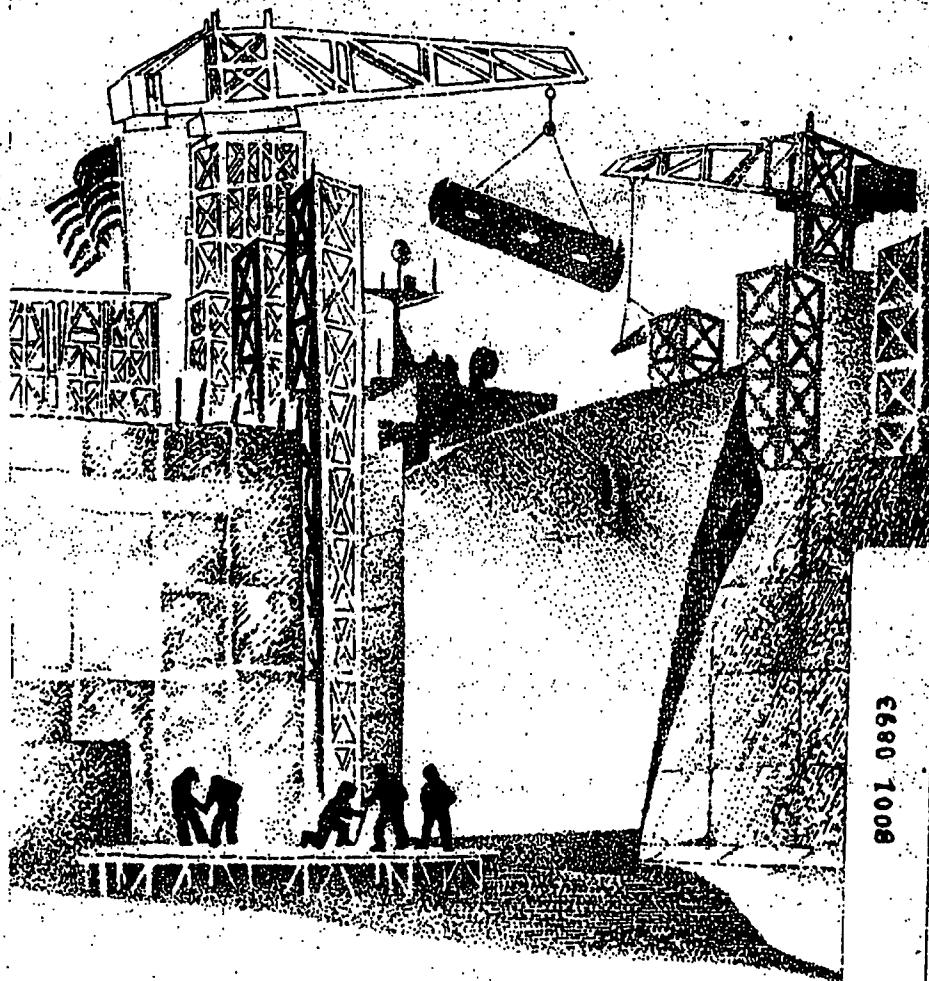


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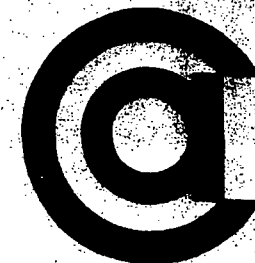
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Epidemiology of Thyroid Cancer

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.

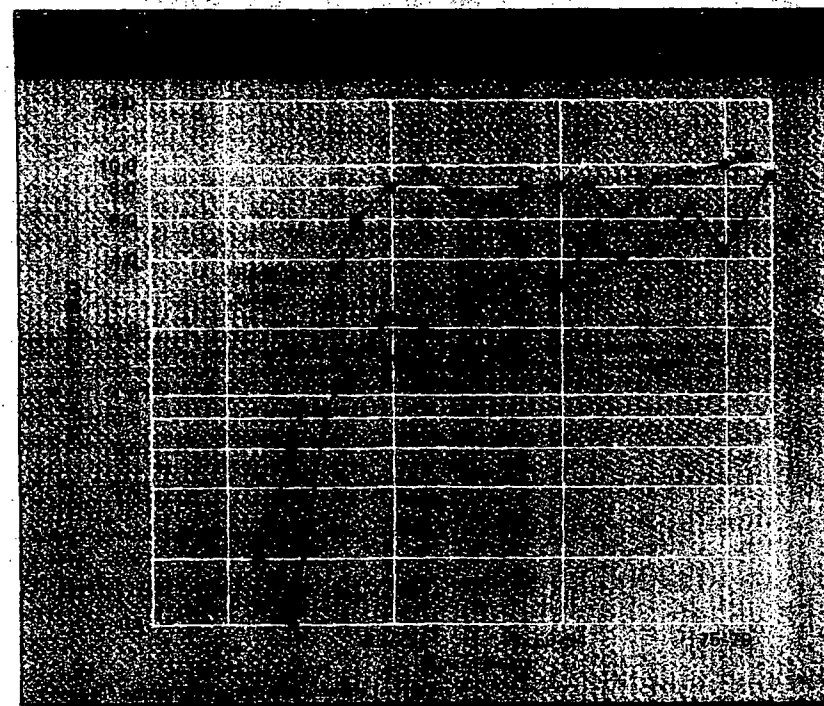
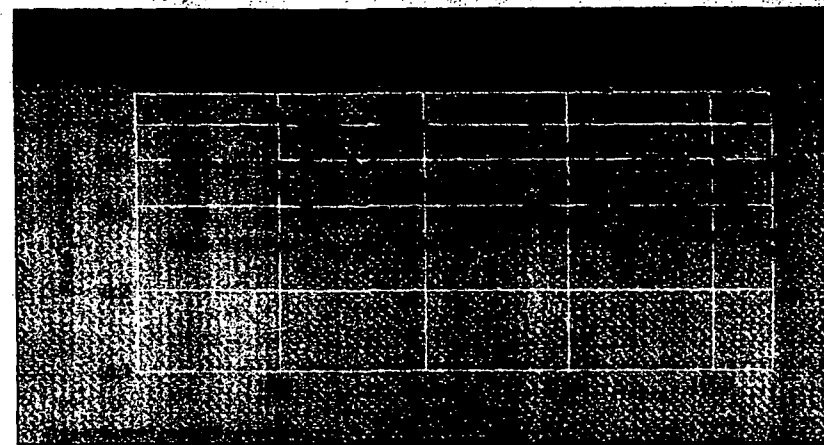
For 1976, the American Cancer Society has estimated that there were 5,900 new cases of thyroid cancer in women and 2,200 cases in men. The average annual age-adjusted incidence rates per 100,000 as determined by the United States Public Health Service Third National Cancer

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).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 three-fold 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).⁴ Carroll et al.⁵ 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-

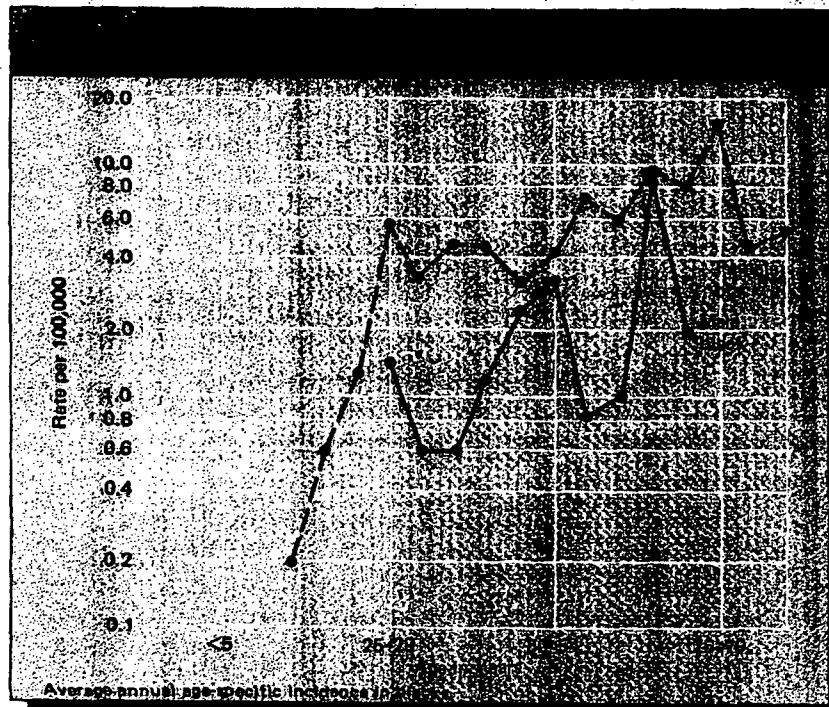
Epidemiology of Thyroid Cancer — Parts I and II are reprinted from *Clinical Bulletin*, 7:2, 47-54, and 7:3, 98-104, 1977. Tables I-VI, figures 1-7 and references 1-29, as well as Table VII and references 30-95 were included.

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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-



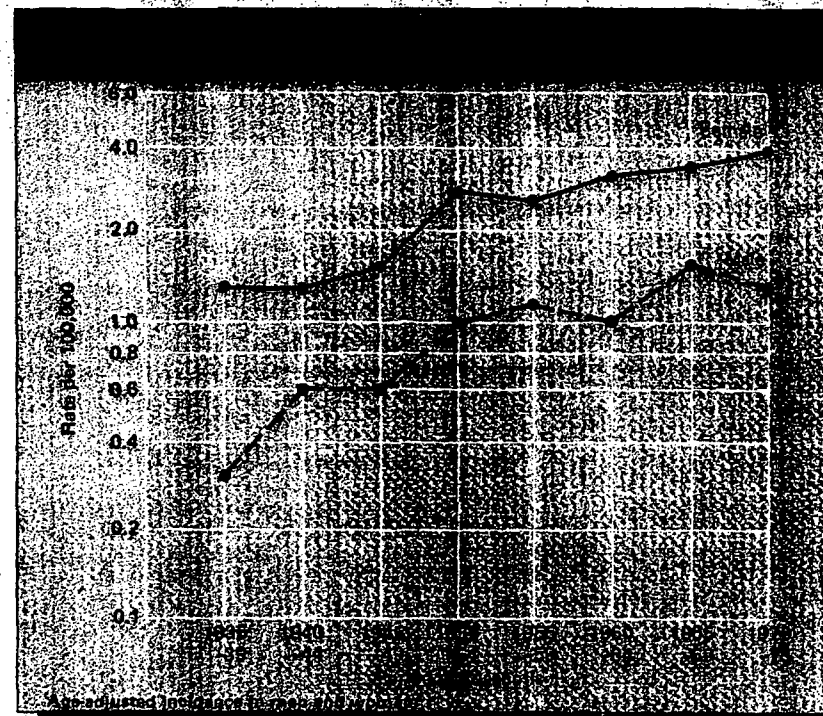
oid hyperplasia and cervical lymphadenitis in infancy and early childhood, and was consistent with the hypothesis that ionizing radiation was a cause of thyroid cancer in children and young adults.

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.⁷ Sampson et al.⁸ 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.⁹⁻¹⁰

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.^{11, 12}

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).¹³⁻¹⁵ 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).¹⁶ 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).¹⁷ 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.¹⁸ Fraumeni and Mason¹⁹ 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 II). 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.²¹

The percentage relative frequency of

	Females		Males	
United States				
Hawaii: Chinese	20.7*	14.1†	3.5*	4.5†
Hawaii: Filipino	14.3	18.7	5.0	4.7
Hawaii: Hawaiian	10.1	18.0	5.7	3.4
Hawaii: Japanese	6.5	7.8	1.7	3.2
Hawaii: Caucasian	5.4	9.2	4.4	3.1
Connecticut	3.0	3.7	0.8	1.5
California, Alameda: White	7.4	5.5	2.8	2.6
California, Alameda: Black	2.3	1.9	0.6	1.6
Israel				
All Jews	4.2	8.3	1.8	4.2
Jews born in Africa or Asia	4.6	6.7	1.6	2.4
Jews born in Europe or America	4.0	6.4	2.0	4.2
Jews born in Israel	2.0	6.1	0.3	4.8
Non-Jews	2.0	1.8	1.2	1.9
Japan				
Okayama Prefecture	3.3	2.4	1.1	0.4
Miyagi Prefecture	2.0	2.1	0.8	0.6
New Zealand				
Maori	5.5	2.3	0.4	0.9
European	2.5	2.0	0.9	1.0
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	1.1	1.6
Urban	2.5	3.1	1.0	1.7
Rural	2.4	4.3	1.1	1.4
Columbia, Cal	6.5	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	0.6	0.6
Sources: *See reference 13. †See reference 14.				

Race	1960-64	1968-72
Chinese	19.9	12.3
Hawaiian	11.8	17.0
Fillipino	8.8	18.4
Japanese	6.1	6.3
Caucasian	4.9	9.4

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 radioiodine

Type	Total		All races Male		Female	
	No.	%	No.	%	No.	%
Papillary carcinoma	1434	64	364	61	1070	66
Follicular carcinoma	403	18	96	16	307	19
Medullary carcinoma	59	3	28	5	31	2
Anaplastic carcinoma	55	3	21	4	34	2
Lymphoma	34	2	11	2	23	1
Sarcoma	4	<1	1	<1	3	<1
Other†	236	11	74	12	162	10
Total number of patients	2225	100*	595	100	1630	100
Type	Total		White Male		Female	
	No.	%	No.	%	No.	%
Papillary carcinoma	1334	65	344	62	990	66
Follicular carcinoma	358	17	85	15	273	18
Medullary carcinoma	56	3	28	5	28	2
Anaplastic carcinoma	55	3	21	4	34	2
Lymphoma	33	2	11	2	22	2
Sarcoma	4	<1	1	<1	3	<1
Other†	218	11	67	12	151	10
Total number of patients	2058	100*	557	100	1501	100
Type	Total		Black Male		Female	
	No.	%	No.	%	No.	%
Papillary carcinoma	63	52	11	41	52	55
Follicular carcinoma	40	33	11	41	29	31
Medullary carcinoma	3	3	—	—	3	3
Anaplastic carcinoma	—	—	—	—	—	—
Lymphoma	1	1	—	—	1	1
Sarcoma	—	—	—	—	—	—
Other†	14	12	5	19	9	10
Total number of patients	121	100*	27	100*	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.²⁵ 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-Shubik²⁶ 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. Doniach²⁸ 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. Christov²⁹ 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 adenomatosis syndromes (MEA I and II) are genetically distinct neoplastic endocrinopathies presumably arising from faulty differentiation of the neuroectoderm³⁰⁻³¹ (Table VII). Both Weichert³² and Pearse³³ 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-

Histologic type	5 years S.E.**	10 years S.E.**	15 years S.E.**	20 years S.E.**
All histologic types	70.4 1.5	63.8 2.1	—	—
Papillary	82.7 1.5	78.2 2.1	73.6 1.9	70.8 2.6
Occult sclerosing	100.0†	—†	—	—
Follicular	55.6 4.2	47.0 6.6	40.5 8.8	40.5 14.9
Hürthle cell	60.8 6.9	42.5 11.1	—	—
Medullary	49.1 6.6	37.6† 11.7	—	—
Spindle and giant cell	3.6 2.4	0.0†	—	—
Lymphoma	31.3† 11.6	—†	—	—

* The observed net survival rates are calculated by the direct method and exclude deaths from other causes.
 ** Survival rates and standard errors are expressed as percentages.
 † Less than 20 patients.

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.³⁴⁻³⁸

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.³⁹ 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.⁴⁰⁻⁴¹

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-organization impairs the ability to synthesize thyroid hormones, resulting in excessive secretion of abnormal iodoproteins.⁴²

Papillary carcinoma of the thyroid has been described in siblings with Gardner's syndrome, an autosomal dominant disorder associated with multiple polyposis

	1940-1949		1950-1959		1960-1964		1965-1969	
	Male	Female	Male	Female	Male	Female	Male	Female
No. of patients	197	500	574	1803	416	989	392	1053
Percent at 3 years	54	72	73	84	80	87	80	88
Percent at 5 years	51	69	73	83	78	87	—	—
Percent at 10 years	48	68	73	83				
Percent at 15 years	48	68						

Source: End Results in Cancer, Report No. 4, End Results Section, Biometry Branch, National Cancer Institute, 1972, p. 162.

and carcinoma of the colon, osteomas and sebaceous cysts.⁴³ The multiple hamartoma syndrome (Cowden's disease) is an analogous disorder first described by Lloyd and Dennis in 1963.^{44,45} 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.^{46,47} 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).⁴⁸ Other reports from Switzerland subsequent to the introduc-

	All Ages		Under 25		25-44	
	Male	Female	Male	Female	Male	Female
Percent at 5 years	75	85	96	99	92	98
Percent at 10 years	74	86	96	99	91	96
	45-54		55-64		65+	
	Male	Female	Male	Female	Male	Female
Percent at 5 years	76	91	61	67	39	46
Percent at 10 years	70	89	49	65	33	44

Source: End Results in Cancer, Report No. 4, End Results Section, Biometry Branch, National Cancer Institute, 1972, p. 164.

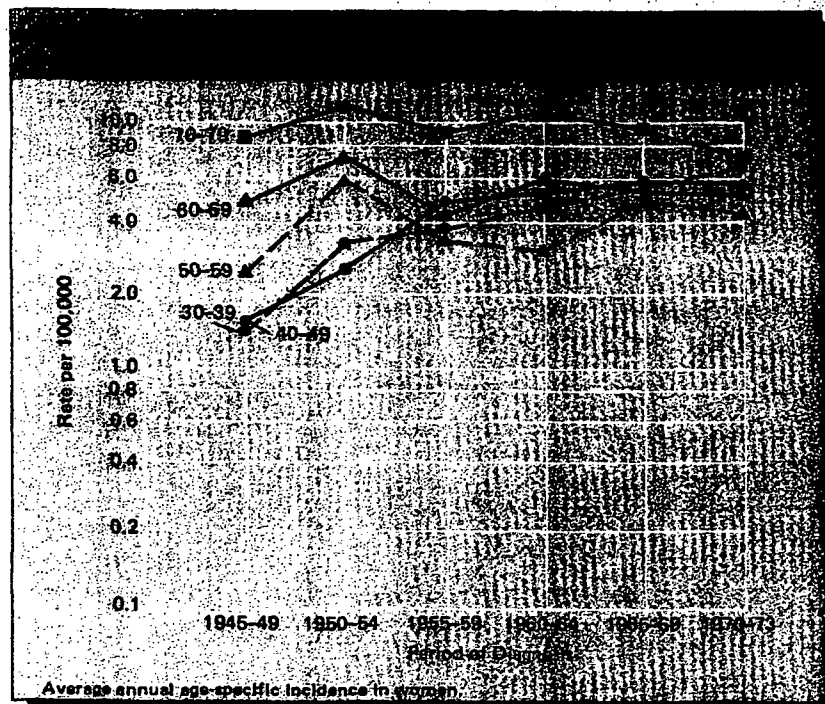
tion of iodized table salt do not substantiate a continuing trend of decreasing frequency of thyroid cancer, but rather emphasize the stable rates of thyroid cancer mortality, decreasing incidence of goiter, and increasing proportion of thyroid cancers that are classified as papillary.^{49,50} The observation 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

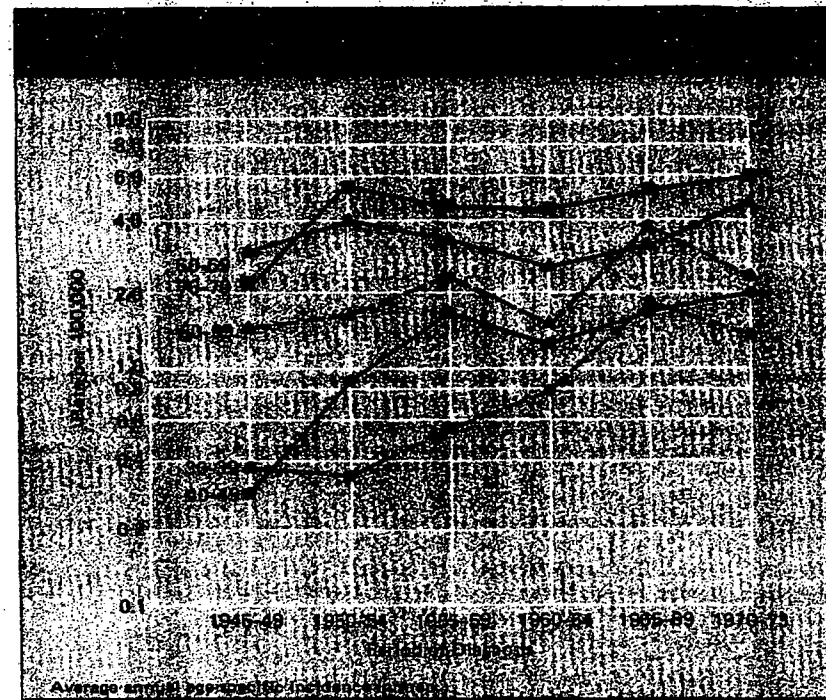
*It has also been suggested that the highly malignant hemangioendothelioma of the thyroid occurs in geographic areas where iodine is deficient and particularly in older patients with chronic goiter. (Cubilla, A.: *Personal Communication*, 1977.)



of 2.5 percent for thyroid carcinoma in patients with toxic goiter is similar to the 2.8 percent reported by Mortensen and colleagues⁵⁴ in their study of subclinical thyroid cancer in 1,000 consecutive routine autopsies. In the Olen and Klinck study of toxic goiter and carcinoma⁵⁵, 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.⁵⁶⁻⁵⁸

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.⁵⁹ 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 immunolog-

ic tests and thyroid scintiscans. Crile and Hazard⁶⁰ 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 Fitzgerald⁶¹ 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 Pasternak⁷¹ 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-workers⁷² 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 hor-

none. 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}Tc Technetium pertechnetate. The ^{99m}Tc thyroid scan delivers 0.1 rad to the adult thyroid, as compared with the ¹³¹I 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 ¹³¹I 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 ¹³¹I 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 ¹³¹I therapy for hyperthyroidism appeared more susceptible to the development of adenomas. Higher ablative doses of 5,000-10,000 rads of ¹³¹I 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, Schoenberg⁸⁰ 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 Berg⁸² 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

	Type I (Wermer) ³⁰	Type II (Sipple) ³¹
Inheritance	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 histaminase activity can serve as biochemical marker for primary and metastatic carcinoma. (Histaminase is found normally in human intestine, kidney and placenta.) Ectopic production of serotonin and prostaglandins may give rise to carcinoid and diarrheal 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 characteristically 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.

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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.⁸³ 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}

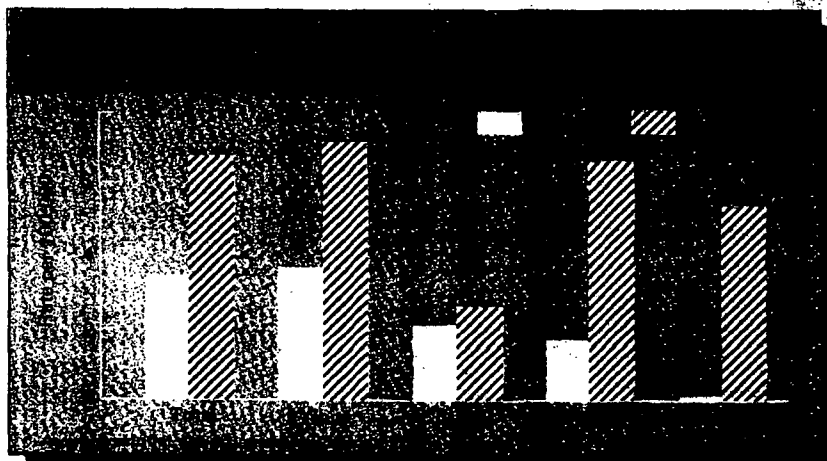
Thyrotropin-releasing hormone (TRH) from the hypothalamus is not only required for the normal synthesis and secretion of thyroid stimulating hormone (TSH), but also stimulates the secretion of prolactin. The concentration of plasma-free thyroxine regulates the responsiveness of TSH to TRH and may also influ-

ence TRH secretion. Mitra⁸⁶⁻⁸⁸ described a prolactin-thyroxine 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 estrone levels have been detected in the daughters of breast cancer patients.⁹⁰

Mitra and Hayward⁸⁶ 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 amphophil 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.⁹³⁻⁹⁵ 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. ©

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Asbestos-associated Disease in United States Shipyards

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CLINICAL LATENCY OF ASBESTOS-ASSOCIATED CANCER

During the past 15 years the important disease potential of asbestos exposure has been clarified. The principal hazards have been demonstrated to be cancer of a number of sites, and asbestosis. Among asbestos workers, approximately 20 percent of all deaths are due to lung cancer, six percent or seven percent to pleural and/or peritoneal mesothelioma, and there is an excess found in several other categories (e.g., cancer of the esophagus, stomach, colon-rectum, oropharynx, larynx, kidney). Table 1 provides an analysis of causes of death among 17,800 asbestos insulation workers in the United States and Canada followed prospectively from January 1, 1967 to January 1, 1977.

Risk of asbestos-associated disease has also been observed in workers in other trades where asbestos exposure occurs—

for example, where individuals simply working near "asbestos workers" are exposed to the same dusts. Risk extends even to individuals not employed in an asbestos-contaminated environment; mesothelioma has been found among family contacts of asbestos workers residing in the same households, as well as among people living within a quarter of a mile or so of asbestos plants or other facilities which have used asbestos-containing materials.

Although mesothelioma is not necessarily the most common disease resulting from asbestos exposure, it provides a very useful index of such problems, since it is only uncommonly seen as a result of exposure to other agents or without identified cause. Large scale investigations of series of cases of mesothelioma in France, Great Britain, the Netherlands^{1,2} and elsewhere have demonstrated that the large majority of these cases can be traced to prior asbestos exposure.

For these neoplasms, as for all cancers due to asbestos exposure (and, indeed, for extensive asbestosis as well), a rather uniform characteristic has been found: the disease usually does not become clinically evident for 15, 25, 35 or more years from onset of asbestos exposure. The initial decades are periods of grace with no illness or disability. While some early X-ray changes may be seen after five to 15 years, they are limited in extent and not usually accompanied by significant symptoms. They merely dem-

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TABLE 1
Deaths among 17,800 asbestos insulation workers
in the United States and Canada
January 1, 1967-January 1, 1977

Number of men Man-years of observation		
17,800 166,855		
	Expected*	Observed
Total deaths, all causes	1,660.96	2,270
Total cancer, all sites	319.90	994
Lung cancer	105.97	485
Pleural mesothelioma	**	66
Peritoneal mesothelioma	**	109
Cancer of esophagus	7.01	18
Cancer of stomach	14.23	22
Cancer of colon-rectum	37.86	59
All other cancer	154.83	235
Asbestosis	**	162
All other causes	1,351.06	1,114

* Expected deaths are based upon white male age specific mortality data of the U.S. National Center for Health Statistics for 1967-1975 and extrapolation to 1976.

** These are rare causes of death in the general population.

The membership of the International Association of Heat and Frost Insulators and Asbestos Workers, AFL-CIO, CLC, was enrolled on January 1, 1967, and has been observed since.

onstrate that enough asbestos exposure has occurred to produce such changes. In this sense, they are harbingers of future risk of clinical disease.

Tables 2-5 illustrate the characteristic latency of asbestos disease. In one group of 1,117 asbestos insulation workers in the New York metropolitan area, most of 725 workers with less than 20 years from onset of exposure (Table 2) had normal X-rays. When changes were present, they were minimal in extent. On the other hand, after the 20-year point, most X-rays were found to be abnormal, frequently exten-

sively so.⁴ Tables 3-5 show that few mesotheliomas and little excess cancer of the lung occurred less than 20 years from onset. Most occurred 30 or more years from onset of exposure. A young man may begin work at the age of 18; his risk of asbestos-associated cancer does not become substantial until he is 40, 50 or older.

EARLY STUDIES: MESOTHELIOMA IN SHIPYARDS

In 1968, the first warning that asbestos

TABLE 2
X-ray changes in asbestos insulation workers⁴

Onset of exposure (yrs.)	No.	% Normal	% Abnormal	Asbestosis (grade)		
				1	2	3
40+	121	5.8	94.2	35	51	28
30-39	194	12.9	87.1	102	49	18
20-29	77	27.2	72.8	35	17	4
10-19	378	55.9	44.1	158	9	0
0-9	346	89.6	10.4	36	0	0
Total	1,117	51.5	48.5	366	126	50

disease might be a serious problem in shipyards was sounded by Harries⁵ in Great Britain and Stumphius⁶ in the Netherlands when they reported instances of mesothelioma among shipyard workers. What was worrisome was that the men were not "asbestos workers" but rather, individuals employed in other trades. At the Devonport shipyard of the Royal Navy, for example, mesothelioma in a boilermaker, a fitter, a shipwright, a welder and a laborer were described.

This raised the important question of whether asbestos use in shipyards might result in the exposure of the workers employed in many trades, to dust derived from the few "asbestos workers" in their midst. In 1943, in the United States, for example, approximately one in 500 shipyard workers was an insulator. The other 499 included welders, shipfitters, machinists, pipefitters, electricians, boilermakers and painters (Table 6). The significance of this question is made apparent by the fact that during World War II, approximately 4,500,000 men and women worked in our shipyards, many of them under conditions in which exposure to asbestos was possible. After World War II the total number of shipyard workers rapidly decreased from a high of 1,700,000 in the last months of 1943 to 200,000 or so. During the period

of 1946-1976, total employment remained in this range, fluctuating with economic conditions and the country's shipbuilding program. The 200,000-250,000 figure characterized the total number in the yards at one time; however, there was much turnover, and the total number of different individuals was much larger. There are no accurate data readily available which could tell us how many different people—carpenters, riggers, electricians, draftsmen, welders, etc.—were so employed. Nevertheless, the early observations (soon augmented by later studies⁷⁻⁹) pointed to a potentially serious problem.

Harries has recently published his further observations at Devonport, through 1973.⁹ By the end of the year, he had observed 55 cases of mesothelioma in that shipyard alone. Again, trades other than "asbestos workers" gave evidence of the hazard. Only two of the 55 worked directly with asbestos (lagger, sprayer). The other 53 included 14 shipwrights, nine boilermakers, eight fitters and eight electricians (Table 7).

John Edge of High Carley Hospital has published similar data from shipyards in Barrow (Table 8)¹⁰; his most recent observations are particularly disturbing. In Barrow, 429 individuals were seen; be-

TABLE 3

Deaths among 17,800 asbestos insulation workers in the United States and Canada January 1, 1967-January 1, 1977: Analysis by duration from onset of employment

Total men Man-years of observation	12,683 89,466	12,051 77,389
	Before 20 years from onset	20 or more years from onset
	Expected* Observed	Expected* Observed
Total deaths, all causes	283.93 324	1,377.01 1,946
Cancer, all sites	42.65 83	277.25 911
Lung cancer	12.03 36	83.94 449
Pleural mesothelioma	** 2	** 64
Peritoneal mesothelioma	** 3	** 106
Cancer of esophagus	0.66 1	6.35 17
Cancer of stomach	1.56 1	12.67 21
Cancer of colon-rectum	4.07 4	33.79 55
Asbestosis	** 8	— 154

* Expected deaths are based upon white male age specific mortality data of the U.S. National Center for Health Statistics for 1967-1975 and extrapolation to 1976.

** These are rare causes of death in the general population.

tween 1964 and 1971, with radiologically evident pleural plaques; these plaques were considered to signal prior shipyard employment. Controls were 429 men from a neighboring city (Carlisle), matched for age and date of X-ray; they had no plaques on their roentgenograms. Both groups were observed through 1976, i.e., for a minimum of five years. Among the 429 men with pleural plaques, there were 127 deaths; those with no plaques suffered 74 deaths. The excess was primarily in two categories, lung cancer and mesothelioma. There were 19 deaths from lung cancer and 23 from mesothelioma among the

former shipyard workers. As for the controls, four died of lung cancer and none died of mesothelioma.

Findings of an extraordinary increase of mesothelioma were also reported last year from the French shipyard area in Western Brittany. Lajarte et al. analyzed cases of pleural mesothelioma in Nantes. In the period 1957-63, there were two cases; from 1964-1970 there were 12; and from 1971-1974 there were 24.¹² This was interpreted as consistent with the markedly increased shipbuilding program during and after World War II, and with its attendant risk of asbestos exposure.

TABLE 4
Deaths among 17,800 asbestos insulation workers in the United States and Canada, Jan. 1, 1967-Jan. 1, 1977: Analysis by duration from onset of employment

Duration from onset (years)	Number of men	Person-years of observation	Lung cancer		Pleural mesothelioma No./1000 person-years	Peritoneal mesothelioma No./1000 person-years
			Expected*	Observed		
<10	5,552	26,393	0.69	0	0	0
10-14	9,083	29,003	2.77	7	0	0
15-19	9,948	34,069	8.57	29	0.06	0.09
20-24	8,887	31,269	17.03	59	0.19	0.10
25-29	6,596	20,657	21.04	104	0.73	0.87
30-34	3,547	11,598	18.48	112	0.86	1.90
35-39	2,019	5,401	11.47	66	2.96	3.33
40-44	1,108	3,160	8.12	39	1.27	5.06
45+	1,030	5,305	17.82	69	2.45	5.47

* Expected deaths are based upon white male age specific mortality data of the U.S. National Center for Health Statistics for 1967-1975 and extrapolation to 1976: Smoking habits not taken into account.

ASBESTOS DISEASE IN U.S. SHIPYARDS

There has been comparatively little written concerning the potential for asbestos-disease hazards in U.S. shipyards. In part, this may have been due to the fact that in the latter part of World War II a survey directed to this question failed to demonstrate the prevalence of significant asbestos disease. At that time, 1,074 insulation workers employed in U.S. yards were examined and, with few exceptions, no evidence of disease was found.¹³ Unfortunately, the significance of the fact that the very large majority of men had begun working only a short time before was not appreciated; neither was it understood that X-ray evidence of disease could not be expected to appear until one or two decades later.

During the 1960's, evidence accumulated that "asbestos workers" (insulation)

employed in shipyards had unhappy disease experience, with markedly increased death rates of cancer (lung cancer, pleural mesothelioma, peritoneal mesothelioma, gastrointestinal cancer) and asbestosis.¹⁴ These observations, however, were confined to insulation workers, and while they pointed to a possible accompanying difficulty among other shipyard trades, especially in view of British experience, detailed observations concerning other workers were not available.

The potential for asbestos disease in U.S. shipyards was further highlighted by accumulating knowledge that the workers who manufactured the asbestos insulation materials used in U.S. yards during and after World War II were themselves found to suffer serious asbestos disease. Investigations of the employees at one such plant showed markedly increased risk of neoplastic disease and asbestosis, including increased risk of death of cancer with as little as one month of employment.^{15, 16}

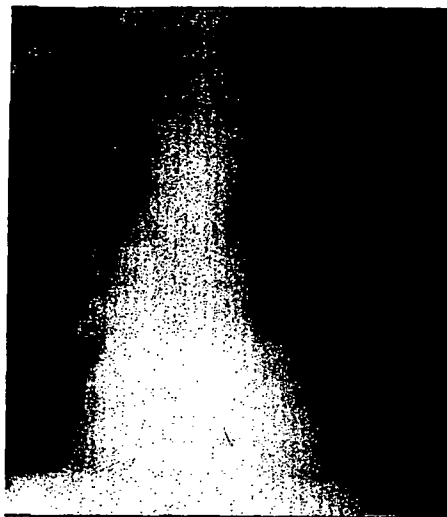


Fig. 1 S.P. & J.M. Extensive bilateral pleural calcification in former shipyard workers. Asymptomatic. No part of pleura is immunecostal; diaphragmatic, mediastinal, pericardial. Bilateral calcification of this sort rarely seen except with prior asbestos exposure.

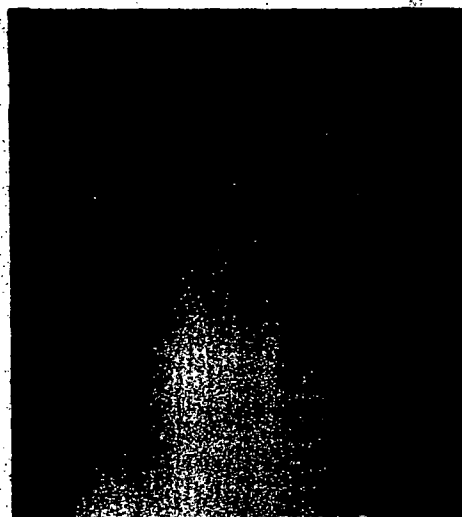


Fig. 2 J.B. Both fibrotic plaques and pleural calcification in x-ray of former shipyard worker. Asymptomatic. Their presence is merely evidence of prior asbestos exposure and not indicative that mesothelioma will necessarily follow.

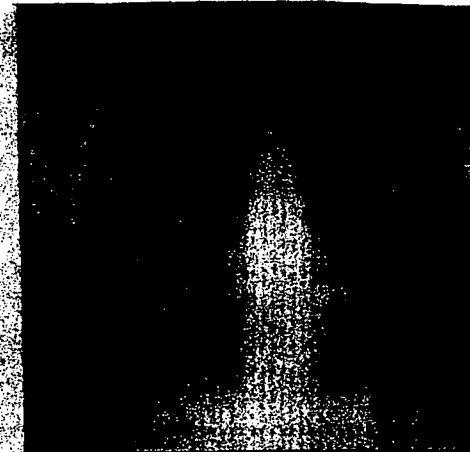


Fig. 3 J.W. Age 49, 1975. Truck driver until 1960, when he became "pipe coverer" in a shipyard. X-ray, fifteen years later, shows reticular (irregular) opacities of moderate profusion (2/2 in the ILO U/C Classification). Some shortness of breath on exertion. Note: infiltrate in lower lung fields, upper lobes clear. This is common.

Even wives and children of the employed workers showed evidence of asbestos disease, indicating that exposure of lesser intensity might be seriously hazardous as well.¹⁷

RECENT SURVEY OF SHIPYARD WORKERS, GROTON, CONNECTICUT

Cases of asbestos-associated disease among workers employed in a shipyard in Groton, in 1974-1975, were brought to our attention. Against the background of what was already known concerning the potential for asbestos disease in shipyards, it appeared useful to obtain information concerning whether there was the likelihood of a high incidence of such disease or whether the cases seen were isolated, random exceptions.

Lung cancer, mesothelioma, extensive asbestosis and other serious complications of asbestos exposure are late findings. Limited X-ray change (parenchymal, with-

in the lung, or pleural) often precede these serious consequences. While such changes may occur to an extent visible by X-ray without subsequent cancer or disabling asbestosis, their appearance among a group of workers provides evidence of prior significant asbestos exposure. Absence of such X-ray changes is no guarantee that important asbestos exposure has not occurred. Many workers may have had asbestos exposure sufficient to cause death from mesothelioma, for example, without showing X-ray change. Nevertheless, taken as a whole, absence of X-ray change in a group of workers suspected of having been exposed to asbestos provides some evidence that the exposure was limited. On the other hand, the presence of characteristic asbestotic X-ray abnormalities is prima facie evidence that, overall, there was important asbestos exposure in the group.

In light of this, we sought to ascertain whether there was significant prevalence of asbestotic X-ray abnormalities among Groton shipyard workers. Examinations

were largely limited to those whose employment had begun 15 or more years before; all were volunteers. A caveat is in order: there is no way of knowing, under these circumstances, whether those who volunteered were necessarily representative of the entire work force, or even of their specific employment category. Altogether, 1,000 men were examined, including 157 boilermakers, 121 pipefitters, 73 insulators, 82 painters, 69 carpenters, 117 welders, 104 electricians, 108 outside machinists, as well as laborers, molders, lead bonders, office workers, draftsmen, guards, and decontamination technicians.

Films were categorized using the International Classification of Radiographs of Pneumoconioses (ILO U/C) (Appendix 1).

Overall, approximately half of the workers examined showed X-ray evidence of pulmonary and pleural changes of the sort regularly seen following direct or indirect occupational exposure to asbestos (pulmonary asbestosis, pleural asbestosis). The findings are outlined in Tables 9 and 10. One or another abnormality was

present in 274 of 636 workers with less than 20 years from onset of exposure (43.1 percent) and among 185 of 364 shipyard workers 20 or more years from onset (50.8 percent). Parenchymal disease was seen in 29.6 percent of the former group and 36.8 percent of the latter. Pleural changes were found in 23.1 percent of the less experienced workers and in 29.7 percent of the men with longer experience. The high prevalence of pleural changes was not unexpected, having been found previously among shipyard workers in Britain and elsewhere.¹⁸

The importance of duration from onset of exposure is clearly seen in Table 10, where it is found that among 303 workers who began work only in 1961 or later, 115 (38.0 percent) had abnormalities on X-ray. In contrast, among 166 workers whose employment began in 1950 or before, 85 (51.2 percent) were abnormal.

No trade was immune to changes. Tables 11 and 12 indicate that this was as true for painters as it was for electricians, for carpenters as for machinists, and for

TABLE 5

Deaths among 17,800 asbestos insulation workers in the United States and Canada, Jan. 1, 1967-Jan. 1, 1977: Analysis by duration from onset of employment

Years from onset of employment	Total deaths	Percent of all deaths			
		Lung cancer	Mesothelioma		
			Pleural	Peritoneal	Total
<10	51	0	0	0	0
10-14	85	8.24	0	0	0
15-20	188	18.43	1.06	1.60	2.60
20-24	320	18.44	1.88	0.94	2.82
25-29	388	26.80	3.86	4.64	8.40
30-34	340	32.94	2.94	6.47	9.41
35-39	253	26.09	6.32	7.11	13.43
40-44	203	19.21	1.97	7.88	9.85
45+	442	15.61	2.94	6.56	9.50
Total	2270	21.37	2.90	4.80	7.70

boilmakers as for welders. Review of work practices makes this quite understandable, of course. The conditions of shipyard work have been such that it is likely that asbestos exposure would have occurred among all individuals at a work site where the material was being installed, repaired or removed. Data are less certain for the less common crafts, where fewer workers were examined. Although evidence of asbestotic changes was found among some of these men and women as well, one can estimate a proportion only with less assurance.

Thus, exposure to asbestos under past conditions, of an intensity sufficient to cause significant asbestotic X-ray change, was common at the shipyard in Groton. As a result, a large number of workers now have pulmonary changes associated with such exposure. The prevalence of such a high proportion of asbestotic X-ray

changes raises the question of increased risk of asbestos-associated neoplasms in the future. Those to be considered include cancer of the lung, pleural mesothelioma, peritoneal mesothelioma, and esophageal, stomach, colorectal, oropharyngeal, laryngeal and renal cancer. The extent of this risk is not now known.

CURRENT SITUATION

In terms of public health, the overwhelming problem is the undoing, ameliorating or modifying of both current and anticipated results of past mistakes. The problems are straightforward and, simultaneously, complex. To a considerable degree, the complexity derives from the fact that we have had little experience to guide us in such matters, especially on the scale found in the present situation.

The following recommendations —

necessarily incomplete and tentative — are offered:

1. Knowledge concerning asbestos exposure:
 - *Dissemination of information:* understanding the disease potential of asbestos exposure (past and future) would be valuable for both worker and management.
 - *Avoidance of additional exposure:* appropriate engineering and industrial hygiene methods are crucial; removal or repair of asbestos materials now in place presents a problem for the future.
2. Medical surveillance programs:
 - *Asbestosis:* awareness of the presence of this disease by both the patient and the treating physician would be important, since most deaths of asbestosis are due to intercurrent respiratory infections, rather than to progressive pulmonary fibrosis. Pulmonary infections can be well treated, and experience has shown that many lives can be saved.
 - *Lung cancer:* early diagnosis can increase the likelihood of successful treatment to some extent (by no means as much as we would like). It is not known whether more energetic surveillance (as with frequent sputum cytology examination) will increase the percentage of those successfully treated. Studies are now in progress to investigate this possibility.
 - *Colorectal cancer:* early diagnosis increases the likelihood of cure.
 - *Oropharyngeal, laryngeal or renal carcinoma:* awareness of the increased risk of these cancers improves chances for early study and diagnosis of the presence of these conditions, which can be cured in many cases.
 - *Pleural and/or peritoneal mesothelioma:* effective therapy is not now available and early diagnosis does not significantly increase the likelihood of survival. However, research concerning therapy is now underway in the United States, Great Britain and France, and it may be hoped that improved treatment methods will become available.
 - *Education programs:*
 - Smoking: lung cancer risk is greatly

TABLE 6

Percentage distribution of trades in private shipyards, June 1943

Trade	Percentage
Welders	15.3
Shipfitters	11.0
Machinists	8.1
Pipefitters	7.2
Electricians	6.6
Carpenters	6.1
Laborers	5.5
Burners	3.8
Painters	3.1
Sheetmetal workers	3.0
Riggers	2.8
Chippers and caulkers	2.8
Boilmakers	2.3
Crane operators	1.3
Pipe coverers	0.2
All other	21.1

Source: Bureau of Labor Statistics, Bulletin 824.

multiplied by asbestos exposure.¹⁹ It is urgent that this information become available to workers who have been exposed to asbestos, and that every assistance be afforded them to help in their efforts to control and eliminate smoking, especially cigarette smoking. Some data are also available suggesting that cessation of smoking will, after a number of years, reduce the risk of lung cancer, even with a history of prior cigarette smoking. Should these experiences be confirmed, it will be even more urgent to identify and alert former shipyard workers, to acquaint them with the important risk of lung cancer should they continue cigarette smoking. Cigarette smoking also increases the risk of serious disability associated with pulmonary fibrosis, and of the develop-

TABLE 7
Mesothelioma tumors in Devonport
Dockyard, England, 1964-1973*

Asbestosis (disability)		Occupation	Mesothelioma (deaths)	
No.	%		No.	%
16	10.3	Sprayers	1	1.8
36	23.1	Laggers	1	1.8
15	9.6	Shipwrights	14	25.5
4	2.6	Boilermakers	9	16.4
16	9.6	Engine fitters	8	14.6
11	7.1	Electricians	5	9.1
6	3.8	Caulkers-Riveters	3	5.5
5	3.2	Welders	3	5.5
48	30.8	All others	11	20.0
156			55	

*Harries, P.G., Envir. Res. 11:261-267, 1976.

TABLE 9

X-ray abnormalities among workers employed in shipbuilding and ship repair

TYPE OF ABNORMALITY	Less than 20 years from onset of shipyard em- ployment (636)		20 or more years from onset of shipyard em- ployment (364)		Total	
	Number	%	Number	%	Number	%
Any abnormality	274	43.1	185	50.8	459	46.9
All parenchyma	188	29.6	134	36.8	322	32.2
Parenchyma only	127	20.0	77	21.1	204	20.4
Parenchyma & pleura	61	9.6	57	15.7	118	11.8
All pleura	147	23.1	108	29.7	255	25.5
Pleura only	86	13.5	51	14.0	137	13.7

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TABLE 8
Mortality experience of 429 shipyard workers in Barrow, England
with pleural plaques on x-ray (1964-1971) compared
with control men in Carlisle, without pleural plaques

Tracing to December 31, 1976	Plaques	Controls
Alive	299	347
Dead	127 (30%)	74 (17.2%)
Not traced	3 (0.7%)	8 (1.9%)
	429	429
Causes of death	Plaques	Controls
Lung cancer	19	4
Mesothelioma	23	0
G. I. cancer	7	4
All other cancer	13	7
Ischemic heart disease	34	29
Chronic bronchitis	9	9
All other causes	22	21

TABLE 10

X-Ray abnormalities among workers employed
in shipbuilding and ship repair:
analysis by duration from onset of work

Onset of work	Total	NORMAL		ABNORMAL	
		No.	%	No.	%
< 1950	166	81	48.8	85	51.2
1951-1955	198	98	49.5	100	50.5
1956-1960	333	174	52.2	159	47.8
> 1961	303	188	62.0	115	38.0
	1000	541	54.1	459	45.9

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TABLE 11
X-Ray abnormalities among shipyard workers
employed in shipbuilding and ship repair:
major crafts

CATEGORY	Years from onset of shipyard work				
	All groups		20 or more years		
	Number	Number	%	Number	%
All crafts	1000	459	45.9	185	50.8
Painters	82	44	53.7	10/25	40.0
Machinists (outside)	108	58	53.7	12/32	37.5
Pipefitters	121	66	54.5	25/34	73.6
Insulators	73	38	52.0	2/7	28.6
Electricians	104	55	52.9	23/34	67.8
Boilermakers	157	80	51.0	41/84	48.8
Welders	117	42	35.9	25/48	52.1
Carpenters	69	38	55.1	12/33	36.4
	831				
Total	1000	459	45.9	185/364	50.8

ment of cancer of the esophagus. Again, educational programs would be of value.

3. Assessment of the potential for shipyard asbestos disease:

■ **Household contact asbestos disease:** while families of asbestos workers are at risk, it is not known whether shipyard workers tended to contaminate their homes with appreciable amounts of asbestos in the past, and whether this has resulted in disease risk. Such

information is required for proper clinical surveillance.

■ **Necessary additional data:** appropriate studies of mortality experience, status of retired workers and effects of minimal exposure are required for complete evaluation of the potential for future shipyard asbestos disease. Nevertheless, enough is now known to warrant rapid development of effective medical surveillance programs. Further research can proceed apace. ©

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TABLE 12
X-Ray abnormalities among workers employed
in shipbuilding and ship repair:
less common crafts

	No.	Abnormal	%
Heavy equipment operators	13	8/13	62
Laborers	7	1/7	14
Inside machinists	30	15/30	50
Molders	12	4/12	33
Lead bonders	21	7/21	33
Decontamination technicians	12	5/12	42
Guards w/o previous job in yard	12	3/12	25
Office workers — Draftsmen w/o previous job in yard	37	16/37	43

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CT Scan— Its Use and Abuse

Robin Caird Watson, M.D.

The concept of computerized transaxial tomography (CT scan) was first envisaged by both Oldendorf in America and Hounsfield in England. It was Hounsfield who produced the first marketable unit, with the backing of the English Musical Instrument Corporation (EMI), in 1971.

This early unit was specifically designed for intracranial examination and, although cumbersome, proved to be an effective diagnostic tool. Then, in 1975, machines capable of scanning the entire body were developed. Since that time, CT scanner manufacturers have proliferated—at a recent meeting of the Radiological Society of North America, some 20 different brands were exhibited—and rapid technological improvements have rendered the CT unit an unparalleled diagnostic instrument.

Using the CT machine, we are now able to accurately locate a disease process anywhere in the body, determine the nature of the process (cystic, solid or inflammatory) and ascertain its extent, including any involvement with adjacent organs. The CT scan is infinitely more sensitive than many other tests, and the type of information gleaned is invaluable in the

diagnostic workup of patients. Surgeons, for example, have benefited enormously from the information provided preoperatively by the CT scanner. Ultimately, of course—and this should be our primary

"Clearly, we have not yet explored all the possible uses of the CT scanner... we must carry out extensive research in order to realize the potentials and determine the limits of CT use."

interest—it is the patient who gains from such diagnostic advances. Unlike many elaborate diagnostic procedures, the scan can be performed on an outpatient basis. Further, it is noninvasive and therefore entails minimal trauma and risk for the patient.

Diagnosis, however, is not the only application of the CT scanner—its greatest effectiveness may well be in its use as a treatment tool for patients with cancer. In radiation therapy, pretreatment planning and posttreatment evaluations are being increasingly determined by CT scans. Similarly, the scan is being incorporated into chemotherapy protocols, both for baseline and follow-up assessments.

Clearly, we have not yet explored all the possible uses of the CT scanner. In addition to performing routine case exam-

inations, we must carry out extensive research in order to realize the potentials and determine the limits of CT use.

Present Uses

Current applications of the CT scan are numerous; in some cases it has replaced long-used, standard procedures. Certain applications remain controversial, however, and one can only seek guidelines and attempt to benefit from others' experiences.

CT examination of the head has been possible long enough that we can compare it to other diagnostic modalities. Based on our experience, it would seem that routine screening of patients with headaches is not indicated. However, since the introduction of the scan there has been a dramatic diminution in the number of arteriograms and pneumoencephalograms performed at most institutions, and this is a very positive development, as these tests are expensive, time-consuming and highly unpleasant for the patients. Certain other examinations, such as skull X-rays and nuclide brain scans, have also been replaced, to a large extent, by CT scans.

Generally, abdominal exploration should include standard, routine examinations—upper GI series, barium enema and I.V.P.—before CT scanning.

In the chest, routine PA and lateral views or stereo films, decubitus views and overpenetrated films should be obtained before CT scanning is ordered. In some medical centers chest tomography has been replaced by CT scanning, based on the opinion that scans are more sensitive.

Within the thorax, the CT scan can accurately localize and delineate mediastinal, pleural and parenchymal tumors, and for examination of osseous or paraosseous soft tissue masses, the CT scan remains the test of choice. However, many centers use both ultrasonography and CT scanning in such cases, as they are complementary procedures.

Though a helpful adjunct, the CT scan has by no means eliminated explorative surgery, despite some claims to this effect. In fact, speaking generally, most invasive techniques—such as angiography—have

not been replaced by CT scanning, since the different methods provide different sorts of information.

A discussion of contemporary diagnostic techniques cannot ignore ultrasonography; significant technological advances have made it a diagnostic modality of utmost importance. Indeed, it is even

"Though a helpful adjunct, the CT scan has by no means eliminated explorative surgery."

less invasive than CT screening, as no radiation and no intravenous contrast are used. In obstetrics, therefore, ultrasonography is vastly preferable to other techniques, and it is also very effective in delineating hepatic, pancreatic and renal tumors, as well as the portal-hepatic region. Major vessels are also clearly seen with ultrasonography, which has the advantage of being multidirectional. In the investigation of pericardial and valvular problems, echocardiography is the technique of choice.

CT Policy Criteria

With the large selection of diagnostic tests available, it is clear that this aspect of medical practice must be considered in physician education. Careful screening, by radiologists, of requisitions for CT scans is of primary importance, in order to eliminate unnecessary examinations. The scanner is not a diagnostic panacea and it must be used with intelligence and restraint.

In establishing diagnostic justification for CT scans, other considerations also enter into the decision. One such consideration is time. Since the body scanner was first introduced, some two-and-a-half years ago, immense technological improvements have been made. Prototype models, although unquestionably a technological breakthrough, provided images

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that can be likened to Dr. Roentgen's early attempts. In addition, the early models required between two and four minutes to render an image of each slice. This time has been considerably reduced and a better image can now be obtained in two to five seconds. However, it must be remembered that a considerable amount of time is usually expended positioning the pa-

"The scanner is not a diagnostic panacea and it must be used with intelligence and restraint."

tients on the table and injecting them with contrast material. Thus, even with the improved scanning time, studies may take 10 to 20 minutes for each patient, as many examinations require evaluation before and after the injection of contrast material. In addition, reproduction of the image on the screen may take an appreciable amount of time, and this in itself can reduce the daily quota of patients.

Another important factor is patient cost. Though fees charged for CT scanning have been reduced during the last year, the cost to the patient—\$100 to \$400—remains high, relative to most other diagnostic tests. Some centers have separate charges for examinations with and without the use of contrast material, and patients must pay the double rate if both examinations are performed.

The amount of radiation delivered during a CT scan is an aspect which has provoked little comment. The older, slower units deliver a dose of approximately two rads per slice, which is in the range of acceptability, but the newer models deliver a significantly larger amount of radiation to the patient. In an age in which we are all sensitive to the amount of radiation exposure patients receive, we must make a hard appraisal of our present practices. It would seem appropriate for medical physics departments to play a dominant role in this matter and compare the doses incurred by various machines currently on

the market. Most patients undergo examination only once; however, repeated examinations of the brain over a prolonged period of time can result in damage to the cornea, and it is the responsibility of the radiologists to see that this sort of trauma does not occur. Future development entails reduction of the amount of radiation while preserving the quality of the image.

In sum, the criteria for formulating policy regarding CT scans are diagnostic reliability and superiority over other techniques, time and cost considerations, and the safety and well-being of the patient.

Governmental Regulation

In reality, CT policy is affected by developments that have little to do with real needs.

Distribution of CT scanners is a major problem currently facing the medical community. The scanner unfortunately made its appearance just at a time when rising medical costs had caught the attention of federal agencies; the scanner itself was blamed for the increase in health care costs, though this assertion actually has no merit. The federal government none-

"In an age in which we are all sensitive to the amount of radiation exposure patients receive, we must make a hard appraisal of our present practices."

theless felt compelled to involve itself in CT planning policy, and the certificate of need concept, making all equipment purchases over \$100,000 subject to federal approval, grew out of these economic concerns. To further complicate the situation, recent HEW recommendations suggest that before a hospital can acquire a CT scan, neighboring units must conduct 4,000 examinations per year. Again, this is not founded upon a realistic assessment, as no CT unit can accommodate this many examinations. While the basic intent of

these federal regulations is to prevent duplication of services and ensure adequate backup in terms of facilities and personnel, this sort of legislated distribution applies more logically to treatment modalities than to diagnostic techniques—and the scanner is primarily a diagnostic tool. The unfortunate result of this governmental interference is a battle over the control of scanning equipment and, particularly where head units are concerned, a source of conflict between radiologists and neurologists. Another potential problem related to government involvement is the complete loss of quality control—for example, making CT units available to untrained practitioners and encouraging mistakes and unnecessary examinations by inciting centers to perform more scans than good policy would dictate. Further, government-imposed restrictions on purchases will depress the market and obviate research incentives among manufacturers.

Hospital Expense

The cost of CT scanning units is very high, with prices ranging up to \$750,000 for the newest and most sophisticated units. It is hoped that over the years prices will be reduced, although this has not been the case with other types of X-ray equipment, where prices have steadily increased. Ohio Nuclear recently marketed a dedicated head scanner at \$95,000, presumably to circumvent the certificate of need stipulation. The drawback to this otherwise commendable unit is that it can accommodate only a relatively small number of patients. Most medical centers have managed to scrape together the necessary funds for a CT unit, recognizing it as a diagnostic necessity, though no one views such a purchase lightly.

The cost of maintaining a scanner is extraordinarily high (at our institution it runs to \$300,000 per year); the claim that scanners are money-making devices is patently false. This maintenance figure includes various elements:

- Salaries for medical, technical and secretarial assistance—we have found it necessary to have two technicians on hand at all times that the machine is

being used, and a physician is required to monitor the tests and inject contrast material.

- Space requirements—these are considerable, as the equipment is bulky.
- Depreciation of the equipment.
- Utilities—the system houses its own air conditioner.
- Servicing costs.
- Charges for contrast material, syringes and other supplies.

The impulse at many centers is to maximally utilize such a marvelous and costly piece of equipment. However, running a scanner on a 24-hour basis only serves to magnify the costs involved—and these costs are ultimately passed to the patient

"The medical and lay communities must act together to prevent this very important achievement from becoming a political football."

—by the requirement for several teams of physicians and technicians and inevitable overtime payments. Examinations conducted at odd hours are inconvenient for patients, and especially so for outpatients who may travel long distances to obtain the test. In addition, it is apparent that excessive use of CT equipment induces an increase in breakdown time.

The Task of the Future

In the CT scanner we have a remarkable tool whose potential has hardly been approached. The medical and lay communities must act together in preventing this very important achievement of modern medicine from becoming a political football. Federal agencies are faced with solving the very pressing problem of increasing medical costs; we in the medical profession are faced with keeping bureaucratic intervention at a minimum. Above all, we cannot allow our accomplishments to go unused, nor our future to be subject to irrational restrictions. ©

Prostate Cancer: Progress and Change

Gerald P. Murphy, M.D., D.Sc.

For several years it has been recognized that prostate cancer constitutes a significant oncologic problem. The relative constancy of both the numbers of new cases and the recorded numbers of deaths have been the subject of numerous reviews and reports.¹

However, we have recently experienced a period of substantial clinical change in the overall approach to prostate cancer: new methods of diagnosis; emphasis on primary care; assessment of histologic prognosis; clinical classifications for prognoses reflecting the extent of disease; and the availability of new therapeutic interventions. With change hopefully comes progress, and there is significant documentation of this progress (Fig. 1). Current national figures on prostate cancer reveal—in terms of population groups, for localized cancers—that there is improvement in the five-year survival rates (Fig. 1). These results, of course, must be followed closely for longer periods of time and can only be evaluated when the specific factors responsible are identified, and when further follow-up and observation times are affordable. This is not the case at the moment.

Epidemiology

There is no question that there are changing cancer death rates by age and race in the United States. Prostate cancer remains a serious problem among blacks.² At-

tempts to identify other high risk groups, possible sexual or transmissible factors and socioeconomic factors involved have been instituted and preliminary reports given.³⁻⁵ These areas must be watched closely since there may be a particular group of individuals who, with further identification, could benefit from improved methods of screening and prevention of prostate cancer.

It should be noted that even this limited amount of information has not been previously available.¹ Careful case control studies of blacks in Washington, D.C. compared with those in Africa have suggested that external, environmental factors other than original racial origin may be affecting prostate cancer growth rates. This is a significant epidemiological advance.²

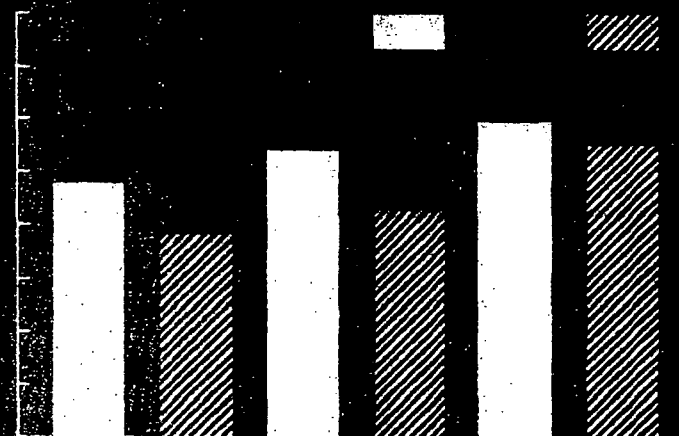
Morphology and Histological Prognosis

The morphology of prostate cancer has been described by individual experts and collaborative groups for some time. This area has been recently reviewed and there is excellent information available for students concerned with this perplexing problem.⁶

All available evidence suggests that, generally, prostate cancer exists as a multifocal carcinoma, as Mostofi and his asso-

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CURRENT NATIONAL 1977 FIGURES ON
PROSTATE CANCER PATIENT SURVIVAL



ciates have pointed out.⁷ Some investigators believe that these multiple foci of prostate cancer represent intraglandular metastases, but this has not yet been resolved.⁷ No matter how early prostatic cancer is detected, it seems to exist at more than one cellular site. There have been a number of attempts to identify those factors in systems espoused by Gleason, Mostofi and others, that could provide a single system for histological prognostic use.⁷ Such a venture represents change and change is usually difficult to apply

widely. In 1978, the American Cancer Society National Prostatic Cancer Task Force will undertake this difficult effort. The comparison of proven systems in the United States and elsewhere will be helpful. The assimilation of all factors that are found reproducible and that can be adapted by many pathologists will alter and significantly affect our current thinking about aggressive approaches and other alterations in early or late treatment of prostate cancer. Since this appears to be possible, it is a most important event.

TABLE 1A
DIFFERENT CLASSIFICATIONS OF
ADENOCARCINOMA OF THE PROSTATE

American System	
Stage	Description
A I, O	Occult Cancer
A ₁	Histologic: well differentiated, ≤ 3 slides
A ₂	Histologic: > 3 slides or not well differentiated
B II, A	Cancer confined within prostate capsule
B ₁	Tumor occupying ≤ 1.5 cm. in 1 lobe only
B ₂ , B	Tumor occupying > 1.5 cm. in one or both lobes, not invading capsule
C III	Cancer with extracapsular extension, no nodal or distant metastases
C ₁	< 70 gm.
C ₂	> 70 gm.
D	Cancer with demonstrable metastases
D ₁	Pelvic lymph node metastases or ureteral obstruction causing hydronephrosis
D ₂	Bony or distant lymph node or organ metastases

Chemical Diagnosis

For some time, acid phosphatase determination has been essential to the diagnosis of prostate cancer. Unfortunately, its elevation, as determined indirectly by substrate assay has usually been clinically associated with extension or metastasis—that is, the prostate cancer is no longer

confined to the gland. Within the past few years, several new assays have been developed by a number of investigators, and are currently under a nationwide field trial by the American Cancer Society Task Force on Prostate Cancer.

Radioimmunoassay
Radioimmunoassay (RIA) techniques⁸

TABLE 1B
DIFFERENT CLASSIFICATIONS OF
ADENOCARCINOMA OF THE PROSTATE

UICC	
Classification	Description
T _x	Incidental finding of cancer in operative specimen
T ₁	Tumor occupying less than half of prostate, surrounded by normal gland
T ₂	Tumor occupying more than half of prostate, but not producing enlargement or deformity
T ₃	Tumor confined within prostate but producing enlargement or deformity of gland
T ₄	Tumor extending beyond prostate
M ₀	No evidence of distant metastases
N ₁ (L)	Regional nodes
M ₀	No evidence of distant metastases
M ₁	Distant metastases only
M _{1a}	Bony metastases only
M _{1b}	Other metastases with or without bony metastases
N ₂	Fixed regional nodes palpable in abdomen

for prostate cancer can provide immunologic specific prostatic acid phosphatase assays. It is hoped that improved RIA will identify the extent of disease in patients earlier and more accurately. Radioimmunoassay, now undergoing a national screening test, is an expensive test, and therefore other alternatives have been reported and are similarly under trial.

Counter-immunoelectrophoresis

Counter-immunoelectrophoresis (CIE)⁹ can provide an immunochemical method for the detection of prostatic acid phosphatase. Early tests demonstrate that it is relatively inexpensive and can be performed in any hospital laboratory equipped with commonly available equip-

ment. The counter-immunoelectrophoresis method may provide a more widely usable test, with equal specificity and accuracy. CIE is also currently under a nationwide American Cancer Society field test.

Further Chemical Assessment

One must not overlook further chemical assessment and determinations of prostatic fluid. In most patients, continuing evaluations of this substance are warranted upon urologic examination. Early tests suggest that certain isoenzymes may be altered.¹⁰ In fact, elevations in LDH in prostatic cancer patients seem to support the concept that the prostate cancer may not only be multi-focal in its histologic origin, but also may exert a general metabolic effect upon the gland.¹⁰

"Within the past few years, several new assays have been developed ... and are currently under a nationwide field trial."

Bone marrow acid phosphatase determinations have been utilized as well as lymph node biopsy in the neck and other areas to detect metastatic disease where it is not thought to be clinically present. The goal and philosophy of therapy can be substantially changed by such tests. Newly purified acid phosphatase determinations previously referred to^{8,9} have been used recently to assess the value of bone marrow acid phosphatase in staging prostatic cancer but the results are still tentative. These tests appear to be more accurate than those used previously and upon which clinical recommendations have been made. At present, it would appear that such determinations will confirm the unexpected presence of microscopic prostatic cancer; further tests and trials will determine how often this occurs. The preliminary results¹¹ from such new tests suggest that it does not occur frequently. One must again separate the newly available methods of staging for the extent of disease beyond the

primary tumor from former methods. Past results using other techniques cannot be applied to present circumstances. Currently, bone marrow acid phosphatase measurement by these new techniques appears to only minimally improve the diagnosis of metastatic disease.

Staging Classifications

In the past, there have been differences in both the staging and end results reporting for a variety of tumors. The American Joint Committee for cancer staging and classification has used Roman numerals I through IV to correspond with Whitmore's A through D.⁶ The International Union Against Cancer (using the TNM classification) has a slightly different approach to clinical staging. These systems are currently under evaluation by several groups. The most current and comprehensive comparison of these classifications was derived from that prepared by Boxer⁶ (Table 1). The most significant difference in all of these approaches seems to occur with the early focal or occult cancer. In the United States, further definition and further subclassification is occurring and, as a result, other recommendations are being made for therapy. The so-called focal localized nodule of the prostate frequently occurs in the B stage. However many believe that its frequency is less than had been thought.⁶ Localized pelvic prostatic cancer, stages C or D, or D₁, are now more frequently defined as a result of bilateral pelvic lymph node dissection. To date, no one can precisely define when a pelvic node dissection is diagnostic, when it is therapeutic, or even when it constitutes a procedure acceptable to all. There are extensive procedures performed in the course of some interventions; lymph node sampling is done in others. The numbers of sections of the lymph nodes considered necessary for the detection of microscopic cancer cells is a problem of institutional variation. Moreover, lymphangiograms have recently been substantially used for preoperative staging with some modification in technique.¹² The advent of CT scanning will doubtlessly provide further changes, additional refinement and more

assistance in the determination of the extent of disease without surgical intervention. Implicit in all of these factors is that the degree of differentiation of the primary prostate carcinoma may affect the survival regardless of the therapeutic intervention. This has been previously not-

"One must not forget Lord Batson's plexus and the prostatic venous drainage! It may prove of continued importance."

ed¹ and has been most carefully determined in a recent study by Whitmore and associates.¹² Important determinants of metastases subsequent to a particular form of therapy probably do indeed seem to relate to:

- The large size of the primary tumor;
- Poor histological differentiation;
- Volume of lymph node metastases;
- Lack of local prostatic response to radiation;
- Possible seminal vesicle invasion.¹²

Such careful studies provide important new factors that will affect the further classification, staging and assessment of our end results.

Randomized selection of cases from institutions doing one form of treatment compared to others who have performed lymph node dissections have been reported.¹³ While these emphasize the importance of lymph node drainage and lymph node assessment in the staging of extent of disease, they also document that even today there are still unanswerable questions or at least instances of clinical variance. One must not forget Lord Batson's plexus and the prostatic venous drainage! It may prove to be of continued importance. The possibility that the interruption of lymph node drainage may have non-beneficial immunological effects has been raised but not resolved.

In addition to the factors mentioned for staging prostate cancer and the variety

of prognoses reflected, improvement may come from other areas of biology. Tumor markers or hormonal (androgen and estrogen) receptor sites have been found to be useful for therapeutic treatment and also for clinical treatment trial stratification. Work on a variety of receptors is underway and promising results have been reported in terms of estrogen receptors in human prostate cancer.¹⁴ While final results will not be available in the near future, current data suggest that some hormonal markers may be useful in the future in clinical classification and further therapeutic stratification.

Physical examination has not been extensively mentioned in this particular report. It remains, however, an essential part of any program of complete evaluation and initial and continuing inspection. Biopsy techniques likewise have not been reviewed since they have been extensively reported upon.⁶ The use of roentgenograms and other forms of scanning are helpful and reports are also available. Prostatic echography is a new tool and initial promising results have been reviewed.⁶ The scanning of bone marrow in prostatic cancer may also be useful for a variety of staging purposes, but more importantly, for therapeutic decisions regarding the efficacy of adjuvant treatment, i.e., chemotherapy. Other immunologic markers and assessments of immunocompetence of status of the host, remain the subject of intensive and widespread individual research studies. They should be watched for further promising reports but at present cannot be translated into widespread therapeutic or diagnostic recommendations.

Primary Treatment

As in the past, perineal prostatectomy and radical retropubic prostatectomy are being performed today (Table 2). The perineal approach has not changed and is being used by some for more selected cases or patients with other medical life-threatening complications. As is reflected in recent reviews (Table 2),⁶ there are some patients who are now benefiting from ret-

ropublic prostatic removal combined with lymph node intervention. Recent reviews and summaries⁷ of the results of this approach appear to justify its use. However, longer follow-up is needed.

Interstitial therapy for localized prostate cancer has been introduced using I¹²⁵. Extensive results have been described by Whitmore and associates and are being followed closely.¹² Thus, one has a variety of surgical approaches to early or localized stages of disease combined with variations in lymph node dissection, with or

"... There are some patients who are now benefiting from retropubic prostatic removal combined with lymph node intervention."

without the addition of interstitial operative applications.⁶ The techniques, the numbers and the degrees of lymph nodes are currently subjects of dispute and debate. There are at present no randomized studies, nor should there necessarily be any. However, it is important to note that these results are promising,⁶ and, in and of themselves, they afford a therapeutic option.

Bagshaw's observations with external radiation for localized disease indicate that short-term, disease-free survival is possible in over 87 percent of patients with negative lymph node biopsies. Patients in an intermediate phase, with positive lymph node biopsies only in the pelvic region following extended field radiation therapy also have an improved survival rate, nearly 72 percent. Patients with positive peri-aortic node and pelvic node biopsies have a diminished survival. The randomized trial conducted by Bagshaw and associates has been recently reported and continued promising results are seen.¹⁵ There are other features of radiation therapy reported and described that cannot be ignored. The question of the use of exogenous estrogens as a form of endocrine therapy, has been most recently reported;

those interested in reviewing the divergent opinions may wish to consult a recent review.⁶ Hormones should be considered essentially palliative and should not be confused with primary treatment.

Surgery and radiation therapy as primary treatment afford a reasonable opportunity for disease-free interval and possible cure. The author does not prefer surgery, interstitial therapy or external radiation therapy on the basis of any results currently available. In the author's present viewpoint, no one mode is definitely proven to be superior to any other. Urologic surgeons and others should afford patients the opportunity for the selection of treatment best suited to their particular needs, depending upon a variety of interpersonal factors and possible medical conditions. In terms of primary therapy, it must be remembered that lymph node dissection is not without its possible complications. Moreover, lymphangiograms may or may not be desirable. Radiation therapy has an important role to play as does primary surgery. An attempted resume of the current status of the therapy as employed today by radiotherapists and urologists is reflected in Table 3. The biggest problem with the interpretation of Table 3 is that many of the stages depend upon precise surgical staging. They are not clinical stages. Whether or not node dissection or node sampling is done remains an important and irresolvable distinction.

Palliation Therapy

Palliation, or hormonal, therapy is neither intended nor claimed to be curative. Whether one uses a different dose of estrogen combined with the presence or absence of orchiectomy, remains a source of occasional concern. It is appropriate to restate results from our own institution as an example of full term follow-up and high percentage autopsy examination of patients with widespread or metastatic prostatic cancer who are treated with either orchiectomy or combination treatment (Table 3). Without question, prostate carcinoma remains the all-time and major cause of death in all such patients. There

TABLE 3
CURRENT STATUS OF
MOST COMMONLY EMPLOYED METHODS OF PRIMARY THERAPY

Stage	Examples of Therapeutic Choices Currently Being Employed
A ₁ A ₂	Some prefer surgery, others observation.
B ₁	1) Radical prostatovesiculectomy (either retropubic or perineal approach*) ± lymph node dissection 2) Radiation therapy
B ₂	1) Radical retropubic prostatovesiculectomy with pelvic lymphadenectomy 2) Radiation therapy ± node sampling
C	1) Radical retropubic prostatovesiculectomy with pelvic lymphadenectomy 2) Interstitial radiation with pelvic lymphadenectomy 3) Radiation therapy ± lymph node sampling 4) Some prefer observation ± endocrine treatment
D ₁	See text
* A few centers employ cryosurgical destruction ± lymph node dissection in all the stages depicted in this table.	

are no significant statistical differences in this particular hormonal program. We are aware of the ability to measure dihydrotestosterone (DHT) and other substances in the serum, but these should not be used as a guide to the adequacy of palliation therapy. The patient himself will inform the clinician regarding pain relief, sense

of well being, weight, appetite, etc. A variety of doses are useful and have been found adequate. Levels of hormones in one partition of the total body compartment cannot possibly be of predictive value, although some may feel that is the case. Only extended metabolic studies over 24 hours including all possible components

TABLE 3
CAUSE OF DEATH BY PRIMARY TREATMENT*

Cause of Death	Orchiectomy	Estrogen + Orchiectomy
Prostatic carcinoma	47.4%	64.7%
Other neoplasms	32.8%	6.0%
Cardiovascular diseases	13.2%	22.9%Δ
Other, mainly respiratory diseases	6.6%	6.4%

* Excluding patients who are alive or have died from unknown causes.

Δ Not statistically significant.

may lead to a valid endocrinologic conclusion. In our own experience, this does not justify a change in clinical judgment and is a research project only. The following viewpoints for conventional hormonal palliation with advanced, untreated prostatic carcinoma are restated:

- Withhold therapy until the patient's symptoms or general condition warrant treatment.
- Generally, use castration alone although many physicians also administer stilbestrol either with or without castration.
- When stilbestrol is administered following symptomatic or clinical relapse after castration, limit the dose to one mg. daily. There is some suggestion, however, that three mg./day may provide better androgen suppression in certain patients.
- High-dose estrogen therapy (natural or synthetic source) is not recommended except for selected use in short-term, acute situations.

Hypophysectomy and adrenalectomy have been discussed previously.¹ The ef-

fectiveness of these two procedures has been established and need not be repeated at this time. Occasional long-term results from this form of extensive hormonal therapy have been described.¹⁶ However, following new forms of chemotherapy for patients relapsing after conventional hor-

"Hormones should be considered essentially palliative and should not be confused with primary treatment."

monal therapy, it has been found that chemotherapy is generally superior.¹⁷ Non-steroidal anti-androgens and other agents that have suppressive effects upon the adrenals have undergone some clinical study.^{18,19} They do not, however, appear to afford a practical or useful alternative for palliation at this time. Metastatic prostatic cancer that has relapsed following conventional hormonal therapy can be

managed usefully according to the results of the National Prostatic Cancer Project.

The National Prostatic Cancer Project participants (see box on page XX) have demonstrated that a variety of forms of chemotherapy in such patients who have had previous radiotherapy or who have not been treated with radiotherapy, can be effective in controlled randomized clinical T values. Although these agents are toxic, under a carefully controlled program they can be used successfully. Their

results have been documented.²⁰⁻²² It is important to emphasize that the criteria and evaluation of the response parameters selected by this particular national group have been found reproducible and useful in the hands of others.²³ Moreover, they too, even in dealing with widespread metastatic disease in patients who have relapsed after all forms of conventional therapy, have found a relationship between primary tumor histologic grade and the response to chemotherapy.²⁴ This im-

portant viewpoint will be pursued and further studied. In addition to the ability of these new treatments to provide an alternative for the relief of pain, other objective and measurable partial responses have been observed. Some of these were first described in 1973 in terms of one agent, and further follow-up has now shown this to be true of still others.²⁵ Steroidal complexes combined with chemotherapeutic agents do have direct effects on human prostate cancer.²⁶ Phase I and

"Palliation, or hormonal, therapy is neither intended nor claimed to be curative."

Phase II trials currently underway will provide opportunities to develop alternatives. As a result of this interest in extensive disease, patients with metastatic prostate cancer at various sites other than bone are now receiving careful clinical evaluation and the assessment of their measurable responses is being documented.^{27,28} It is recognized that chemotherapy in the advanced stage of disease will not be the final answer but rather an alternative to treatment which already has proved useful and at this point justifies our earlier optimism in 1973.²⁹

Future Perspectives

Combination chemotherapy of selected agents and other new single agents has been proved active under national randomized trial conditions. Under this affordable and desirable parameter, patients newly diagnosed, or those with stable stage D prostate metastatic cancer, are being afforded the opportunity for treatment with these drugs. The studies are underway and will take some time before complete evaluation. At no time in their conduct will the patient be denied an opportunity for exposure to conventional or hormonal therapy. While this may complicate the evaluation of possible chemotherapy

cures, it will also assure the quality of life and the maintenance of our high clinical standards. In the very near future, adjuvant chemotherapy in patients with positive periaortic nodes or other advanced stages of surgical disease will be undertaken, expanding parameters and knowledge. This is the basis for reasonable and justifiable optimism and may well produce future reports from the National Cancer Institute reflecting improvement in survival rates for greater durations and for larger numbers of patients. It is unfortunate and regretful that we cannot separate our goal of primary therapy from that of palliative therapy. On the one hand we must have a concern for the welfare of our patients³⁰ but this should be tempered with the realization that many require treatment and many present with advanced prostate cancer despite our current highly developed medical facilities and technology.³¹ This, however, can be altered as demonstrated by the alternatives of chemotherapy.

We are defining metastatic disease in new ways: it is being defined by surgical intervention, by lymphangiogram and by

"Multidisciplinary treatment remains most important... Hormonal palliation is still a mainstay."

other external means to a degree never done before. As a result, we have larger numbers of patients at an earlier phase of their disease, compared to the early 1970's. Multidisciplinary treatment remains most important; so-called surgical staging, urological-operative intervention and radiological treatment have established their abilities to provide significant and substantial improvements in survival of primary tumors. Hormonal palliation is still a mainstay and will unquestionably remain so for the future. The role of adjuvant chemotherapy has, since 1973, progressed to the point of being appropriately considered for controlled trials in those

patients with early diagnosed, microscopic, occult or progressive disease. Comparing their results with palliative therapy will be a fruitful endeavor and should provide us with a basis for optimism and hope.

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Questions and Answers on Cancer



Phenyl-beta-naphthylamine

Recent investigations have disclosed that phenyl-beta-naphthylamine can undergo N-dephenylation in humans, with recovery of small amounts of beta-naphthylamine, a potent carcinogen, in the urine of exposed subjects. Has bladder cancer or any other form of cancer been associated with exposure to phenyl-beta-naphthylamine?

M.D., Peoria, Illinois

Phenyl-beta-naphthylamine is manufactured in this country by BASF Wyandotte Company. In the past it had been used in the manufacture of rubber tires. According to the company only 10 lbs. was used in the U.S. last year.

There are a number of chemicals used in rubber manufacture, notably benzene, and occupationally exposed workers in the rubber industry have been reported to have excess rates of bladder cancer and leukemia. But it is not possible to attribute any of the higher risk to use of phenyl-beta-naphthylamine.

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Hodgkin's Disease

My patient is a 21-year-old auto mechanic with the proved diagnosis of Hodgkin's disease, stage III/B of mixed cellularity, discovered in May of 1977. He was completely staged and retroperitoneal nodes were negative, as was the spleen. During the first cycle of MOPP chemotherapy he developed an unquestionable allergy to procarbazine, and a small re-challenge brought back the anaphylactoid reaction. I was then forced to use the ABVD regimen of Dr. Bonnadonna. After three cycles of ABVD, he received irradiation of up to 3000 rads to the bulky sites, according to the suggestion of Dr. Leonard R. Prosnitz (Ca 26:2826, 1976). Soon he will complete his sixth and last cycle of ABVD.

Most reports state that ABVD is comparable to MOPP; one exception is a short abstract that appeared in the Proceedings of the Society of Hematology meeting held in San Diego last December. This report prompts me to ask you two questions:

- 1) Do you give much credence to this recent assertion that ABVD is not as effective as MOPP?*
- 2) If you agree with this report, would you recommend that this man (stage III/B of mixed cellularity) be followed by a total nodal irradiation in the usual manner, as suggested by the Stanford group?*

M.D., San Clemente, California

The MOPP program remains the standard and most proven chemotherapy regimen for the treatment of Hodgkin's disease. There are a number of other combinations which have been reported to produce complete response rates comparable to those of MOPP, but none has shown the quality or duration of the MOPP response, at least as reported by DeVita and confirmed at Stanford.

The MOPP program can produce 80% complete response, on the average, for all patients treated; two-thirds of the complete responders remain free of disease at five and 10 years on an actuarial basis.

The ABVD program of Dr. Bonnadonna has been compared to the MOPP regimen; the ABVD treatment is a combination modality in which radiation is also given. To date these two approaches show equivalent results. However, there are not enough data in the literature to demonstrate how ABVD, used alone as a primary treatment, compares with MOPP.

With regard to the patient with clinical Stage III/B, but pathological Stage II/B Hodgkin's disease of mixed cellularity type, the following comments can be made:

The Stanford study shows that patients with pathologic Stage II/B disease do not

benefit from adjuvant chemotherapy if total nodal radiation is given. If, in fact, the patient had pathologic Stage III/B disease then radiation therapy is an inadequate treatment program and chemotherapy should be the primary approach. If, as has been described, there has been an allergy to procarbazine one can substitute for procarbazine in the MOPP regimen, utilizing a nitrosurea or adriamycin. As stated, the ABVD regimen may be equivalent, but would not be the first choice in a primary treatment program. There are experimental and chemotherapy for Stage III/B disease but the role of radiation therapy has not yet been established. If the patient has pathologic Stage II/B disease and has received 3,000 rads to known sites of disease as well as 6 cycles of ABVD, this can be considered a very acceptable treatment program since, in this case, the ABVD will be given as an adjuvant and the radiotherapy is the major form of disease control.

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Oral Contraceptives and Cancer

The Editor Interviews:

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Editor: *There are about 10 million American women and 50 million women world-wide who now take oral contraceptives. In the 18 years since the Pill was first marketed, more and more has become known about its potential health hazards, and fear has arisen about a possible link to cancer. Is there any convincing evidence that oral contraceptives are associated with breast cancer, for example?*

Dr. Kretzschmar: No, there isn't. There is no evidence that the Pill increases the risk of breast cancer and in fact, it has been shown that oral contraceptives may offer some protection against benign breast disease. For example, when Vessey and his group compared 345 women admitted to London teaching hospitals with breast lumps (90 malignant and 255 benign) against a matched control group admitted for acute medical or surgical conditions, it was found that oral contraceptives were in no way related to the risk of breast cancer. It was discovered that the risk of admission to a hospital for a breast biopsy among Pill-users was reduced by about 75 percent, compared to those women who had never used the Pill at all.

The Boston Collaborative Drug Surveillance Program did another retrospective study, and had similar findings. One hundred twenty-one patients with breast disease (cancer, fibrocystic disease, fibroadenoma and miscellaneous problems such as fibrolipoma or benign duct ectasia) were compared to 842 patient controls. Among the women with newly diagnosed breast cancer, three of 23 (13 percent) had received oral contraceptives, compared to 20 percent who had received oral contraceptives among the controls. Of the patients with benign breast tumors, six percent had received oral contraceptives, compared to the 20 percent among the controls. When these findings were analyzed for the patients' ages, it was revealed that at each age level, Pill usage was less common in those with benign breast tumors. According to their data, hospital admissions in the Boston area for breast diagnosis were reduced by almost half for those women using oral contraceptives.

The prospective study being done by the Royal College of General Practitioners in Great Britain has also ruled out an association between breast cancer and oral contraception. Their 1974 interim report showed that of 46,000 women — 50 percent using the Pill continuously, and 50 percent not — 11 cases of malignant neoplasm of the breast were found in Pill-takers, four cases in ex-takers, and 16 among the non-taking control group. A lower incidence of benign breast neoplasm became apparent after two years of continual Pill usage.

Editor: *Aside from causing cancer de novo, is there any evidence that the Pill might exacerbate existing tumors?*

Dr. Kretzschmar: As far as the belief that women with benign breast tumors have a higher risk of developing breast cancer, the apparent protective effect of oral contraceptives against benign breast tumors could be considered a protection against subsequent development of breast malignancy as well. Also, prolonged use of oral contraceptives simulates pregnancy in some ways, and we know that, relative to other women, those who become pregnant early in life are at a lower risk of developing breast cancer.

There is some evidence that women who have fibroids may have enlargement of their fibroids related to the Pill. Of course, women with a strong family history of breast cancer should be followed with caution, and should have careful breast examinations at frequent intervals; women with known or suspected carcinoma of the breast should choose another form of contraception. But I am quite convinced that oral contraceptive intake is in no way responsible for breast carcinoma, *de novo* or otherwise.

Editor: *Have oral contraceptives been linked to ovarian cancer?*

Dr. Kretzschmar: No. There is no relationship. If anything, the Pill has an inhibitory effect on the development of ovarian cancer. In the British study of 46,000 women, there have been fewer deaths from both breast and ovarian cancer among those women using the Pill than among those who did not.

Editor: *Is there a relationship between the Pill and uterine cervical cancer?*

Dr. Kretzschmar: No. Among women receiving estrogen from a combination-type oral contraceptive, no convincing relationship to cancer of the uterine cervix has been established. In a case-control study done at the State University of New York-Downstate Medical Center in Brooklyn between 1969 and 1975, 689 consecutive patients with cervical carcinoma were interviewed and compared with a control group of 1,300 with normal cervical smears. Each case subject was matched with a control subject for age, ethnic origin, age at first coitus, age at first pregnancy, and socioeconomic status. The findings: no significant

difference between the case and control subjects in the use of oral contraceptives.

This conclusion duplicates the results of many other studies as well. Worth and Boyes compared the use of oral contraceptives among 310 women, 20 through 29 years of age, who had carcinoma in situ of the cervix with 682 control subjects matched for age who had negative smears. Again, there was no significant difference in the use of oral contraceptives. Thomas compared 324 women who had positive cervical smears showing dysplasia or carcinoma in situ of the cervix with 302 women from the same locality. No difference was found in their use of the Pill.

Although there has been a significant increase in recent years in pre-invasive lesions of the uterine cervix, this increase has been found in both users and non-users of the Pill.

This brings out one of the more positive aspects of the Pill. Just think of the number of women who routinely see their physicians now and obtain a Pap smear because they are on the Pill. Women who are on the Pill have a much better chance for earlier diagnosis of changes in their cervical epithelium than those who are not — and that's certainly a plus factor in the relationship of cancer to oral contraception.

Editor: *You discount a link between oral contraceptives and uterine cervical cancer. But if a Pap test reveals cervical dysplasia in a patient, would you advise her to stop taking the Pill?*

Dr. Kretzschmar: No, I would manage the dysplasia with selective biopsies and appropriate treatment. I would not advise her to stop taking the Pill.

Editor: *Are oral contraceptives associated with endometrial cancer in your view?*

Dr. Kretzschmar: No, there is no relationship. The sequential tablets, which provided estrogen alone for 14 days, and then estrogen and progestogen in combination for seven more days, were taken off the market when controversial evidence linking estrogen with possible cancer of the uterus came to light. In 1975, 21 cases of endometrial cancer among Pill-taking women under the age of 40 had been recorded, but in eight of the cases, factors were found which militated against a close relationship between oral contraceptives and carcinoma, and of the remaining 13 cases, 11 had taken sequential agents. So, there is absolutely no evidence to link endometrial cancer with combination or progestin-only oral contraceptives. In fact, since only about eight percent of women taking oral contraceptives at that time used sequential agents, the unduly high incidence of sequential agent therapy in these 21 cases might suggest that women who are predestined to develop this tumor are actually protected against it by the combination pills.

If you wish to discuss replacement estrogen, exogenous long-term estrogen for menopausal women, that's controversial. According to an article published in the *New England*

Journal of Medicine in 1975, the use of these exogenous estrogens in menopausal and post-menopausal women was associated with a 4.5 times greater risk of endometrial cancer. However, some physicians do not believe that there is a connection, and there are many knowledgeable people on both sides of the fence. Women taking estrogens should have frequent pelvic cancer-screening examinations and physicians should be on guard if abnormal bleeding develops. I would point out, in this respect, that the Pap smear is not a totally effective screening device for endometrial cancer; in fact, 40 to 60 percent of patients with adenocarcinoma of the uterus will have negative Pap results. An evaluation of the endometrial cavity with a suction curette, or an endometrial biopsy should be performed on all patients at high risk, or on those with a suspicious history. If a physician then feels he has not gotten a sufficient sampling, a dilation and fractional curettage should be done under local or general anesthesia. Our diagnostic procedures in this area should be further developed.

Editor: *Would you comment on the evidence linking oral contraceptive use to benign liver tumors?*

Dr. Kretzschmar: Yes, this was looked at carefully, and in April 1977, the American College of Surgeons released documented evidence on the increased incidence of benign hepatomas related to oral contraceptives. Their survey material consisted of 543 cases of primary liver tumors among both sexes; 378 in females and 165 in males. Among the males, 8.5 percent were benign, while among the females, 56.1 percent were benign. A positive history of oral contraceptive use was reported in 49.5 percent of the female patients, and in 29 percent the contraceptive history was unknown. However, it is reasonable to assume that a certain number of these "unknowns" included Pill-users; therefore, among the female patients in this study, more than 50 percent of primary liver tumors occurred in users of oral contraceptives.

The majority (73.8 percent) of the liver tumors diagnosed in Pill-users were benign. On the other hand, among non-users, the percentages of benign and malignant tumors were roughly equal. This difference in the proportion of benign to malignant tumors among users and non-users is substantial, and further supports the association between Pill use and the occurrence of benign liver tumors. Also, the frequency of malignant tumors in this study increased with age, and resembled the distribution of malignant liver tumors in the various age groups of the general population. But the distribution of benign liver tumors peaked in the age group of 26-30 years, and this parallels the age distribution of oral contraceptive use in the general population.

Editor: *What were the histologic types of these benign liver tumors?*

Dr. Kretzschmar: The survey showed that among non-users, the benign tumors were proportionately divided among four histologic types. But

among users, there was a preponderance of hepatic cell adenomas and focal nodular hyperplasia; together, these two types represented 82.6 percent of all benign tumors in users. So it appears that the association between oral contraceptives and benign liver tumors applies only to these two types. The incidence of adenomas peaked significantly in the 26-30 year-old group, and then declined sharply; the incidence of focal nodular hyperplasia peaked in the 31-35 year-olds and then remained rather constant in the older groups.

Editor: *Do the statistics vary with different types of oral contraceptives?*

Dr. Kretzschmar: Two synthetic estrogens are used in oral contraceptives: ethinyl estradiol and mestranol. (Mestranol is demethylated in the liver to ethinyl estradiol.) Where information was available on the type of synthetic estrogen used, 66.7 percent of the tumors were found in women who had used mestranol. But that correlation should be interpreted rather cautiously, since mestranol was marketed first, and until 1970, was used more frequently than ethinyl estradiol by the general population.

Editor: *What were the most common presenting symptoms, and how were these tumors treated?*

Dr. Kretzschmar: Many presented with symptoms of intraperitoneal bleeding, although masses and pain were generally the most frequent presenting symptoms in the survey. It would appear that contraceptive users had highly vascularized tumors, and this might suggest that oral contraceptives exacerbate clinical symptomatology of these tumors. But it should be noted that a high proportion of these benign liver tumors were asymptomatic and were discovered incidentally. I think clinicians should be especially aware of this diagnostic possibility when examining young women who appear otherwise healthy.

Most hepatic cell adenomas studied in this survey were treated by surgical resection, but 13 percent were untreated, and of the cases of focal nodular hyperplasia, 14 percent were untreated. There may be a spontaneous regression of these tumors once oral contraceptive use has been discontinued.

These two types of benign liver tumors have not been shown to be precursors of hepatocellular carcinoma, and there is no evidence that because of different pathogenic mechanisms, the benign tumors in patients on oral contraceptives have any proclivity for malignant degeneration. But benign hepatic lesions can suddenly and unexpectedly rupture, and hemorrhage into the abdominal cavity. Emergency resection of the tumors has not always prevented fatalities. Clinicians should be aware that oral contraceptive users are at risk in relation to these benign liver tumors, and should follow their patients accordingly.

Editor: *Do you recommend the use of DES as a morning-after pill, given its proven correlation with vaginal carcinoma in female*

children of women who received the drug early in pregnancy?

Dr. Kretzschmar: I think that for any patient who is fully aware of the controversies about it, DES is an appropriate management for the morning-after situation, as is menstrual extraction.

Editor: *What are the major contraindications to the use of oral contraceptives?*

Dr. Kretzschmar: Women with present or past thrombophlebitis or thromboembolic disorders should not take the Pill. Similarly, patients with a history of cerebrovascular and coronary artery disease should use another form of contraception. Impaired liver function, known or suspected carcinoma of the breast or estrogen-dependent cancers are other contraindications. The Pill should not be used when pregnancy is suspected, and any undiagnosed abnormal genital bleeding should be investigated and treated before an oral contraceptive is prescribed.

Editor: *In your experience, what is the most common side effect of the Pill, and how should it be treated?*

Dr. Kretzschmar: The most common side effect is breakthrough bleeding, and this should be treated with an increased dosage of estrogen. As a general principle, a patient should begin with the lowest level of estrogen that will prevent ovulation. If breakthrough bleeding persists, the estrogen dosage can be gradually increased. And I'm sure the physician can find another oral contraceptive—assuming the patient is healthy—that will not cause this side effect.

Editor: *Should the Pill be prescribed for uses other than contraception?*

Dr. Kretzschmar: This is done, and I think it's acceptable. For example, it's effective and relatively safe in the management of severe dysmenorrhea.

Oral contraceptives also provide an effective control of prolonged or excessive bleeding. When there is no pathologic basis for the menorrhagia—such as leiomyomas, polyps, and the like—combination agents are very successful in reducing the blood flow. The advantage of this is obvious.

Editor: *To sum up, for whom is it safe to prescribe the Pill?*

Dr. Kretzschmar: A safe candidate for the Pill is any healthy young woman who wishes to have temporary control of her fertility. And I emphasize the word *temporary*. Neither patients nor physicians should avoid the Pill out of fear of carcinogenicity. There is simply no convincing evidence that the Pill causes cancer.

Editor: *Thank you Dr. Kretzschmar.*

Medicine as an art demands constant evaluation, weighing new treatments against old practices, benefits against risks, successes against failures. On occasion, the evidence leads to different conclusions. Nowhere is this more evident than in the management of the cancer patient.

OPINIONS will present the views of specialists on a wide spectrum of controversial subjects. It is hoped that the frank expression of ideas will provide a framework within which our readers may form their own opinions.

Publication does not constitute endorsement by the American Cancer Society.

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WARNING: FALSE CANCER CLAIMS MAY BE HAZARDOUS TO YOUR HEALTH

In the fall of 1974, a rash of newspaper and magazine headlines claimed that contaminants discovered in the lower Mississippi Valley drinking water were associated with a grave risk of cancer. One accompanying illustration, playing upon the story's shock-value, showed the face of a man drinking a glass of water, and was captioned: "Will he get cancer?"

It is highly unlikely that the trace contaminants of drinking water would pose specific risks of cancer in the general population. Yet these unfounded claims, sensationalized in the media, have greatly alarmed the public. We can say that environmental factors cause about 80 percent of all human cancers, and this knowledge is grounded in both epidemiologic and

experimental data. The major human cancers are due to our lifestyle, among which cigarette smoking and diet, especially high-fat, low-fiber foods and mode of cooking, are key elements.

When the public is informed of newly found environmental cancer hazards, it is imperative that the information be supported by definitive documentation. Scare tactics are counter-productive. If baseless assertions continue, society will only become deafened to *bona fide* evidence of real carcinogenic hazards. Valuable research funds and time will be diverted in useless investigations, and efforts to focus on the key causes and prevention of major human cancers will be neglected for lack of resources.

The stories dealing with the "carcinogenic" contaminants in the Mississippi River were spun before any scientific evidence had even established what that drinking or river water contained. Scientists in the fields of chemical carcinogenesis and cancer etiology were left wondering as to the nature and basis of the problem. Months after the announcements had alarmed the general public, a paper appeared in *Science*, but it merely listed the chemicals found in the water of that region; its tables gave no information concerning the amounts of those chemicals. The carcinogenicity of the agents was implied, but not specifically discussed in relation to the publicly announced cancer hazard. Buried in the text was a statement that the salient contaminant was

chloroform, and that it was present at the level of three parts per million. Chloroform had been shown to induce liver tumors in mice in about 1945. While I was at the National Cancer Institute, additional tests on this and other chlorinated hydrocarbons had been started under my direction; however, detailed and carefully evaluated results of these tests were not available at the time of the publicity.

Most chemical carcinogens have one or more specific target organs. No agent is known which leads to a generalized increase in diverse tissues. Yet, the implication of the publicity about contaminants in water was that these contaminants served to increase the cancer risk at diverse sites for people using such water. This is scientifically unsound extrapolation. Aflatoxin, for example, causes cancer mainly in the liver in many experimental species and is strongly suspected of doing so in man. Aromatic amines in an occupational setting have led to cancer in the urinary bladder in man and in most experimental species in which these same chemicals were tested, although in mice they also led to tumors of the liver. The fact that this is so probably stems from the specific biochemical transformation required to convert procarcinogens to the ultimate active forms. The required enzymes are probably similarly located in organs across species lines, although admittedly, more research in this area is necessary. Nonetheless, if chloroform and other such chlorinated hydrocarbons did cause cancer in man, the preferred site would be the liver or kidney. These are among the rare cancers of man in the United States.

Not all carcinogens are alike. The mold toxin and aflatoxin B₁ causes liver cancer in rats even at one part per billion in the diet; the flavoring agent safrole requires 2000 to 5000 parts per million, a considerable difference! Yet the FDA has banned safrole, but has set a tolerance of 15 parts per billion for aflatoxin B₁. The latter is a sound practical decision, for setting a "zero tolerance" for foods with aflatoxin B₁ would require a ban on many of our foods! Thus, the FDA also tacitly underwrites the existence of "no effect" levels

even for powerful carcinogens.

The other question is whether chemicals which are carcinogenic in experimental animals at high dose levels can actually lead to cancer in man in trace amounts even when present for an entire life span. All known chemical carcinogens have a classical pharmacological dose response. The higher the dose, the higher the cancer yield and the shorter the latent period, and vice versa. To be sure, there are synergistic effects like inhalation of asbestos and smoking of cigarettes where the asbestos enhances manifold the risk due to smoking alone. Nevertheless, it is most unlikely that the trace contaminants of drinking water or river water would be associated with specific carcinogenicity in the general population. In this instance, the press reports thoroughly frightened the public. This does not mean we should not clean up our rivers and water. This is an urgent aim, meritorious for its own sake. But we should not have to use a cancer scare to reach this goal.

Misguided concern about the relationship of certain food additives to cancer is yet another case where facts were grossly misrepresented and funds needlessly spent. When a study performed abroad found that the food dye Red #2 had a "carcinogenic effect," well-meaning but ill-informed lay groups exerted pressure on the United States Food and Drug Administration (FDA) to re-examine the data in their hands. The foreign investigation claimed to have obtained evidence for carcinogenicity in a test where the treated animals developed cancer in different target sites, mostly in the endocrine-sensitive organs such as pituitary, gonads and uterus. In a lifetime study, the control animals reportedly had no cancer. This is a most unusual finding: the cancers seen in the experimentally treated group were the ones normally present in aged untreated controls. Yet these were the results which apparently caused the FDA to set up another expensive research project to re-test this dye, even though in the mid-1950's, FDA scientists of excellent standing and reputé had conducted a test series involving large numbers of mice and rats; and had concluded that this dye presented no

This review is an adaptation of a paper entitled "Social and Ethical Implications of Claims for Cancer Hazards", published in *Medical and Pediatric Oncology* 3:137-140 (1977) by Alan R. Liss, Inc., 150 Fifth Avenue, New York, New York 10011.

cancer hazard. But these were discounted in favor of clearly specious findings in an attempt to assuage the fears that unfounded publicity had aroused in the American people.

In the field of azo dye carcinogenesis, a considerable number of studies on structure-activity correlation have been performed by many scientists and, in particular, in the laboratory of the Millers at the University of Wisconsin. The general conclusion was drawn that substitution of polar groups or of solubilizing groups like hydroxy, carboxy, and especially sulfonate, uniformly decreased, and in the latter instance abolished, the carcinogenic effect. Pure Red Dye #2 has the structure of an azo dye with sulfonic acid substitution on the aryl rings on both sides of the azo bond. On the basis of what is known in the field, it seems unlikely, therefore, that this polar, water-soluble azo dye or its metabolites should be carcinogenic. This was also the conclusion of the extensive FDA studies performed in 1954-1956.

However, the FDA went to the trouble of performing one more test series. For various reasons, this series was inadequately supervised and poorly conducted. Yet, the data generated were evaluated mathematically and the conclusion was drawn that excess cancers were seen in female animals. These cancers were not at specific target sites. They were not in organs affected by known carcinogenic azo dyes for which many structures have been examined. They were, instead, in organs where neoplasms are often seen in aged animals. Given such random distribution of cancers, one is entitled to ask: Why does it affect only female rats and not males? In fact, males treated with Red #2 had a lower disease incidence than untreated males. Yet, all of this information taken together was used by administrative and legislative authorities, and boards of scientists and physicians, to rule that insufficient evidence existed to declare Red Dye #2 a safe dye. It was, therefore, banned. The public must have been relieved that government authorities had protected it

from a grave risk of cancer!

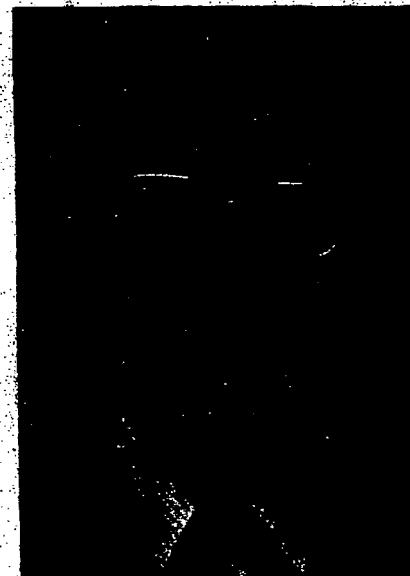
Dr. F. Ingelfinger, the editor-emeritus of the *New England Journal of Medicine*, in an editorial on the "cancerophobia" being induced in the public, indicated that too many claims for cancer hazards, which eventually are found wanting, immunize and make the public resistant to what might be valid, proper and real cancer hazards. Thus, the efforts to control cancer, which are the concern of all in the field of cancer and medical research, are rendered ineffective. The public will ignore any statements if they come too often and do not discriminate between claims based on sound evidence and those which are flimsy.

It is important that when the public is alerted, the alert have the backing of authoritative, reliable documentation. It is important that when scientists go to Federal or State agencies in order to modify the environment through regulatory and legislative action, that their evidence be strong and irrefutable. It is important that interpretation of the existing literature rest on a sound foundation and not represent frivolous imagination. It is important to construct protocols for new studies, which consume a good fraction of our limited resources for medical research, so that such studies, if successful and properly conducted, will actually contribute knowledge which can be used to reduce human cancer risk. Finally, it is important that we emphasize and deliberately foster public action on those cancer risks which are already well defined, such as those seen in occupational settings and, most urgently, those due to our lifestyle, such as the smoking of cigarettes, the consumption of diets high in fat and low in fiber, and other conditions which are epidemiologically and experimentally fully documented as real cancer hazards.

Let us not waste time and effort, and delude the public and ourselves through irrelevant busybody actions. Let us, rather, concentrate on what is important to all mankind—the effective prevention and control of cancer. ©

EDITORIAL

A Personal Tribute to Robert M. Taylor, M.D.



When Robert Mackay Taylor began his long and distinguished career in cancer research and treatment, the prognosis for patients with cancer was poor. Recently, in a special lecture, he recalled his first year of graduate medical training in the cancer ward at the Toronto General Hospital: "At that time the surgeon had no antibiotics with which to control infections... he had no blood bank on which he could call for massive support when carrying out radical procedures." In Dr. Taylor's early experience, physicians' efforts were directed primarily to alleviating pain and controlling infection and bleeding.

Since that time, there has been remarkable progress in the understanding and management of cancer. Improved survival statistics of certain cancers and the increasing sophistication of diagnostic and treatment capabilities are gratifying indeed to a man who has focussed his professional energies on the prevention and early detection of cancer, as well as on management and rehabilitation. Dr. Taylor has contributed enormously to these developments through his role in the Canadian Cancer Society and his participa-

tion in international cancer programs.

Last September Dr. Taylor retired as Executive Vice President of the Canadian Cancer Society and Executive Director of the National Cancer Institute of Canada, a dual post he had held since 1955. During

"It is misleading to hold up mortality as the only criterion for determining success or failure of the effort directed against cancer."

his tenure, these two related organizations grew stronger both financially and philosophically, and the scope of their research, education and service activities expanded considerably.

Dr. Taylor can be justifiably proud of the growth of the Canadian Cancer Society, and of its sponsored research and treatment programs. He can speak with knowledge and confidence of the quality of his Canadian colleagues' work, for he has a long and thorough familiarity with

international cancer activities. His travels have included many lectures, seminars with oncologists and site visits to laboratories throughout the world. From 1966 to 1974 Dr. Taylor served as Secretary-General of the International Union Against Cancer (UICC). Prior to that appointment he was chairman of the UICC's Cancer Control Commission.

Among his many other accomplish-

"The fight against cancer will fail unless the people accept their responsibility to participate."

ments and appointments were: five years of overseas service in the Canadian Army; a five-year directorship at the Medical Division of the Atomic Energy of Canada Limited at Chalk River (where, in 1950, he participated in the first cobalt treatment experiments); a long-term clinical teaching appointment at the University of Toronto Department of Medicine; at the same University, an appointment as Lecturer in the Department of Medical Biophysics; and a general medicine consultancy at Princess Margaret Hospital in Toronto. Dr. Taylor has also served on governmental agencies and is a member of many professional organizations.

To all the institutions and the causes he has served, Dr. Taylor has demonstrated magnificent leadership and has been an exemplar for his co-workers. He has im-

bued the field of cancer research with a deeply humanitarian perspective. In his view, "It is... misleading to hold up mortality as the only criterion for determining success or failure of the effort directed against cancer." The improvements in cancer management and the quality of survival are extremely important in his assessment of progress, reflecting a sincere concern for people.

Dr. Taylor has always been a realist about the promises of cancer research because the vicissitudes often make it a discouraging endeavor. Its history has been punctuated by false leads and subjected to various fads and fancies. Dr. Taylor understood and accepted this inevitability, all the while retaining an unwavering conviction that "... this scourge will be lifted from us... I am optimistic."

Dr. Taylor considers cancer "a people's disease" because he has always believed that a number of cancers are caused by personal habits and lifestyles. Accordingly, he has placed a fair share of the cancer burden squarely on the public's shoulders: "The fight against cancer will fail unless the people accept their responsibility to participate." This holistic approach to the problem of cancer, with the insistence upon mutual responsibility, is one of Dr. Taylor's great contributions to our understanding of, and our successful effort against, this disease.

We are grateful to Dr. Taylor for all his efforts and we can assure him that his fine example will be followed by all of us who have learned so much from him. ©

Arthur I. Hollander, D.

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