Cancer of the thyroid is a rare disease. Only 350 deaths from thyroid malignancy were recorded in England and Wales in 1957 out of a total of 95,600 deaths due to malignant disease, and 1,050 in the United States of America out of 253,000. However, considerable information about thyroid cancer is accumulated in the many hundreds of cases reported, chiefly in the United States of America, during the past 15 years. Aspects of particular interest are the comparatively high incidence in children, the remarkably protracted course in many patients and the therapeutic effects of radioactive iodine on the one hand and of thyroxine on the other. Further, views have changed radically in recent years on the aetiological significance in thyroid cancer of iodine deficiency, thyroid adenomata and previous irradiation of the thyroid gland.

Aetiology

Clinicians and pathologists have long been aware that thyroid carcinoma may be divided into two main groups: a slow growing, though metastasizing, histologically differentiated type and a rapidly growing, rapidly fatal, undifferentiated type. The assumption formerly accepted that many of the differentiated cancers arise in adenomas is giving way to the concept that these malignant tumours are low grade carcinomas from the start and that thyroid adenomas show little or no predisposition to malignant change. This concept is supported by the finding that in contrast to the rarity of thyroid carcinoma, adenomas are present in about one-fourth of all post-mortem thyroids and by the histological finding that there is a papillary element in at least 50% of differentiated thyroid carcinomas whereas benign papillary tumours are rarely seen. So great a proportion of papillary tumours have been associated with secondary deposits in cervical lymph nodes, either at the time of operation or subsequently, that in many clinics nowadays they are all regarded as malignant.

The relegation of the follicular thyroid adenoma and adenomatous goitre from a precancerous role demands reassessment of the assumption that human thyroid carcinoma may be the occasional price paid for dietary iodine deficiency. It is a fact that prolonged iodine deficiency in rats stimulates hypersecretion of pituitary thyrotrophic hormone and the subsequent production of hyperplastic goitre with eventual development of thyroid adenomas and carcinomas. But thyroid cancers arise in patients in whom there is no evidence of previous dietary iodine deficiency and are seen in countries such as Iceland where the diet is particularly rich in iodine. If prolonged iodine deficiency leads to thyroid cancer in humans, then the incidence of the disease should be higher where goitre is endemic and should fall some years after the introduction of iodized salt. The data are conflicting on these points. Wynder refers to Thalmann who found no reduction in incidence of thyroid malignancy concomitant with a decrease in goitre in the canton of Zurich in the years following the introduction of iodized salt. But Winship refers to Thalmann who found no reduction in incidence of thyroid cancer in Switzerland during the past 40 years in spite of the marked recent decrease there of endemic goitre. Saxén and Saxén found no correlation in Finland between geographical distribution of goitre and fatal thyroid cancer.

The mechanism of development of adenomatous goitre in humans and its relation to dietary iodine deficiency, stress, periods of extra demand for iodine and inherited thyroid enzyme deficiencies which condition lowered thyroxine synthesis is unresolved. However, resolution of this mechanism might not throw much light on the aetiology of thyroid carcinoma since in countries where goitre is not endemic the non-neoplastic thyroid tissue in many of the malignant glands shows no histological abnormality suggestive of past hyperactivity. Indeed, the clinically-solitary thyroid nodule proves much more often to be a thyroid cancer than a nodule in a multinodular goitre.

The discovery of Duffy and Fitzgerald in 1950
that 10 out of 28 children with thyroid cancer had been submitted to X-irradiation of the thymus in infancy stimulated a series of investigations which have established that gamma or X-irradiation to the thyroid gland in infants and children carries a risk of the development of thyroid carcinoma in childhood or adult life. Thus, 10 out of 1,502 children, traced out of a total of 1,722 who had received a few hundred rads to the thyroid in the course of therapeutic irradiation of the thymus in infancy subsequently developed thyroid cancer, whereas none developed in 1,933 non-irradiated sibs. Approximately 20% of all children with thyroid carcinoma in the United States of America give a history of therapeutic X-irradiation to the thymus in infancy. It is an interesting paradox that no thyroid cancers have been attributed to therapeutic X-irradiation or treatment with radioactive iodine for hyperthyroidism in adult life. It has been suggested that malignant change initiated in infant thyroid cells by small doses of irradiation might be promoted to tumour formation by the natural mitotic tenfold growth of the gland from infancy to puberty, whereas in the adult thyroid submitted to therapeutic irradiation, ability of the heavily irradiated cells to sur-

The prolonged treatment of rats with goitrogens results regularly in the induction of thyroid hyperplasia, adenomas and eventually of metastasizing carcinomas. The hyperplasia results from the goitrogenic-conditioned excessive secretion of thyrotrophic hormone. It must be emphasized that the degree of thyrotrophic stimulation is intense in these experiments and must be prolonged for at least two-thirds of the rats' lifetime before carcinomas develop. The only comparable thyroids seen in human pathology are those of the rare dyshormonogenetic cretins. McGirr et al. have recently reported local malignant infiltration without metastases in such a case in a girl aged nine.

**Histology**

The basic histological patterns seen in differentiated thyroid carcinoma are papillary and follicular. These may be mixed or pure, but it is thought that an increase in number of sections examined in individual tumours would reveal mixtures in many of the apparently pure examples. Papillary tumours must be distinguished from
papilliform epithelial infoldings in cystic follicles. The tumour papillae contain a fine vascular stroma, often show a serried arrangement like the branches of a Christmas tree, and may contain round subepithelial calcified psammoma bodies sometimes encrusted with haematoxyphilic iron salts\(^\text{I}\) (Fig. 1). In mixed tumours, follicles may be seen within the stroma of the papillae or lying separately elsewhere in the tumour. Sometimes the papillae are elongated and crowded together to form trabeculae of tumour cells flanking a compressed fine stroma. In follicular carcinomas the follicles may appear normal or in the form of colloid accumulations within rounded masses of epithelial cells (Fig. 2). Elongated and otherwise distorted follicles are seen. Colloid may be abundant and strongly eosinophilic or pale and peripherally vacuolated. Non-colloid-containing follicles and larger cell masses, termed solid alveolar and trabecular variants or just solid carcinoma, are frequently seen (Fig. 3). In these the cells may be round and somewhat vacuolated or columnar or spindle formed. The arrangement in varying-sized alveoli and trabeculae and in larger solid masses is confirmed by reticulin impregnation. It is important to separate solid forms of follicular carcinoma from the undifferentiated growths since the prognosis is that of the differentiated type. A further variant of the follicular pattern is that showing Hürthle (or Askanazy) cell change in which the follicular lining cells are large, polygonal and filled with fine eosinophilic granules (Fig. 4). Colloid may be absent or present in small quantities. From the point of view of prognosis, there is no need to separate the Hürthle cell, small acinar large-celled carcinoma from follicular carcinoma. The Askanazy cell change may be regarded as a metaplasia of the follicular epithelium.

An occult, sclerosing, non-encapsulated differentiated carcinoma, a few millimetres across, is an occasional chance finding at post mortem or in thyroids resected for hyperthyroidism. The histology is characteristic and shows groups of elongated follicles or papillary processes separated by fibrous trabeculae radiating from a central core of fibrous tissue containing further incarcerated follicles. These tumours are only occasionally associated with cervical lymph node metastases.\(^\text{10}\)

Whole sections of resected carcinomatous thyroids and associated draining lymph nodes have revealed the unsuspected presence of minute carcinomatous deposits in the healthy lobe and in the nodes in a large proportion of cases examined.\(^\text{3}\)
The deposits often show a varied pattern from the primary. There is a rough correlation between degree of nuclear pleomorphism and mitotic activity in the carcinoma and prognosis. Thus the differentiated carcinomas may be divided into two or three grades according to the histological degree of differentiation and evidence of activity of growth. In addition, it has been found clinically that differentiated carcinomas tend to a slow protracted course in people under forty and that many, though not all, of them show a more rapid course in patients over fifty years of age. A slowly growing metastasizing carcinoma present from the age of twenty is likely to take on a malignant behaviour fairly abruptly after forty. The pathologist’s hardest problem is the differentiation of follicular carcinoma from adenoma, especially since the latter often contains solid alveolar elements. At times the diagnosis cannot be made and is only revealed by the identification of secondary deposits of colloid containing follicular growth in lymph nodes (Fig. 5) or bone. Apart from identification of areas of papillary growth, the usually accepted criterion of malignancy is the presence of tumour within the lumen of veins of a size in which the muscle coat is recognizable. The presence of thyroid follicles within sinusoids or outside the capsule is seen occasionally in non-malignant thyroid glands as is the sequestration of follicles in a thickened capsule or intraglandular strand of hyalinized collagen. However, obvious streaming of tumour cells through the thyroid capsule is indicative of malignancy. The presence of a capsule round the tumour suggests slow growth and is not necessarily an index either of its benign nature, or, if a cancer, of its origin in an adenoma. Apart from venous or capsular invasion or infiltration of adjacent normal thyroid gland, or gross lymphatic permeation by neoplastic cells, the combined findings alone of distortion of follicles by compression, crowding of nuclei and the presence of mitotic figures point to malignancy in a well-differentiated follicular tumour. In practice the pathologist’s burden is sometimes lightened by the fact that not rarely the patient first presents with an enlarged cervical node, biopsy of which reveals a thyroid papillary or occasionally follicular carcinoma, the primary of which is not clinically evident but is found in the ipsilateral thyroid lobe when the gland is resected.

Approximately 15% of the differentiated thyroid carcinomas occur in children and young adults; the cell type is predominantly papillary. The remainder occur throughout middle and old age when both cell types are seen but the follicular predominates. The overall sex ratio is 1 male to 4 females, but in children it is nearer 1 to 1. The chief sites of metastasis are lymph-borne to the cervical and upper mediastinal lymph nodes, and blood-borne to the skeleton and lungs. The predominantly papillary cancers spread to the nodes and occasionally to lungs and bones. The follicular carcinomas also spread to nodes but show a greater tendency to metastasize to bones. Radiographic evidence of pulmonary metastases may be present for years without overt interference with lung function. Skeletal metastases are osteolytic, painful and deforming and interfere with function. Slow growing, widespread metastases may reach a total mass of some kilograms and very occasionally produce hyperthyroidism.

The functional ability of follicular thyroid carcinoma has led to the application of radioactive iodine both for the identification of the nature and distribution of metastases and for radiation therapy. After ablation or removal of the competing thyroid gland, radioactive iodine may be taken up by metastases in quantities sufficient for their recognition and destruction. Functioning growths usually show a follicular pattern with colloid formation, though not all well-differentiated follicular carcinomas are able to concentrate and bind iodine. The varied
morphology of metastases in the same patient is reflected in varying avidity for iodine. The recognition of function in thyroid carcinomas and their hormone dependency has led to treatment with thyroxine. This is given in sufficient dosage to inhibit endogenous secretion of pituitary thyrotrophic hormone and thus remove any hormonal stimulus to growth of the carcinoma. It has been observed that this treatment leads occasionally to disappearance of the tumour and of pulmonary metastases. Crile believes that the raised secretion of thyrotrophic hormone which follows removal of the thyroid gland might lead through hormonally-induced proliferation of differentiated tumour cells to development of anaplastic hormone-independent forms. There is a conflict of views between experts with regard to the choice of radical surgery, radioactive iodine or thyroxine therapy in the treatment of differentiated thyroid carcinoma.

Undifferentiated thyroid carcinoma grows with frightening rapidity, usually in elderly women with no history of previous goitre, killing within a few months, often as a result of malignant ulceration of the trachea. The histological types described are giant-celled, spindle-celled and small round-celled. The picture may be mixed. The giant cells are both single and multinucleated (Fig. 6). The spindle-celled tumours are sarcomatous in appearance (Fig. 7), but may contain more typically carcinomatous foci. The small-celled carcinoma is difficult to distinguish from malignant lymphoma and can only be differentiated by the finding of a pattern suggestive of arrangement of tumour cells in occasional epithelial-like clumps surrounded by a fibrous stroma. Mitoses are abundant in all three types of undifferentiated carcinoma. Tumours are also seen made up of undifferentiated spheroidal cells intermediate in size between the small and giant varieties.

Focal thyroiditis is found in the thyroid tissue surrounding differentiated and undifferentiated carcinomas or in the unaffected lobe in 10% of cases. This corresponds with the expected incidence of focal thyroiditis found in non-malignant thyroids in patients of the same age and sex distribution. However, in diffuse thyroiditis (Hashimoto's goitre) both carcinoma, usually papillary, and primary malignant lymphoma are said to occur more frequently than expected.

During the past decade a series of case reports has broken down the former resistance to the diagnosis of primary malignant lymphoma of the thyroid. Oddly enough, help was gained in
establishment of the disease by the finding that in groups of cases of primary round-celled 'anaplastic carcinoma' of the thyroid about one-third survived unexpectedly well after resection of the thyroid and radiotherapy to the neck. A number of the survivors turned up within a few years with deposits of malignant lymphoma in the stomach or small intestine. The finding of a slowly growing malignant lymphoma, restricted for a few years to one organ and its draining lymph nodes and not rarely cured by resection of the diseased tissue, is recognized in stomach, small intestine, bone and lungs. It is therefore acceptable in the thyroid too. The difficulty for the pathologist is that though histological examination yields the diagnosis it is not possible to foretell from the microscopical appearances whether the patient will die in a few months from spread of the lymphoma in spite of post-operative radiotherapy and thyroxine, or survive many years in perfect health on thyroxtone medication (except for the possible perforation of small intestine by infiltration of a deposit of malignant lymphoma). Nor in truth can the histologist be confident that any group of cases of malignant lymphoma is not in reality a heterogeneous collection of thyroid diseases. These may consist variously of examples of particularly vicious-looking diffuse thyroiditis, or of anaplastic round-celled carcinoma, or of malignant lymphoma including lymphosarcoma and reticulosarcoma.

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