Epidemiology of Thyroid Cancer

David Schottenfeld, M.D., and
Susan T. Gershman, M.P.H.

Thyroid cancer mortality in the United States in 1976 has accounted for approximately 1,150 deaths, or 0.5 percent of all cancer deaths in women and 0.2 percent in men.¹ The age-adjusted mortality per 100,000 in 1967 was 0.9 in non-white women, 0.6 in white women, and 0.3 in white men and 0.2 in non-white men.² The time trend analysis for age-adjusted mortality (1950-1967) indicated significantly decreasing mortality in white women and men. For non-whites, there were no significant trends in age-adjusted mortality (Figure 1). The female: male ratio of age-adjusted mortality rates was 2.0 in the white and 4.5 in the non-white populations.

For 1976, the American Cancer Society has estimated that there were 5,900 new cases of thyroid cancer in women and 2,200 cases in men. The average annual age-adjusted incidence rates per 100,000 as determined by the United States Public Health Service Third National Cancer Survey (1969-1971) were 5.2 in white women, 3.2 in black women, 2.2 in white men and 1.1 in black men. The age-specific incidence in white women peaks initially at the interval 30-34 years (9.6/100,000), and then again after 65 years (9.2-10.4/100,000). The age-specific incidence in white men tends to fluctuate, but the overall pattern is one of gradually increasing incidence with increasing age (Figure 2). A similar pattern suggesting bimodality is evident in the curve for age-specific incidence in black women (Figure 3).

Although secular or temporal trends in the incidence of thyroid cancer are not available for the entire United States, they are provided by the population-based registries that are maintained by state health departments. The age-adjusted incidence in women, reported by the Connecticut Tumor Registry, increased from an average annual rate of 1.4/100,000 (1940-1949) to 4.0/100,000 (1970-1973), almost a threefold increase. The age-adjusted incidence in men increased from 0.6 (1940-1949) to 1.5/100,000 (1970-1973), a relative increase of 2.5 and similar to the trend noted in women (Figure 4). In both women and men, the increasing incidence during the past 25 years has been limited to persons under age 50 years (Figures 5 and 6).² Carroll et al.⁴ reported in New York State that the age-standardized incidence rates for thyroid cancer more than doubled between 1941 and 1962. When the age-specific incidence rates were examined, the in-
creases between 1941 and 1962 were limited to persons under age 55. Cohorts born after 1910 and before 1949 demonstrated a doubling of age-specific incidence with each successive decade of birth. The change in the cohort pattern after 1910 coincided with the administration of X-ray for thymic enlargement, oropharyngeal lymph-
oid hyperplasia and cervical lymphadenitis in infancy and early childhood, and was consistent with the hypothesis that ionizing radiation was a cause of thyroid cancer in children and young adults.

Whether increasing incidence rates are real or artifactual depends upon the degree to which they have been influenced by changing diagnostic criteria and completeness of reporting. For example, the occult sclerosing non-encapsulated papillary carcinomas and intraglandular encapsulated follicular carcinomas with minimal vascular invasion have received increasing recognition during the past 20 years. In their review of thyroid cancer in Olmsted County (1935-1965), Verby et al. 6 attributed the observed substantial increase in incidence to the greater recognition of occult papillary tumors during the 1955-1965 decade.

Variations in the incidence of clinically apparent thyroid cancer by country and race may reveal important interactions between host and environmental factors. However, such comparisons must be interpreted cautiously since they are subject to variations in the procedures used for neoplastic classification and registration and in the quality of diagnostic and therapeutic services. The pattern of geographic and racial differences in the incidence of clinical thyroid cancer should be distinguished from that observed for occult thyroid cancer.

In 5,636 consecutive autopsies on cancer patients at Memorial Hospital, the prevalence ratio of occult thyroid cancer as an independent primary cancer was 6.4 per 1,000 autopsies. The method of examination consisted usually of a single section from each lobe when no tumor was grossly visible. The peak prevalence in women was 19.6 per 1,000 at 20-29 years of age,
and 10.4 per 1,000 in men at 30-39 years. Unlike most carcinomas, there was no indication that subclinical thyroid cancer increases with increasing age. Sampson et al. arrived at a similar conclusion in their autopsy study in Hiroshima and Nagasaki. In autopsy studies conducted in the United States where the thyroid gland was examined meticulously, the observed prevalence of occult thyroid cancer varied between 1.0-5.7 percent. Whereas the prevalence due to clinically apparent thyroid carcinoma predominates in women, occult thyroid cancer occurs almost as frequently in men.

The prevalence of latent thyroid cancer (i.e., 1.5 cm. or less in maximum dimension) diagnosed at autopsy in the Hawaiian Japanese and native Japanese (17.9-24 percent) is at least four times that observed in comparable autopsy studies from Canada and the continental United States. However, clinically apparent thyroid cancer incidence rates in the Hawaiian Japanese and the native Japanese are not significantly different from those in the Hawaiian whites and the continental United States whites (Table I). The age-adjusted incidence in the Hawaiian Chinese women is greater than that observed in the Japanese and Caucasian groups in Hawaii and is almost 18 times that reported in Singapore Chinese women.

More recent information on this finding has been furnished by Kolonel and Rellahan from the Hawaii Tumor Registry (Table II). These rates were based upon a total of 110 patients in 1960-1964 and 184 patients in 1968-1972. The small number of cases in each racial group allowed for wide sampling fluctuations. The rates in the Chinese and Hawaiian women were in contrast to those seen in the Japanese and Caucasian women. For
example, between 1960 and 1964 the Chinese women (six percent of all women) incurred almost nine percent of all incident cancers and 20 percent of incident thyroid cancers; the Japanese women (36 percent of all women) incurred 35 percent of all cancers and 32 percent of thyroid cancers. The proportional incidence would suggest that the Chinese women in Hawaii may be at high risk for thyroid cancer. The age-standardized morbidity ratio indicated a 43 percent excess of thyroid cancer in the Chinese women, but the 95 percent confidence limits were not statistically significant for a Poisson distribution. Austin provided incidence data by race for the San Francisco-Oakland Standard Metropolitan Statistical Area (Figure 7.)\(^7\) The age-adjusted rates were computed by the direct method using the 1950 population of the continental United States as the standard. The incidence in the Chinese women was similar to that registered in white United States women, and exceeded the rates seen in Japanese and black women.

The female: male ratio of age-adjusted incidence rates in the Hawaiian Chinese is 5.9 and, in the Hawaiian Chinese men, the age-adjusted incidence is seven times that noted in the Singapore Chinese men. Fraumeni and Mason\(^18\) reported that thyroid cancer mortality in the Chinese residing in the United States during 1950-1969 was increased, particularly in males, when compared with the United States white and black populations. The geographic and racial patterns for thyroid cancer incidence and mortality should be studied carefully for differences in histopathology and natural history, and particularly among different generations of Chinese immigrants to the United States. It is possible that the complex of host and environmental factors that promote clinical expression of disease are distinctive from those that initiate tumorigenesis.

**Pathology**

The majority of thyroid tumors arise from the epithelial elements of the gland. Most tumors originate from the follicular (acinar) cells, and at least one type, medullary carcinoma, develops from the parafollicular cells. The biologic behavior of thyroid cancer is extremely variable, and any system of histologic classification should serve to identify important differences in epidemiology, natural history, prognosis and the rationale of therapy. At Memorial Hospital, we have classified the epithelial tumors into papillary, occult sclerosing, follicular, Hurthle cell, medullary, and spindle and giant cell.

The occult sclerosing carcinoma may be classified as a subtype of the papillary carcinoma; it is a small (commonly less than 1.5 cm. in diameter), unencapsulated low grade carcinoma, showing marked desmoplasia. The Hurthle cell carcinoma represents a variety of follicular carcinoma and is composed of large cells with small hyperchromatic nuclei and relatively large amounts of pink cytoplasm. The resulting simplified taxonomy of thyroid carcinoma—papillary, follicular, medullary and anaplastic—is currently in common use.

The percentage distribution by cell type will vary by age, sex, geographic area, and source of pathologic material. Surgical materials tend to select the differentiated carcinomas (i.e., papillary and follicular), whereas mortality studies tend to select the anaplastic carcinomas (i.e., spindle and giant cell).\(^20\)

In the Third National Cancer Survey, papillary carcinoma was the most common form, accounting for 64 percent of all primary malignant tumors (Table III). This type of tumor has a peak incidence in the third and fourth decades, and occurs three times more frequently in women than in men. The disease is distinctly less malignant in children and young adults. In our experience at Memorial Hospital, not more than 10 percent of these tumors may be classified as pure papillary carcinomas. The remainder of these tumors variously contain follicular, trabecular, Hurthle cell, epidermoid or spindle and giant cell features. The finding of foci of giant or spindle cell anaplastic carcinoma interspersed throughout the papillary and follicular structures is considered a poor prognostic sign.\(^31\)

The percentage relative frequency of
**TABLE I.**

**THYROID CANCER.**
Comparative international average annual
age-adjusted incidence per 100,000 population.

|                | Females | Males |
|----------------|---------|-------|
| **United States** |         |       |
| Hawaii: Chinese  | 20.7*   | 14.1†  |
| Hawaii: Filipino | 14.3    | 18.7   |
| Hawaii: Hawaiian | 10.1    | 16.0   |
| Hawaii: Japanese | 6.5     | 7.8    |
| Hawaii: Caucasian| 5.4     | 9.2    |
| Connecticut  | 3.0     | 3.7    |
| California, Alameda: White | 7.4 | 5.5 |
| California, Alameda: Black | 2.3 | 1.9 |
| **Israel** |         |       |
| All Jews | 4.2    | 8.3    |
| Jews born in Africa or Asia | 4.6 | 6.7 |
| Jews born in Europe or America | 4.0 | 6.4 |
| Jews born in Israel | 2.0     | 6.1    |
| Non-Jews | 2.0    | 1.8    |
| **Japan** |         |       |
| Okayama Prefecture | 3.3 | 2.4 |
| Miyagi Prefecture | 2.0 | 2.1 |
| **New Zealand** |         |       |
| Maori | 5.5    | 2.3    |
| European | 2.5    | 2.0    |
| **South Africa** |         |       |
| Natal: African | 3.3    | 0.2    |
| Natal: Indian | 3.0    | 1.0    |
| Cape Province: White | 3.0 | 1.2 |
| Cape Province: Bantu | 2.7 | 0.0 |
| Cape Province: Non-white | 1.1 | 0.6 |
| **Norway** |         |       |
| All | 2.4    | 3.7    |
| Urban | 2.5    | 3.1    |
| Rural | 2.4    | 4.3    |
| **Columbia, Cali** |         |       |
| 5.5    | 5.5    | 3.5    | 2.7 |
| **Canada, Quebec** |         |       |
| 2.5    | 2.7    | 0.9    | 1.0 |
| **Finland** |         |       |
| 2.4    | 2.9    | 1.0    | 1.1 |
| **India, Bombay** |         |       |
| 1.5    | 1.8    | 0.7    | 0.7 |
| **Denmark** |         |       |
| 1.4    | 1.8    | 0.8    | 0.8 |
| **U.K., England and Wales** | | |
| (Liverpool Region) | 1.3 | 1.2 |

**Sources:** *See reference 13. †See reference 14.
the remaining cell types was follicular (18 percent), medullary (three percent), anaplastic (three percent), sarcoma (less than one percent), lymphoma (two percent) and other (11 percent) (Table III). Follicular carcinoma has a peak incidence in the fifth decade of life, and occurs with greater frequency in women. Anaplastic carcinoma tends to be diagnosed at a later age than the differentiated carcinomas, and occurs about equally in men and women. Russell et al. 22 found a differentiated component in all anaplastic carcinomas, and concluded that the undifferentiated foci were derived from the more differentiated papillary and follicular elements. It is reasonable to assume that in the bimodal age-incidence curve evidenced by women, the first mode is comprised predominantly of papillary and, to a lesser extent, follicular carcinomas, and the second mode is comprised of predominantly anaplastic and, to a lesser extent, papillary and follicular carcinomas.

The prognosis in patients with thyroid carcinoma is variable and correlates with histologic type, extent of disease, age at diagnosis and sex. The survival rate for papillary carcinoma is significantly higher than for follicular carcinoma, and is lowest for the spindle and giant cell carcinomas (Table IV). 22, 23 In follicular carcinoma, the encapsulated subtype with minimal vascular and capsular invasion is characterized by a 10-year survival rate that is almost twice that of non-encapsulated, primary, operable follicular carcinoma.

The survival rate in women as reported by the End Results Group of the National Cancer Institute was consistently better than that noted in men (Table V). During 1955-1964, 54 percent of women as contrasted with 39 percent of men were diagnosed as having localized disease. Relative survival rates at five and 10 years in men and women decreased with increasing age (Table VI). Women and the younger age groups are characterized by a higher prevalence of papillary and follicular carcinomas and earlier stage of disease. 24 Relative survival rates at three and five years for women and men have improved substantially between 1940-1949 and 1960-1964. If these data can be generalized, then the declining age-adjusted mortality in the face of increasing age-adjusted incidence since 1950 in the United States has occurred because of more significant gains in survival and in average duration of disease.

Medullary carcinoma or solid carcinoma with amyloid stroma is typified by a lack of follicular and papillary differentiation, colloid formation and radiiodine

| Race      | 1960-64 | 1968-72 |
|-----------|---------|---------|
| Chinese   | 19.9    | 12.3    |
| Hawaiian  | 11.8    | 17.0    |
| Filipino  | 8.8     | 18.4    |
| Japanese  | 6.1     | 6.3     |
| Caucasian | 4.9     | 9.4     |
### TABLE III.
**THYROID CANCER.**
Distribution of histologic types, United States 3rd National Cancer Survey, 1969-1971.

| Type                  | All races |                |                |
|-----------------------|-----------|----------------|----------------|
|                       | Total     | Male           | Female         |
|                       | No.       | No. %          | No. %          |
| Papillary carcinoma   | 1434      | 364            | 1070           | 61 66 |
| Follicular carcinoma  | 403       | 96             | 307            | 16 19 |
| Medullary carcinoma   | 59        | 28             | 31             | 5   2  |
| Anaplastic carcinoma  | 55        | 21             | 34             | 4   2  |
| Lymphoma              | 34        | 11             | 23             | 2   1  |
| Sarcoma               | 4         | <1             | 3              | <1  <1 |
| Other†                | 236       | 74             | 162            | 11  10 |
| **Total number of patients** | **2225** | **595**       | **1630**       | **100** |

| Type                  | White     |                |                |
|-----------------------|-----------|----------------|----------------|
|                       | Total     | Male           | Female         |
|                       | No.       | No. %          | No. %          |
| Papillary carcinoma   | 1334      | 344            | 990            | 62 66 |
| Follicular carcinoma  | 358       | 85             | 273            | 15 18 |
| Medullary carcinoma   | 56        | 28             | 28             | 5   2  |
| Anaplastic carcinoma  | 55        | 21             | 34             | 4   2  |
| Lymphoma              | 33        | 11             | 22             | 2   2  |
| Sarcoma               | 4         | <1             | 3              | <1  <1 |
| Other†                | 218       | 67             | 151            | 11  10 |
| **Total number of patients** | **2058** | **557**       | **1501**       | **100** |

| Type                  | Black     |                |                |
|-----------------------|-----------|----------------|----------------|
|                       | Total     | Male           | Female         |
|                       | No.       | No. %          | No. %          |
| Papillary carcinoma   | 63        | 11             | 52             | 41 55 |
| Follicular carcinoma  | 40        | 11             | 29             | 41 31 |
| Medullary carcinoma   | 3         | 3              | 3              | 3   3  |
| Anaplastic carcinoma  |            |                |                |     |
| Lymphoma              | 1         | 1              | 1              | 1   1  |
| Sarcoma               |            |                |                |     |
| Other†                | 14        | 5              | 9              | 19  10 |
| **Total number of patients** | **121**  | **27**        | **94**         | **100** |

†Other includes carcinoma or adenocarcinoma (not otherwise specified), carcinoma simplex, clear cell adenocarcinoma, squamous carcinoma and malignant neoplasm (not otherwise specified).

*Does not total 100 percent because of rounding.
uptake. Its biologic behavior is of an intermediate grade of severity when compared with the differentiated and anaplastic carcinomas. Medullary carcinoma originates from the parafollicular C cells. The epithelial follicular cells, which are concerned with the iodination of thyroglobulin and the release of thyroxine and triiodothyronine, arise from foregut endoderm and give rise to the differentiated (papillary and follicular) and anaplastic (giant and spindle cell) carcinomas. The parafollicular C cells have a neuroectodermal (neural crest) origin, presumably derived from the ultimobranchial body, and synthesize the peptide hormone, calcitonin. The tumor may appear either in a single member or in multiple members of a family.

Experimental Thyroid Tumors

Thyroid neoplasia develops predictably in experimental animals exposed to ionizing radiation or to any procedure that induces prolonged, excessive thyroid-stimulating hormone (TSH) secretion. Excessive TSH secretion may be produced through dietary iodine deficiency, sub-total thyroidectomy, implantation of autonomous thyrotrophic hormone-secreting pituitary tumors, or by the administration of chemical goitrogens. Augmentation of neoplasia, as evidenced by shortening of the latency period or increasing tumor incidence, or both, is achieved by the prior administration of a carcinogen such as 2-acetylaminofluorene or ionizing radiation followed by experimental induction of increased TSH stimulation.

How does TSH-induced hyperplasia lead to neoplasia, and to what degree does rapid proliferation of the follicular cells independently initiate the neoplastic process? The number of cytogenetic abnormalities within the thyroid epithelium apparently increases with the duration of increased TSH stimulation. Various investigators have interpreted experimental thyroid neoplasia as being analogous to the Berenblum-Shubik 26 2-stage hypothesis of carcinogenesis in mouse epidermis. The 2-stage hypothesis presumes two consecutive processes: initiation which occurs quickly and is irreversible, and promotion which occurs slowly, is reversible, and for which cell proliferation may be a necessary although not sufficient condition. Initiators may include ionizing radiation, chemical or biologic agents and genetic factors. The major promoting factor may reside within the hypothalamic-pituitary-thyroid axis and be triggered by an excessive secretion of TSH. 27

The 2-stage hypothesis is particularly applicable to neoplasia in tissues in which a high rate of cell renewal or mitosis is normally present. Experimental carcinogenesis in the thyroid is correlated with the effect of a sustained growth stimulus on a tissue in which the normal rate of cell renewal is negligible. It would appear, therefore, that the mechanism of carcinogenic promotion of thyroid tumors by TSH is somewhat different from the model for experimental skin tumors in mice. Doniach 28 suggested that experimental thyroid neoplasia results from the chromosomal and mutational abnormalities induced by the imposition of accelerated mitosis in a tissue in which the normal rate of cell renewal is minimal. Christov 29 has shown that irradiation of the thyroid gland in adult rats achieved the highest incidence of tumors when administered after treatment with a goitrogen and at the time of peak cellular proliferation. The experimental manipulation of TSH secretion has its clinical counterpart in patients with endemic goiter due to iodine deficiency and in the genetic disorders of the thyroid that lead to hypothyroidism.

Genetic Factors

The multiple endocrine adenomatisis syndromes (MEA I and II) are genetically distinct neoplastic endocrinopathies presumably arising from faulty differentiation of the neuroectoderm. 30-31 (Table VII). Both Weichert 32 and Pearse 33 have advanced the concept that the C cells of the thyroid and extrathyroid tissue share a common embryologic origin in the neural crest with the enterochromaffin serotonin-producing cells of the gastrointestinal tract, the islet cells of the pancreas, the neurochromaffin cells of the adrenal me-
dulla and the cells of the anterior pituitary that secrete ACTH. These polypeptide-secreting neuroendocrine cells share functionally the APUD mechanism and the propensity for ectopic hormone production by neoplastic tissues. The letters APUD describe the process of amine and precursor uptake and decarboxylation of various endocrine substances such as dopamine and its precursor, 3,4-dihydroxyphenylalanine and serotonin and its precursor, 5-hydroxytryptophan. A syndrome of papillary and follicular carcinoma of the thyroid and chemodectoma, a non-chromaffin paraganglioma of the carotid body, aortic body or glomus jugulare has been described in humans. The carotid and aortic bodies, like the adrenal medulla, are of neuroectodermal origin. The chemodectoma is histologically similar to the pheochromocytoma, a chromaffin paraganglioma, although it rarely produces catecholamines. In contrast to the pheochromocytoma-medullary carcinoma in the thyroid syndrome, the chemodectoma-papillary and follicular carcinoma of the thyroid syndrome is rarely familial or characterized by multicentricity and bilaterality. There are several reports within families of multiple cases of differentiated carcinoma of the thyroid in association with goiter and neurosensory deafness (Pendred syndrome). In this disorder, an inborn error of iodine organification impairs the ability to synthesize thyroid hormones, resulting in excessive secretion of abnormal iodoproteins. Papillary carcinoma of the thyroid has been described in siblings with Gardner's syndrome, an autosomal dominant disorder associated with multiple polyposis...
and carcinoma of the colon, osteomas and sebaceous cysts. The multiple hamartoma syndrome (Cowden's disease) is an analogous disorder first described by Lloyd and Dennis in 1963. Patients with this autosomal dominant disorder exhibit some form of thyroid neoplasia, most often as goiter or multicentric adenomas, but in some cases as carcinoma. Other prominent familial features of this syndrome include mucocutaneous papillomas, lichenoid keratoses of the face, neck, hands and forearms, angiomas, subcutaneous and retroperitoneal lipomas, ovarian cysts, fibrocystic disease and carcinoma of the breast. Adenomatous, metaplastic or inflammatory polyps and ganglioneuromas of the gastrointestinal tract have been described.

Iodine Deficiency as a Co-factor in Thyroid Carcinogenesis

In experimental animals such as rats, mice, and Syrian hamsters, chronic iodine deficiency may eventuate into carcinoma of the thyroid after a succession of pathogenic events which include intense follicular hyperplasia, hypertrophy and nodule and adenoma formation. The evidence in man for an etiologic association between severe iodine deficiency and thyroid cancer has consisted of increased thyroid cancer incidence and mortality, particularly of the follicular and anaplastic types, in geographic areas considered to be at high risk for adenomatous or nodular goiter. The foci of carcinoma have usually been located in otherwise normal parenchyma rather than within hyperplastic nodules. It has even been suggested that the frequency of goiter and thyroid cancer in Switzerland diminished after the introduction of iodized table salt. Those who argue against a direct causal relationship between endemic goiter and thyroid carcinoma point to prior studies in geographic areas where there was no correlation (i.e., Australia, Austria, Finland and the United States), or where the frequency of goiter was low and thyroid cancer was high (i.e., Hawaii, Iceland and Newfoundland). Other reports from Switzerland subsequent to the introduc-
The observation of increased thyroid cancer mortality in an endemic goiter area, i.e., where the prevalence of goiter is 10 percent or greater, may be due to the higher proportion of anaplastic carcinomas.\(^*\) In addition, thyroid enlargement due to iodine deficiency may obscure the existence of a cancer, and because of delay in seeking medical care, the majority of malignant tumors are diagnosed at more advanced stages.\(^51\) In studies conducted in the United States during 1939-1951, the average annual age-adjusted mortality due to thyrotoxicosis (secondary to toxic nodular goiter and the diffuse hyperplasia of Graves' disease) diminished significantly in relation to the decreasing prevalence of endemic goiter; during the same period of time, the age-adjusted mortality due to thyroid cancer increased slightly.\(^52\) To summarize, the epidemiologic evidence that endemic iodine deficiency may serve as a necessary and sufficient cause of the follicular type of thyroid carcinoma is unconvincing, although iodine prophylaxis may alter the histologic pattern of thyroid cancer, and ultimately diminish the mortality due to thyrotoxicosis.

**Graves' Disease and Hashimoto's Thyroiditis**

The coincidence of thyrotoxicosis and thyroid cancer was considered to be extremely rare. In more recent statistical surveys, the prevalence of thyroid carcinoma in patients with toxic goiter has been reported variously as being between 0.2 and 5.0 percent.\(^53\) The average prevalence

---

*It has also been suggested that the highly malignant hemangioendothelioma of the thyroid occurs in geographic areas where iodine is deficient and particularly in older patients with chronic goiter. (Cubilla, A.: Personal Communication, 1977.)*
of 2.5 percent for thyroid carcinoma in patients with toxic goiter is similar to the 2.8 percent reported by Mortensen and colleagues in their study of subclinical thyroid cancer in 1,000 consecutive routine autopsies. In the Olen and Klinck study of toxic goiter and carcinoma, 50 percent of the carcinomas were “occult sclerosing” or papillary in type, and in no instance did carcinoma arise from a pre-existing adenoma.

It is now accepted that Graves' disease, myxedema and Hashimoto's thyroiditis are closely related immunogenetic disorders. Two of these diseases may co-exist in the same patient, aggregate in the same family, or demonstrate a high concordance rate in monozygotic twins. The incidence of each disease is at least four times greater in women than in men. Hashimoto's disease tends to be uncommon in American blacks and increases in incidence with age, whereas Graves' disease (diffuse toxic goiter) is not uncommon in blacks, tends to peak during the third and fourth decades, and is distinctly uncommon after age 60. Hashimoto's thyroiditis and Graves' disease are significantly associated with a number of other diseases characterized by abnormal immune reactivity to autologous antigens such as pernicious anemia, primary (Addison's) adrenal insufficiency and myasthenia gravis. The prevalence of thyroid carcinoma in patients with the diffuse chronic lymphocytic thyroiditis of Hashimoto has been reported variously as being between 1.5 and 3.0 percent. Focal lymphocytic thyroiditis is commonly seen in association with papillary and follicular carcinomas. The frequency and significance of these focal lymphocytic infiltrations are not known precisely, although they may represent secondary immune responses to
proliferating parenchymal tissues. 

In the National Cancer Institute's Veterinary Medical Data Program, it was observed that the beagle, boxer and golden retriever breeds were at increased risk of developing clinically apparent thyroid cancer. Several beagle colonies used in laboratory research have exhibited a familial predisposition to lymphocytic thyroiditis, indistinguishable from Hashimoto's disease. Although thyroid neoplasia was not identified in these colonies, further follow-up beyond six years and careful pathologic study may serve to describe the incidence of thyroid cancer in dogs with antecedent thyroiditis.

A prospective epidemiologic study would determine whether Hashimoto's thyroiditis is a specific precursor of thyroid carcinoma. The diagnosis of struma lymphomatosa may be established through a biopsy or a combination of immunologic tests and thyroid scintiscans. Crile and Hazard did not observe a single case of clinically apparent thyroid cancer in 222 patients with Hashimoto's thyroiditis after follow-up of more than 1,000 person-years. Most of these patients were maintained on daily doses of two-three grains of desiccated thyroid, which may have diminished any inherent risk of their developing subsequent neoplasia.

Human Radiation Exposure and Thyroid Cancer

From the 1920's through the 1950's, many infants, children and young adults received X-ray therapy to the head, neck and mediastinum for cervical lymphadenitis, mastoiditis, enlarged palatine and nasopharyngeal lymphoid tissues, pertussis, acne, hemangiomas or keloids, or to shrink an allegedly enlarged thymus gland that...
was thought to cause acute respiratory distress and sudden death. Duffy and Fitzgerald\textsuperscript{64} 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.\textsuperscript{62-69} In a recent publication from Israel by Modan et al.,\textsuperscript{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\textsuperscript{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\textsuperscript{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.\textsuperscript{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 \textsuperscript{99m}Technetium pertechnetate. The \textsuperscript{99m}Tc thyroid scan delivers 0.1 rad to the adult thyroid, as compared with the \textsuperscript{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.\textsuperscript{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.\textsuperscript{15, 76}

There have been isolated case reports of thyroid cancer occurring between four and 12 years after \textsuperscript{131}I therapy for hyperthyroidism.\textsuperscript{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 \textsuperscript{131}I and 14,000 patients treated with surgery or antithyroid medications.\textsuperscript{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 \textsuperscript{131}I therapy for hyperthyroidism appeared more susceptible to the development of adenomas. Higher ablative doses of 5,000-10,000 rads of \textsuperscript{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.\textsuperscript{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\textsuperscript{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.\textsuperscript{81}

In a survey of multiple primary cancers at Memorial Sloan-Kettering Cancer Center, Schottenfeld and Berg\textsuperscript{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...
TABLE VII.
COMPARISON OF THE MULTIPLE ENDOCRINE ADENOMATOSIS SYNDROMES.

| Inheritance | Type I (Wermer)\(^{30}\) | Type II (Sipple)\(^{31}\) |
|-------------|--------------------------|--------------------------|
|             | Autosomal dominant with high degree of penetrance. | Autosomal dominant with high degree of penetrance. |

| Clinical and pathological features | Thyroid |                         |
|-----------------------------------|---------|--------------------------|
|                                   | Thyroid disorder in 20% usually adenoma, but may include differentiated carcinoma (not medullary), colloid goiter, thyroiditis or thyrotoxicosis. | Medullary carcinoma, frequently multifocal. Elevated serum calcitonin with exaggerated response to calcium or glucagon infusion may facilitate diagnosis of carcinoma or C-cell hyperplasia. Increased serum and tissue histamine activity can serve as biochemical marker for primary and metastatic carcinoma. Histamine is found normally in human intestine, kidney and placenta. Ectopic production of serotonin and prostaglandins may give rise to carcinoid and diarrhoeal syndromes, respectively. |

| Adrenal medulla |                         |
|----------------|--------------------------|
|                | Pheochromocytoma may be bilateral. Diffuse or local hyperplasia may precede tumor formation. |

| Adrenal cortex |                         |
|----------------|--------------------------|
|                | Adenoma, diffuse hyperplasia or carcinoma. Cushing's syndrome may be secondary to ectopic secretion of ACTH. Aldosteronoma. | Diffuse hyperplasia secondary to ACTH secretion by medullary thyroid carcinoma. |

| Parathyroid |                         |
|-------------|--------------------------|
|             | Hyperparathyroidism due to adenoma or hyperplasia in most patients. | Less common and characteristic hyperplasia rather than adenoma. More likely a secondary response to the hypocalcemic action of calcitonin, than an expression of genetic pleiotropism. |

| Pancreas |                         |
|---------|--------------------------|
|         | Adenoma, hyperplasia (microadenomatosis) or carcinoma of non-beta islet cells. Accompanied frequently by elevated fasting serum gastrin and intractable peptic ulcer diathesis (Zollinger-Ellison syndrome). Glucagon and insulin-secreting adenomas have also been described. |

| Pituitary |                         |
|----------|--------------------------|
|          | Adenomas in about 65% of patients. Frequently non-functional, but may give rise to acromegaly or Forbes-Albright syndrome (amenorrhea and galactorrhea). |

| Other phenotypic features |                         |
|--------------------------|--------------------------|
| Bronchial and intestinal carcinoid tumors, multiple lipomas, schwannomas and thymomas. | Multiple mucosal neuromas of lips, tongue, eyelids, segmental ganglioneuromatosis of large intestine resulting in megacolon, neurofibromas, cafe au lait spots and marfanoid body habitus. These phenotypic features in conjunction with medullary carcinoma and pheochromocytoma are now designated MEA III. |
patients, or four times that expected. The observed risk of thyroid cancer in women with breast cancer was statistically significant at the one percent level. The incidence of breast cancer in 827 patients with thyroid cancer, although not statistically significant, was 0.9 per year per 1,000 patients or 1.5 times expectation. The magnitude of increase in the incidence of thyroid cancer in our breast cancer patients did not exceed that observed throughout our population of hospital cancer registry patients. We observed a 5.7-fold excess of second primary carcinomas of the thyroid in 41,341 cancer patients and after 123,531 person-years of follow-up. Because the incidence of breast cancer was not seen to increase significantly in thyroid cancer patients, and because of the generally observed increase of second primary thyroid cancers, we were unable to determine if a common etiology for both breast and thyroid cancer might have existed.

Experimentally, ionizing radiation and hypothyroidism augment tumorigenesis in the thyroid and breast. Previous case control studies of women with breast cancer that used conventional tests of thyroid function failed to provide unequivocal evidence that hypothyroidism predisposes to breast cancer. Although a positive correlation has been suggested for countries at increased risk of endemic goiter and breast cancer mortality, a similar correlation is not evident between thyroid cancer and breast cancer incidence. For example, the Chinese women living in Hawaii do not exhibit an increased risk of breast cancer. Although a study in Japan suggested that the risk of breast cancer was significantly increased in women with Hashimoto's thyroiditis, this was not confirmed, at least in the population studied at the Mayo Clinic. 84,85

Thyrotropin-releasing hormone (TRH) from the hypothalamus is not only required for the normal synthesis and secretion of thyroid stimulating hormone (TSH), but also stimulates the secretion of prolactin. The concentration of plasma-free thyroxine regulates the responsiveness of TSH to TRH and may also influence TRH secretion. Mitra 86-88 described a prolactin-thyroxin antagonism in the rat whereby, in the absence of thyroid hormones, the mammotrophic effect of endogenous prolactin was enhanced.

Prolactin is a sustaining factor in the growth of mammary carcinoma in some laboratory animals. For example, in the absence of the ovaries and adrenals, prolactin alone can maintain the growth of an existing mammary carcinoma in the rat. The role of prolactin in human breast cancer is less certain. Significant prolactin stimulation occurs during pregnancy and lactation, yet pregnancy before age 30 is relatively protective against breast cancer when compared with the risk noted in nulliparous women or in women whose first pregnancy is after age 30, and neither the duration nor the frequency of lactation is significantly correlated with the risk of breast cancer. 89 Blood prolactin concentrations are not consistently aberrant in women with breast cancer, although elevated prolactin, estradiol and estriol levels have been detected in the daughters of breast cancer patients. 90

Mitra and Hayward 86 studied the role of the thyroid in breast cancer by assessing the adaptive alterations in the hypothalamic-pituitary-thyroid axis. By measuring levels of TSH before and after TRH stimulation, they observed evidence of hypothyroidism in 10 percent of women with early breast cancer, 14 percent with advanced breast cancer, and in none of their age-matched hospital controls. The plasma concentration of TSH was significantly higher in patients with breast cancer. These recent studies are of interest if we recall that Sommers in 1955 reported in a controlled necropsy study that pituitary amphibol hyperplasia ("thyrotropic basophils") and thyroid atrophy were present with significantly greater frequency in breast cancer patients. Thyroid atrophy was interpreted as the most significant anatomical alteration in explaining an "endocrine imbalance that predisposed to breast cancer." 91

The role of the thyroid in breast cancer is a question that has been pursued since at least the time of Beatson in 1896. 92
There is now an apparent renewal of interest in thyroid dysfunction as an etiologic factor in cancers of the breast, ovary and endometrium, and in invoking common factors within the hypothalamus and anterior pituitary to explain a presumed association of breast and thyroid cancer. In our view, the multiple primary cancer studies that have been described previously do not substantiate the inference of a common cause for thyroid cancer and breast cancer.

References

1. Cancer Statistics, 1976. CA: 26:14-29, 1976.
2. Burbank, F.: Patterns in Cancer Mortality in the United States: 1950-1967. National Cancer Institute, Bethesda, Maryland, 1971.
3. Cutler, S.J., and Young, J.L., Jr., (eds.): Third National Cancer Survey: Incidence Data. Bethesda: Nat. Cancer Inst. Monogr. 41, 1975.
4. Cancer in Connecticut: Incidence and Mortality Rates 1935-1973, Connecticut Tumor Registry, Hartford, Connecticut.
5. Carroll, R.E.; Haddon, W., Jr.; Handy, V.H., and Wieben, E.E.: Thyroid cancer: cohort analysis of increasing incidence in New York State, 1941-1962. J. Natl. Cancer Inst. 33: 277-283, 1964.
6. Verby, J.D., et al.: Thyroid cancer in Olmsted County 1935-1965. J. Natl. Cancer Inst. 43: 813-820, 1969.
7. Berg, J.W.; Hajdu, S.I., and Foote, F.W., Jr.: The prevalence of latent cancers in cancer patients. Arch. Pathol. 91:183-186, 1971.
8. Sampson, R.J.; Key, C.R.; Buncher, C.R., and Iijima, S.: Thyroid carcinoma in Hiroshima and Nagasaki. I. Prevalence of thyroid carcinoma at autopsy. JAMA 209:65-70, 1969.
9. Klinck, G.H., and Winship, T.: Occult sclerosing carcinoma of the thyroid. Cancer 8: 701-706, 1955.
10. Woolner, L.B., et al.: Occult papillary carcinoma of the thyroid gland: a study of 140 cases observed in a 30-year period. J. Clin. Endocrinol. Metab. 20:89-105, 1960.
11. Fukunaga, F.H., and Yatani, R.: Geographic pathology of occult thyroid carcinomas. Cancer 36:1095-1099, 1975.
12. Fukunaga, F.H., and Lockett, J.L.: Thyroid carcinoma in the Japanese in Hawaii. Arch. Pathol. 92:6-13, 1971.
13. Doll, R.; Payne, P., and Waterhouse, J.: Cancer incidence in five continents: A Technical Report, Vol. II. Berlin: Springer-Verlag, New York, 1966.
14. Waterhouse, J.; Muir, C.; Correa, P., and Powell, J.: Cancer incidence in five continents, Vol. III. Lyon, France: IARC Scientific Publications No. 15, 1976.
15. Haber, M.H., and Lipkovic, P.: Thyroid cancer in Hawaii. Cancer 25:1224-1227, 1970.
16. Kolonel, L.N., and Relihan, W.: Personal communication.
17. Austin, D.F.: Personal communication.
18. Tan, K., and Path, D.: Cancer of the thyroid in Singapore. Cancer 21:549-551, 1968.
19. Fraumeni, J.F., and Mason, T.J.: Cancer mortality among Chinese Americans, 1950-1969. J. Natl. Cancer Inst. 52:659-665, 1974.
20. Franssila, K.: Value of histologic classification of thyroid cancer. Acta. Pathol. Microbiol. Scand. (Suppl.) 225:5-76, 1971.
21. Lieberman, P.H.; Foote, F.W., Jr., and Schottenfeld, D.: A study of the pathology of thyroid cancer, 1930-1960. Clin. Bull. 2:7-12, 1972.
22. Russell, W.O.; Ibanez, M.L.; Clark, R.L., and White, E.C.: Thyroid carcinoma: classifi-
cation, intraglandular dissemination, and clinicopathological study based upon whole organ sections of 80 glands. Cancer 16:1425-1460, 1963.

23. Franssila, K.: Prognosis in thyroid carcinoma. Cancer 36:1138-1146, 1975.

24. Biometry Branch, National Cancer Institute: End Results in Cancer Report No. 4. DH&EW Publication No. (NIH) 73-272. Bethesda: 161-164, 1972.

25. Hazard, J.B.; Hawk, W.A., and Crile, G., Jr.: Medullary (solid) carcinoma of the thyroid; a clinicopathologic entity. J. Clin. Endocrinol. Metab. 19:152-161, 1959.

26. Berenblum, I.: The two-stage mechanism of carcinogenesis as an analytical tool. In: Emmetott, P., and Muhlbuch, O. (eds.): Cellular Control Mechanism and Cancer. Amsterdam: Elsevier Publishing Co., 1964. Pp. 259-267.

27. Nadler, N.J.; Mandavia, M., and Goldberg, M.: The effect of hypophysectomy on the experimental production of rat thyroid necroplasms. Cancer Res. 30:1909-1911, 1970.

28. Doniach, I.: The effect of radioactive iodine alone and in combination with methylthiouracil and acetylaminothiouracil upon tumor production in the rat's thyroid gland. Br. J. Cancer 4:223-234, 1950.

29. Christov, K.: Thyroid cell proliferation in rats and induction of tumors by X-rays. Cancer Res. 35:1256-1261, 1975.

30. Werner, P.: Genetic aspects of adenomatosis of endocrine glands. Am. J. Med. 16:363-371, 1954.

31. Sipple, J.H.: The association of pheochromocytoma with carcinoma of the thyroid gland. Am. J. Med. 31:163-166, 1961.

32. Weichert, R.F.: The neural ectodermal origin of the peptide-secreting endocrine glands. Am. J. Med. 49:233-241, 1970.

33. Pearce, A.G.E., and Polak, J.M.: Neural crest origin of the endocrine polypeptide (APUD) cells of the gastrointestinal tract and pancreas. Gut 12:738-788, 1971.

34. Wolfe, H.J., et al.: C-cell hyperplasia preceding medullary thyroid carcinoma. N. Engl. J. Med. 289:437-441, 1973.

35. Baylin, S.B.; Beaven, M.A.; Buja, L.M., and Keser, H.B.: Histaminase activity: a biochemical marker for medullary carcinoma of the thyroid. Am. J. Med. 53:723-733, 1972.

36. Carney, J.A.; Sizemore, G.W., and Tyce, G.M.: Bilateral adrenal medullary hyperplasia in multiple endocrine neoplasia, type 2. Mayo Clin. Proc. 50:3-10, 1975.

37. Baylin, S.B.; Gann, D.S., and Hsu, S.H.: Clonal origin of inherited medullary thyroid carcinoma and pheochromocytoma. Science 193:321-323, 1976.

38. Schimke, R.N.: Multiple endocrine adenomatosis syndrome. Adv. Int. Med. 21:249-265, 1976.

39. Albores-Saavedra, J., and Duran, M.E.: Association of thyroid carcinoma and chemodectoma. Am. J. Surg. 116:887-890, 1968.

40. Sato, T., et al.: Concurrence of carotid body tumor and pheochromocytoma. Cancer 34:1787-1795, 1974.

41. Hayes, H.M., Jr., and Fraumeni, J.F., Jr.: Chemodectomas in dogs: epidemiologic comparisons with man. J. Natl. Cancer Inst. 52:1455-1458, 1974.

42. Elman, D.S.: Familial association of nerve deafness with nodular goiter and thyroid carcinoma. N. Engl. J. Med. 259:219-223, 1958.

43. Camiel, M.R.; Mule, J.E.; Alexander, L.L., and Benninghoff, D.L.: Association of thyroid carcinoma with Gardner's syndrome in siblings. N. Engl. J. Med. 259:1056-1058, 1958.

44. Lloyd, K.M., and Dennis, M.: Cowden's disease: a possible new symptom complex with multiple system involvement. Ann. Intern. Med. 48:136-142, 1963.

45. Weary, P.E., et al.: Multiple hamartoma syndrome (Cowden's disease). Arch. Derm. 106:682-690, 1972.

46. Cuello, C.; Correa, P., and Eisenberg, H.: Geographic pathology of thyroid carcinoma. Cancer 23:230-239, 1969.

47. Wahner, H.W., et al.: Thyroid carcinoma in an endemic goiter area, Cali, Colombia. Am. J. Med. 40:58-66, 1966.

48. Ramalingaswami, V.: Iodine and thyroid cancer in man. In: Hedinger, C.E. (ed.): Thyroid Cancer. Berlin: Springer-Verlag, 1969. Pp. 111-123.

49. Thalman, A.: Incidence of malignant goitre at the Berne Pathological Institute during the period 1910-60. Relation to iodine prophylaxis against endemic goitre. Schweiz Med. Wschr. 84:474-478, 1954.

50. Walther, B.: The influence of the iodine prophylaxis of goitre on the frequency of cancer of the thyroid gland and on its structure. In: Pitt-Rivers, R. (ed.): Thyroid Research. Oxford: Pergamon Press, 1961. Pp. 350-351.

51. Riccabona, C.: Hyperthyroidism and thyroid cancer in an endemic goiter area. In: Dunn, J.T. (ed.): Endemic Goiter and Cretinism: Continuing Threats to World Health. Washington, D.C.: Pan American Health Organization, 1974. Pp. 156-165.

52. Pendergrast, W.J.; Milmore, B.K., and Marcus, S.C.: Thyroid cancer and thyrotoxicosis in the United States: their relation to endemic goiter. J. Chronic Dis. 13:22-38, 1961.

53. Shapiro, S.J.; Friedman, N.B.; Perzik, S.L., and Catz, B.: Incidence of thyroid carcinoma in Graves' disease. Cancer 26:1261-1270, 1970.

54. Mortensen, J.D.; Bennett, W.A., and Woolner, L.B.: Incidence of carcinoma in thyroid glands removed at 1,000 consecutive routine necropsies. Surg. Forum 5:659-663, 1954.

55. Olen, E., and Klink, G.H.: Hyperthyroidism and thyroid cancer. Arch. Path. 81:531-535, 1966.

56. Zonana, J., and Rimoin, D.L.: Genetic disorders of the thyroid. Med. Clin. North Am. 59:1263-1274, 1975.

57. McKenzie, J.M.; Zakariga, M., and Bonyns, M.: Graves' disease. Med. Clin. North Am. 59:1177-1192, 1975.
86. Parker, L.N., et al.: Thyroid carcinoma after exposure to atomic radiation. Ann. Intern. Med. 80:600-604, 1974.
77. Hayek, A.; Chapman, E.M., and Crawford, J.D.: Long-term results of treatment of thyrotoxicosis in children and adolescents with radioactive iodine. N. Engl. J. Med. 283:949-953, 1970.
78. Dobyns, B.M., et al.: Malignant and benign neoplasms of the thyroid in patients treated for hyperthyroidism: a report of cooperative thyrotoxicosis therapy follow-up study. J. Clin. Endocrinol. Metab. 38:976-998, 1974.
79. Conard, R.A.: A 20-year review of medical findings in a Marshallse population accidentally exposed to radioactive fall-out. Upton, New York: Brookhaven National Laboratory, 1973.
80. Schoenberg, B.: Multiple primary malignant neoplasms: the Connecticut experience, 1935-1964. New York: Springer Verlag. (In press.)
81. Horn, J.W.: Personal communication.
82. Schottenfeld, D., and Berg, J.W.: Incidence of multiple primary cancers. IV: Cancers of the female breast and genital organs. J. Natl. Cancer Inst. 46:161-170, 1971.
83. Schottenfeld, D.: The relationship of breast cancer to thyroid disease. J. Chronic Dis. 21:303-313, 1968.
84. Itoh, K., and Maruchi, N.: Breast cancer in patients with Hashimoto's thyroiditis. Lancet 2:1119-1121, 1975.
85. Maruchi, N.; Annegers, J.F., and Kurland, L.T.: Hashimoto's thyroiditis and breast cancer. Mayo Clin. Proc. 51:263-265, 1976.
86. Mittra, I., and Hayward, J.L.: Hypothyroidic-pituitary-thyroid axis in breast cancer. Lancet 1:885-888, 1974.
87. Mittra, I.; Hayward, J.L., and McNelly, A.S.: Hypothyroidic-pituitary-prolactin axis in breast cancer. Lancet 1:889-891, 1974.
88. Mittra, I.: Mammatropic effect of prolactin enhanced by thyroidectomy. Nature 248:525-526, 1974.
89. Schottenfeld, D.: Epidemiology of breast cancer. Clin. Bull. 5:135-143, 1975.
90. Henderson, B.E., et al.: Elevated serum levels of estrogen and prolactin in daughters of patients with breast cancer. N. Engl. J. Med. 293:790-795, 1975.
91. Sommers, S.C.: Endocrine abnormalities in women with breast cancer. Lab. Invest. 4:160-174, 1955.
92. Beatson, G.W.: On the treatment of inoperable cases of carcinoma of the mamma—suggestions for a new method of treatment with illustrative cases. Lancet 2:104-162, 1896.
93. Stadel, B.V.: Dietary iodine and risk of breast, endometrial, and ovarian cancer. Lancet 1:890-891, 1976.
94. Edington, G.M.: Dietary iodine and risk of breast, endometrial, and ovarian cancer. Lancet 2:1413-1414, 1976.
95. Williams, R.R.: Breast and thyroid cancer and malignant melanoma promoted by alcohol-induced pituitary secretion of prolactin, TSH and MSH. Lancet 1:996-999, 1976.

58. Bastenie, P.A.; Ermans, A.M., and Delespesse, G.: Chronic lymphocytic thyroiditis and cancer of the thyroid. In: Bastenie, P.A., and Ermans, A.M. (eds.): Thyroiditis and Thyroid Function. Oxford: Pergamon Press, 1972. Pp. 159-170.
59. Hayes, H.M., Jr., and Fraumeni, J.F., Jr.: Canine thyroid neoplasms: epidemiologic features. J. Natl. Cancer. Inst. 55:931-934, 1975.
60. Crile, G., Jr., and Hazard, J.B.: Incidence of cancer in struma lymphomatosa. Surg., Gynecol., Obstet. 115:101-103, 1962.
61. Duffy, B.J., Jr., and Fitzgerald, P.J.: Cancer of the thyroid in children: a report of 28 cases. J. Clin. Endocrinol. 10:1296-1308, 1950.
62. Clark, D.E.: Association of irradiation with cancer of the thyroid in children and adolescents. JAMA 159:1007-1009, 1955.
63. Pincus, R.A.; Reichlin, S., and Hempelmann, L.H.: Thyroid abnormalities after radiation exposure in infancy. Ann. Intern. Med. 66:1514-1564, 1967.
64. Winship, T., and Rosvoll, R.V.: Thyroid carcinoma in childhood: final report on a 20-year study. Clin. Proc. Child. Hosp. 26:327-348, 1970.
65. DeGroot, L.J., and Paloyan, E.: Thyroid carcinoma and radiation: a Chicago epidemic. JAMA 225:487-491, 1973.
66. Consequences of thyroid radiation in children. (Editorial) N. Engl. J. Med. 292:204-205, 1975.
67. Retefooff, S., et al.: Continuing occurrence of thyroid carcinoma after irradiation to the neck in infancy and childhood. N. Engl. J. Med. 292:171-175, 1975.
68. Becker, F.O.; Economou, S.G.; Southwick, H.W., and Eisenstein, R.: Adult thyroid cancer after head and neck irradiation in infancy and childhood. Ann. Intern. Med. 83:347-351, 1975.
69. Favus, M.J., et al.: Thyroid cancer occurring as a late consequence of head and neck irradiation. N. Engl. J. Med. 294:1019-1025, 1976.
70. Modan, B., et al.: Radiation-induced head and neck tumors. Lancet 1:277-279, 1974.
71. Shore, R.E.; Albert, R.E., and Pasternak, B.S.: Follow-up study of patients treated by X-ray epilation for tinea capitis. Arch. Environ. Health 31:21-28, 1976.
72. Hempelmann, L.H., et al.: Neoplasms in persons treated with X-rays in infancy: fourth survey in 20 years. J. Natl. Cancer Inst. 55:519-530, 1975.
73. Silverman, C., and Hoffman, D.A.: Thyroid tumor risk from radiation during childhood. Prev. Med. 4:100-105, 1975.
74. Information for physicians on irradiation-related thyroid cancer. Report of Workshop on the Late Effects of Irradiation to the Head and Neck in Infancy and Childhood. CA 26:150-159, 1976.
75. Jablon, S.; Belsky, J.L.; Tachikawa, K., and Steer, A.: Cancer in Japanese exposed as children to atomic bombs. Lancet 1:927-932, 1971.