation before plunging the world into nuclear warfare.

References
1. Furth, J., and Furth, O. B.: Neoplastic diseases produced in mice by general irradiation with x-rays; incidence and types of neoplasms. Am. J. Cancer 28: 24-45, 1938.
2. Bond, V. P., et al.: Studies on radiation-induced mammary gland neoplasia in the rat. III. Relation of neoplastic response to dose of total-body radiation. Radiation Res. 11: 372-395, 1960.
3. Shellabarger, C. J., and Schmidt, R. W.: Mammary neoplasia after in vitro x-irradiation of mammary tissue. Nature (London) 218: 192-193, 1968.
4. MacKenzie, I.: Breast cancer following multiple fluoroscopies. Brit. J. Cancer 19: 1-8, 1965.
5. Mettler, F. A., Jr., et al.: Breast neoplasms in women treated with x-ray for post-partum mastitis: preliminary report. Submitted for publication.

Dear Doctor Grant:

It is no news that radiation, in sufficiently high doses, can be carcinogenic. What is uncertain and of prime importance to us are:

1. Whether low doses of radiation carry significant hazards of carcinogenesis;
2. What influence other carcinogenic factors have played in any study population;
3. What basis there is for practical decisions as to how much radiation is justified for a given beneficial purpose.

The ABCC* paper on breast cancer is interesting, but does not give very satisfying answers. It seems to me to be far less significant than the Editor of the New England Journal of Medicine thought. The data in Table 2 show 22 cases expected and 22 cases observed. The excess of cases observed in the "high dose" groups justifies including radiation among the possible carcinogenic factors but it should be remembered that these are also the same people who had higher exposure to blast, injury, nutritional disturbance, infections and all the other circumstances of being closer to the epicentres of the explosions. The same data could also be interpreted as showing that radiation doses of 10 rads and less protected women from breast cancer!

The use of radiation should be kept in competent hands. Low doses such as are needed in most diagnostic procedures should be kept low by excellent equipment, appropriately skilled operations and highly qualified supervision, but neither patients, the medical profession nor the public at large are served by "scare" tactics. We have a current unsolved problem in how extensively mammography, with moderately high radiation exposures (for diagnostic procedures), should be used. The data in the New England Journal of Medicine article are so far different in dose pattern and other circumstances that they offer little help for such problems. They also appear to be too indecisive to be the basis of antiwar philosophizing. Nuclear warfare should be so repugnant to all of us, from every standpoint of human values, that there is no need for distorting these limited scientific observations beyond their context.

RICHARD H. CHAMBERLAIN, M.D.

Dear Doctor Grant:

Since the editorial, "More Hazards of Radiation," which appeared in the September 26, 1968 issue of the New England Journal of Medicine, was apparently prompted by the article, "Breast Cancer after Exposure to Atomic Bombings," by Wanebo et al., in the same issue, my remarks will be directed primarily to that article.

If physicians look for cancer, more will be found (particularly breast can-
cer, which is second only to skin cancer in frequency). Stevens' mammography survey of clinically normal women over the age of 40 years revealed 8 unsuspected breast cancers in 1,223 women, an incidence of 6.5/1,000. Four of these women were actively menstruating. In the series of Japanese women studied by Wanebo, there were 45 cases of suspected breast cancer, with only 27 cases proved and 4 retained as possible cases. Sweeping statements apparently were based on categories that differed by only two or so cases; such materials are not very convincing. The autopsy rate varied with the amount of radiation received by the patients; only 75 percent of breast tumors were histologically proved.

At Emory, 80 percent of our breast cancers are Stage O or I with a tendency toward a younger than average age group. Even with such early lesions, over 10 percent of these breast cancers are clinically unsuspected, being detected by mammography. Breast cancer can be detected by mammography as early as two years prior to clinical recognition: evidence is accumulating that many breast cancers are slow-growing. Since breast cancer is the leading cause of death in women age 40-44 years in the United States, it is not unreasonable to assume, as our methods of detection improve, that the mean age of onset in the United States could be less than that of 43.3 years in the exposed Japanese women.

There may be fewer variables by considering consecutive breast cancers found in this series and the estimated radiation to the patients as recorded in the following Table:

| Total Dose in Rads | Women With Breast Cancer |
|--------------------|--------------------------|
| 0 (no known radiation) | 11 |
| 18-55               | 6 |
| 86-96               | 2 |
| 116-799             | 12 |

Thus, the number of breast cancer patients with no known radiation was the same as the number having greater than 100 rads. There were more than 1½ times as many cancers with less than 100 rads than with more than 100 rads. Some insecurity exists when methods of estimation of dose must be changed, and four of 31, or 13 percent of the cases, have an unknown quantity of radiation. The numbers of cases as opposed to the expected number are so small that a few cases could easily change the data by several hundred percent one way or another. Patients with unknown radiation had the same incidence of cancer as those receiving 40-89 rads and differ from the 90-199 rads and 200+ rads group only by 2 and 3 cases respectively. If these two cases fell into the 10-39 rad group, as the authors feel they were well shielded, that would be one of the greatest discrepancies between observed and expected incidence. Over one half of the cancers were found in subsequent examinations, and yet many women had only one examination; these small totals could be readily reversed by observation of only a very few more cancers.

The human body is complex and there are complexities of influences upon it. One of the few known facts about human breast cancer is that it is sex linked (it is 49 times more common in the female than the male). This has led to the conjecture that hormonal status is implicated. Whole body irradiation may then only be influential on the breast by indirect action through the ovaries or pituitary gland and not the "irradiated target tissue." The innuendo that whole body irradiation by neutron and gamma irradiation from atomic bombs is the same as that of diagnostic X-irradiation of a body part is tenuous. Local irradiation as opposed to whole body irradiation may be no more comparable than mice and men. Linking patients with 100 rads to those having
such massive dosages to cause radiation dermatitis is hardly acceptable.

To me, no definite carcinogenic effect on the breast "seems" established, but, as suggested, whole body irradiation particularly may deserve investigation.

Two things are clearly shown by this report: 1) breast cancer can be found if looked for; and 2) the expected incidence of breast cancer of 2.2/1,000 in these Japanese women studied may be more realistic than the usually published extremely low incidence of the disease in Japan.

ROBERT L. EGAN, M.D.

Dear Doctor Grant:

I am responding to your inquiry of August 19, 1969, regarding occasional reports of a relationship between rather large total body or regional exposures to ionizing radiations and subsequent appearance of breast cancer many years later. I had anticipated some increase in cancer in several sites as well as other less dramatic late sequellae following the bombings in Hiroshima and Nagasaki. While the number of cases of breast cancer are relatively small, the statistics seem to have been reasonably well handled. I would be more alarmed if there had been a shift or predominance of cell type in these breast cancer cases.

The fact that none have been reported in males may possibly indicate an endocrine facilitating requirement. At the National Breast Cancer Conference this year I was intrigued with an implied possible relationship between estrogen effect and ionizing radiation.

Another group of patients, undoubtedly numbering several thousand in this country, received small therapeutic doses of radiation for acute postpartum mastitis 25 or more years ago. Most cases had one breast treated. They were considerably younger than the indicated premenopausal special hazard group at the time of the bomb radiation exposures. A careful, continuing follow-up on these patients is especially valuable as far as effect on a lactating breast in a relatively young adult female is concerned; i.e., in helping detect a possible age risk factor with radiations.

The possible hazards of fluoroscopy in relation to development of breast cancer have almost been eliminated through improvement in fluoroscopes and, more importantly, improved methods of treating and evaluating chest diseases.

The resurgence in interest in diagnostic mammography has not been lacking in constant concern over radiation dosage to normal tissues. Precise radiation dosage measurements, rigid adherence to specified techniques of exposure, and continuing interest and cooperation in evaluating other diagnostic tools such as thermography, ultrasound, and xerography reflect a genuine concern of all those working in this field for the best and safest detection method.

There is a slight hazard with any form of widely-applied disease detection program whether it be technique, interpretation, or device. As long as the group being surveyed is in positive balance with yield over risk, then it is a justifiable procedure.

ROGER A. HARVEY, M.D.

Dear Doctor Grant:

In response to the editorial in the New England Journal of Medicine entitled, "More Hazards of Radiation," I can only agree fully with the thoughts expressed by the author concerning the probable carcinogenicity of ionizing radiation for human breast tissue. There is no doubt that radiation exposure can induce neoplastic transformation in almost any human or animal tissue if exposure conditions are optimal. The gradual unfolding of the story of radiation carcinogenesis in man has been carefully documented in the 1964 report of United Nations Scientific Committee on
the Effects of Atomic Radiation. Although this report describes many varieties of radiation-induced cancer in man, only in the case of leukemia and thyroid cancer is there enough information about exposure dose and disease incidence to permit quantitative estimates of the risks involved.

In expressing risks of developing a specific form of cancer after irradiation, the most conservative attitude must be adopted. In the risk estimates mentioned above, it has been assumed that there is a linear relationship between dose and cancer incidence. It was assumed further that this dose relationship holds in the very low dose range approaching zero. The best estimates of risk of developing leukemia or thyroid cancer are approximately one and five cases per year, respectively, per million people exposed to one rad each. Whether these risk values apply to the very low dose range, is of course, uncertain. There is the hope that chromosomal damage in somatic cells exposed to small doses or to low dose rates may be almost completely repaired as it appears to be in mouse ova. Unfortunately, there is accumulating evidence that small doses in children can be oncogenic (e.g., 20 rads for thyroid nodularity, presumed neoplastic) and leukemogenic or carcinogenic in fetuses (e.g., several rads). Therefore, we cannot dismiss the possibility of serious late consequences when large populations are exposed to small doses.

In the editorial, the possible hazards of irradiating breast tissue are discussed. In the three female populations considered, each with a higher than expected breast cancer rate, it seems quite likely that radiation exposure was an etiologic factor. The doses to the breast due to localized fluoroscopy in the Nova Scotia women were probably high even though protracted. In the irradiated Japanese women treated with X-rays for acute mastitis, the doses were much lower, e.g., over 90 rads (total body) and less than 200 rads (localized), respectively. Although a dose response was not demonstrated in these reports (probable because of the small number of cases), such a possibility must be considered because of the linear dose response in rats down to 25 rads. The potential carcinogenicity of exposure to small doses in the range of 5 rads used in mammography is of considerable contemporary interest. The risk of cancer in each individual patient is small but the number of persons affected when large populations are exposed may be substantial. The chances of discovering an existing lesion must be weighed against the risks of possible serious late effects when mammography is contemplated in the screening of large groups.

I agree with the author that more epidemiologic studies are needed to establish with greater certainty the risks of irradiation to the female breast.

LOUIS H. HEMPELMANN, M.D.

Dear Doctor Grant:

I have read with considerable interest the article entitled, "Breast Cancer After Exposure to the Atomic Bombings of Hiroshima and Nagasaki," and an editorial entitled, "More Hazards of Radiation," which appeared in the September 26, 1968 issue of the New England Journal of Medicine, and a page from the August 8, 1969 issue of Medical World News entitled, "When Fluoroscopy Causes Cancer."

The article on breast cancer among the survivors of the atomic bombings in Japan suggests that "a fairly definite carcinogenic effect seems established." Those women exposed to 90 rads or more total body irradiation developed breast cancer at a rate of 2 to 4 times the rates observed for the study sample. This report represents a detailed study and appears to be statistically valid.

MacKenzie has found breast cancer to be significantly more frequent in wom-
en who have had multiple fluoroscopic examinations during the treatment of pulmonary tuberculosis.

The typical fluoroscopic examination involved a 10 to 15 second exposure of three to five milliamperes at about 90 kv. This would correspond to between 1.0 and 2.5 R per exposure to the skin of the back of a supine patient (assuming normal filtration and tube to table distance). The breast would then receive only the exit dose which would be much less than 10 percent of the exposure rate mentioned above.

My reactions to articles of this type are as follows:

1. The uses of radiological procedures are going to increase both in quality and quantity in this country.
2. As a result of studies which suggest a correlation between ionizing radiation and the later development of thyroid cancer and of leukemia, a more cautious attitude has developed, especially toward exposure of infants and children. Women who are pregnant are carefully considered before receiving any pelvic radiation.
3. Education beginning with medical students and extending through the postgraduate years about radiation protection, the use of proper radiologic techniques, and of the potentially harmful effects of the use of unnecessary ionizing radiation must be given.
4. Approximately 58 percent of the radiation exposure to man comes from natural sources, and about 41 percent is man-made, with less than 1 percent from fallout from nuclear weapons.
5. The changes in man resulting from exposure to ionizing radiation may be somatic, that is, occurring during his own lifetime, or they may be of genetic significance and be transmitted to future generations.

6. It is not known what the threshold dose is for the development of somatic injury, that is, the amount of radiation to which an individual or part of an individual may be exposed before permanent injury results. There may be no threshold dose for the causation of genetic effects.

7. Stone has recommended that every precaution be taken to protect the patient from any unnecessary radiation; however, he also commented that “A method of comparing the genetic danger to our human race from allowing the mentally deficient to reproduce with the genetic danger of using roentgen rays in medicine has not been developed. If geneticists would produce as much educational material on the dangers of propagating known mental defects as they are producing on the dangers of roentgen rays they might even accomplish more for posterity than they are now.”

8. Physicians, and particularly radiologists, have taken steps to deal with the hazards of ionizing radiation. The tolerance dose of radiation was listed as 0.2 R per day in 1931; 0.1 R per day (measured in air) in 1936; in 1948 the maximum permissible dose was given as 0.3 R per week.

9. It has been known for many years that ionizing radiation can produce a carcinogenic effect. The mechanisms of the carcinogenic effects of radiation are not known. The effect may be both the result of a direct and indirect action. Radiation is one of the best mutagenic agents and this action may produce the malignant change by altering the hereditary material of the cell and rendering it free of the normal growth control.
In the Japanese study the women were exposed to 90 rads or more of total body radiation. In the MacKenzie study the women were exposed to very small doses of radiation fairly frequently over a period of time. Fortunately, modern methods of therapy have greatly decreased the need for numerous fluoroscopic examinations in the same patient who has pulmonary tuberculosis. The risk from the small dose of radiation (approximately 5 R per skin port) to the breast received during mammography is fully justified when this procedure is indicated. The potential risk from the radiation is exceedingly minimal as compared to the possible medical benefits. Also, mammography is the preferable way of detecting the earliest of the early breast cancers—lobular carcinoma in situ. Its use in patients in the high-risk group can be very beneficial.

10. I see no reason for heated debate pro and con about articles involving ionizing radiation. We know so little about it. We must increase our knowledge as rapidly as possible and see to it that individuals who use ionizing radiation are properly educated and that they observe all the known rules for radiation protection. One of the best ways to increase our knowledge is to study the long-term effects on man, and such studies should be encouraged.

In conclusion, patients accept risks when undergoing surgical operations and in taking drugs of various types. There certainly should be no hesitancy of anyone having diagnostic X-ray examinations or of accepting radiation therapy when it is indicated and is properly administered.

JUSTIN J. STEIN, M.D.

Reference
Stone, R. S.: Common sense in radiation protection applied to clinical practice. Am. J. Roentgenol. 78: 999-999, 1957.

Bibliography
Stein, J. J.: The carcinogenic hazards of ionizing radiation in diagnostic and therapeutic radiology. Co-A Cancer Journal for Clinicians 17: 278-287, 1967.

WILL FOR A WORLD FREE OF CANCER

Official probate records reveal that nearly 70 percent of all Americans die intestate. This subjects their estates to the management of court-appointed administrators and requires their assets be distributed in a rigid manner as prescribed by statutory law. The net result is often 180 degrees apart from that which the deceased would have willed! . . . What legacy or greater blessing can thoughtful legators, in planning the distribution of their assets, hope to pass on to their loved ones than a world free of cancer—man’s most vicious of killing diseases?

—Thomas P. Ulmer, from a speech entitled, “The Value of Research and Analysis in Promoting Legacies,” presented at the American Cancer Society’s Southern Area Seminar, Atlanta, Georgia, October 16-17, 1969.