was thought to cause acute respiratory distress and sudden death. Duffy and Fitzgerald[61] made the important observation in 1950 that more than one third (36 percent) of children with papillary and follicular carcinomas of the thyroid had received radiation therapy to the upper mediastinum or neck. Subsequent publications in the United States reported that from one-third to three-fourths of all children and young adults with benign and malignant thyroid neoplasia received prior irradiation to the head, neck and/or mediastinum during the first five years of life.[62-69] In a recent publication from Israel by Modan et al.,[70] the risk of thyroid cancer was significantly enhanced in children 12-23 years after receiving X-ray epilation treatment of the scalp for tinea capitis. In New York City, Shore, Albert and Pasternak[71] observed an increasing incidence of thyroid adenomas 15-30 years after X-ray epilation for tinea capitis. Radiation-induced thyroid cancer may be characterized by multi-focal malignant lesions.

It is evident from all such studies that irradiation to the thyroid in infants, children and young adults up to 20 years of age carries a far greater risk of inducing neoplasia than does similar exposure in adults. This increased risk is probably due to the far greater rate of mitosis in the young thyroid and, as a consequence, the greater likelihood of inducing cytogenetic abnormalities in viable cells.

Hempelmann and co-workers[72] noted that following irradiation of the thymus in infancy, the incidence of thyroid cancer in women 15-29 years of age increased five times over that of the rest of the irradiated population. In contrast, the incidence of thyroid cancer in irradiated women younger than age 15 or older than age 30 years was almost identical with that found in the irradiated men. The age period 15-29 years coincides with the onset of ovulatory menstrual cycles and maximal reproductive activity. During pregnancy, the thyroid gland frequently undergoes physiologic hypertrophy, presumably secondary to an increased renal loss of iodide and heightened secretion of thyroid-stimulating hormone. In areas of endemic goiter secondary to low dietary intake of iodine, the prevalence of thyroid hypertrophy during gestation is further enhanced. These observations are particularly pertinent when we recall that in animal experimentation, increasing amounts of thyroid-stimulating hormone after radiation exposure are associated with an increasing incidence of thyroid cancer.

On the assumption of linearity in the dose-response curve, the National Academy of Sciences has estimated that the risk of thyroid cancer developing in irradiated children was within the range of 1.6-9.3 cases/year/million exposed children/rem.[73] (In terms of biologic damage, the rem is equivalent to 1 rad of 250 KVP X-rays.) The assumption of linearity was questionable under 20-50 rads until Modan's study which suggested a mean exposure dose to the thyroid of 6.5 rads.

In terms of a clinical approach to ensuring early diagnosis, all children and young adults who have had X-ray treatment to the chest, neck, face or scalp should be kept under continuing surveillance. The thyroid gland, cervical lymph nodes and salivary glands should be examined meticulously. When there is a history of irradiation and particularly when palpable thyroid disease is suspected, the clinical examination should be followed by a thyroid scan using ^{99m}Technetium pertechnetate. The ^{99m}Tc thyroid scan delivers 0.1 rad to the adult thyroid, as compared with the ^{131}I scan which delivers 100-200 rads. Although information on past X-ray exposure may not be known by a young patient, nor readily volunteered by parents, the examining physician should pursue any uncertain aspect of the past medical history by securing copies of pertinent medical records.

The optimal therapeutic approach to the young adult with no currently detectable abnormality but with a past history of irradiation is less clear. The efficacy of thyroid hormone to suppress thyroid stimulating hormone (TSH) in preventing malignant neoplasia is unproven although suppressive therapy has been used in the evaluation of a thyroid nodule.[74]

The tumorigenic effect of irradiation on the thyroid has also been documented through a prospective study by the Atomic Bomb Casualty Commission and the Japanese National Institute of Health (ABCC-JNIH). The ABCC-JNIH Adult Health Study Program commenced in 1958 and includes standardized biennial medical examinations of about 20,000 persons selected from the 1950 cohort of 109,000 atomic bomb survivors. Prior to 1955, excessive mortality due to leukemia was the only evidence of radiation carcinogenesis among the atomic bomb survivors. When compared with a risk of 1.0 in age and sex-matched controls with little or no exposure, the relative risk of clinically diagnosed thyroid cancer in the high exposure subgroup was increased significantly to 5.0 in women and 9.4 in men. Whereas the relative risk of clinically apparent thyroid cancer in men who were exposed within 2,000 meters from the hypocenter of the bomb explosion was increased significantly only during the examination period 1958-1962, the risk in women with similar exposure continued to be excessive, even after 25 years of follow-up. The cumulative risk of thyroid cancer was highest in subjects who were under 20 years of age in 1945 and were exposed to at least 50 rads of gamma and neutron radiation.[75,76]

There have been isolated case reports of thyroid cancer occurring between four and 12 years after ^{131}I therapy for thyrotoxicosis.[77] A preliminary analysis of the Cooperative Thyrotoxicosis Follow-up Study indicated that the incidence of thyroid cancer or leukemia was not significantly different between 22,000 patients treated with ^{131}I and 14,000 patients treated with surgery or antithyroid medications.[78] In this comprehensive study, the mean follow-up time was 15 years, and most of the patients examined were over 40 years of age when first treated. The report concluded that children and young adults treated with lower dose ^{131}I therapy for hyperthyroidism appeared more susceptible to the development of adenomas. Higher ablative doses of 5,000-10,000 rads of ^{131}I will lead to a higher incidence of hypothyroidism, and a greater destruction of thyroid parenchyma which may preclude all replication and tumorigenesis. Since the latency period for radiation-induced thyroid cancer may be as long as 20 to 40 years, the final chapter on the treatment of thyrotoxicosis in children with radioactive iodine has not yet been written.

In 1954, the population of the Rongelap Atoll in the Marshall Islands was exposed to radioactive fallout from a thermonuclear bomb.[79] The inhaled and ingested beta and gamma radionuclides included the short-lived isotopes of radioactive iodine which resulted in an estimated exposure dose to the thyroid of between 700-1,400 rads in children and 220-450 rads in adults. The highest incidence of benign and malignant thyroid nodules was recorded clinically in the heavily exposed groups who were under 10 years old at the time of exposure. The annual incidence of thyroid cancer was estimated to be 2.1 per million children per rad.

Thyroid and Breast Cancer—Is There a Common Etiology?

In a review of the Connecticut experience between 1935-1964, Schoenberg[80] failed to observe a statistically significant increase in the incidence of thyroid cancer in breast cancer patients. The risk of breast cancer was increased 1.8 times to expectation in thyroid cancer patients, but this was not determined to be statistically significant.

During the brief interval of follow-up obtained in the Third United States Cancer Survey (1969-1971), the incidence of histologically diagnosed thyroid cancer was increased significantly in women with breast cancer, but the converse relationship, i.e., an increased incidence of breast cancer in women with thyroid cancer, was not observed.[81]

In a survey of multiple primary cancers at Memorial Sloan-Kettering Cancer Center, Schottenfeld and Berg[82] observed that the incidence of clinically diagnosed papillary and follicular thyroid carcinomas in 9,792 women with previously diagnosed breast cancer was 0.2 per year per 1,000