THE EARLY STAGES OF THYROID CARCINOMA

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The relation between benign and malignant growth is not academic. If a malignant process can really arise within the capsule of a benign tumour, enucleation of the tumour should be a suitable method of prevention. But if, on the contrary, cancer occurs round a benign nodule more radical treatment is indicated.

Controversy is especially sharp in the case of the thyroid gland, as has been remarked by Brenizer and McKnight (1940). A clinician's opinion about degeneration in a goitre may be quite different from that of a pathologist. It is generally admitted in Europe by Swiss authors (de Quervain, 1940; Wegelin, 1926), as well as by German (Barthels, 1931), British (Dunhill, 1931; Joll, 1932), Russian (Kholdin, 1940), and French workers (Bérard and Dunet, 1924; Cuneo, 1938; Herbert, 1936; Velti and Huguenin, 1938), that carcinoma arises in a previous adenoma. American pathological opinion seems to be more divided. For instance, Pemberton in 1939 writes explicitly about cancer: "It arises either within an adenoma or from the portion of the gland free from adenomas. I believe that the latter origin is more common than the history would indicate." Even authors like Graham (1924) and Lahey, Hare, and Warren (1940), who admit that in general carcinoma arises in an adenoma, describe malignant growths occurring directly in apparently healthy parenchyma. Recently Cole, Slaughter, and Rossiter (1945) stated that only 37% of cancers arise in foetal adenomas.

We have collected aetiological data, experimental results, and pathological findings to prove that a true thyroid adenoma will probably never become malignant.

Before passing to a more detailed discussion we must give a better definition of an adenoma and a carcinoma. An adenoma is a true benign tumour, composed of follicles filled with colloid and a thick well-defined capsule, easily enucleated from surrounding tissues. Bielschowsky (1944) points out that such tumours are not influenced by pituitary thyrotropic hormone; they are subject to trophic disturbance—i.e., cystic degeneration, haemorrhage, and calcareous alteration. Surrounding hyperplasia may decrease or increase, but the adenoma will not alter unless vascular or trophic changes occur, and will be free from hormonal influence. According to Van Dyke and Miss Thelma Dunn (1944), there may be discovered in a gland congenital cysts with ciliated cells which are not true adenomas but will probably remain benign. Like most pathologists, we think that the so-called Wölfler's foetal adenoma is merely a form of hyperplasia—not a congenital tumour.

On the other hand, in practice we admit that there are four principal types of cancer: (a) the orthoplastic or differentiated cancers—namely, vesicular, trabecular, papillary types—and almost polymorphic ones which are papillary in some places and vesiculo-trabecular in others (so-called "Wucherndes" adenoma of Langhans), including also the Hürthle-cell tumours; (b) anaplastic

growths, small- or large-celled; (c) spindle-celled tumours, very rare; and (d) sarcomas, including haemangioendotheliomas. These appear rather frequently in Switzerland, and we recently reported two cases (Dargent, 1947; Martin, Dargent, and Guinet, 1947).

One must admit that there is no clear dividing line between the less-differentiated vesicular or even papillary forms and undifferentiated or anaplastic ones. Spindle-celled forms may possibly be metaplastic.

Aetiological Data

The well-known relation between frequency of endemic goitre and that of carcinoma has been emphasized by Barthels (1931), Limacher, and McClendon (1939). Nevertheless, Klose and Helwig point out the low rate of carcinoma in the Main valley, where multinodular goitres are frequent. Bircher, in Argau, found 25 carcinomas for 1,425 goitres; and here, where 22 to 50% of children are goitrous, four cases of carcinoma were found in the two first decades: so-called papillary adenoma and the papillary carcinoma do not occur in previously goitrous glands. De Quervain thinks that such cases in Switzerland are probably imported ones. It is particularly striking to find that, in France, statistics for Paris and its surroundings (Velti and Huguenin) show 11 papillary tumours in 88 cases, while in the Lyons region, where endemic goitre is more important, we find only four typical cases out of 32. But endemic goitre is obviously disappearing everywhere, and these arguments become less and less valuable. Considerations of sex, age, and clinical history are more important.

Sex.—We tried to find a ratio, R, between the frequency of different types of thyroid disease in males and females, using 472 cases of goitre and 116 of carcinoma from 1934 to 1940 in the surgical departments of Professor Bérard and the Centre Anticancéreux (see Table).

Sex Ratio in Various Types of Thyroid Disease

	No.	Females	Males	R (approx.)
Graves's disease	113	106	7	15
Toxic goitre	81	71	10	7
Diffuse atoxic goitre ..	99	71	28	2.5
Nodular atoxic goitre ..	179	133	46	3
Orthoplastic carcinoma ..	56	33	23	1.5
Anaplastic carcinoma ..	60	36	24	1.5

R is particularly high for Graves's disease and less for diffuse atoxic goitres, the lowest ratio, 1.5, being obtained for the two principal forms of carcinoma. Many authors (Joll, Von Eiselsberg, Eerland (in Java), and recently Cole, Slaughter, and Rossiter) have found figures of the same order. The nearest R to that of cancer is the value for diffuse atoxic goitre, in which sectioning may show micro-nodular nodes which are not true adenomas.

Age.—We have plotted several graphs of frequency of disease at different ages. Well-known facts appear: for instance, Graves's disease has two peaks—one in puberty, and one in the menopause in the female. The average age for toxic adenoma is slightly later. For diffuse atoxic and nodular goitres the graphs are less interesting on account of difficulty in ascertaining the exact time of onset of the disease. If carcinoma can arise in a pre-existing adenoma the average age for malignancy should be later; this is true for anaplastic forms occurring mainly after 60 years. However, it is important to point out that in our group of cases only 24 of 61 patients with the anaplastic form had previously had a goitre. On the contrary, it is obvious that the average age for the orthoplastic forms of cancer is the same as for goitre (Figs. 1 and 2)—Pemberton and Lovelace (1941) and Cole, Slaughter, and Rossiter (1945) agree with us on this point—and the frequency of such carcinoma in childhood and youth is even comparable with

FIG. 1.—Average age for the orthoplastic forms of carcinoma of the thyroid.

FIG. 2.—Average age for the anaplastic forms of carcinoma of the thyroid.

forms, especially papillary and vesicular, we agree with Velti and Huguenin that if a goitre appears in less than eight years from the first complaint one must think the tumour malignant from the first. Having carefully gone through the observations of Lahey on cancer in adenomas, we wonder if goitres developing in two, three, or four years, or as little as 10 months, were not always carcinomas. In our view one cannot be sure of the degeneration of an adenoma unless it has existed for 8 or 10 years, and on this criterion we find that only 50% of carcinomas arise in a previous goitre, as already ascertained by Bérard and Dunet, Velti and Huguenin, and Müller.

Experimental Facts

The early work of Gaylord, Marine, and Lenhardt in 1910-11 showed a diffuse benign hyperplasia of structures throughout the gland submitted to stimulation, liable to regress if the stimulus stopped. But if the stimulation had been long continued a true papillary adenoma might remain afterwards. These findings are most important, as Dunhill remarks, though they do not concern carcinoma. Bielschowsky's experiments in 1944-5, however, give very important data on the occurrence of thyroid carcinoma. Briefly, he states that malignant growths may occur in a parenchyma treated with allylthiourea and simultaneously with a known carcinogenetic agent—namely, *o*-aminofluorene. The adenocarcinomatous nodules escaping through their capsules do not arise in previous simple adenomas, which appear only in animals fed for a long time with allylthiourea alone. Similar facts have been described by Griesbach, Kennedy, and Purves (1945).

If, at first, thiourea or *Brassica* seeds bring on a simple hyperplasia, this hyperplasia gives way later to a well-defined adenoma. Simultaneous addition of a carcinogen such as *o*-aminofluorene may convert this hyperplasia to a malignant growth instead of a benign one. We cannot say whether the association of a thio- group with the carcinogen is really necessary.

the frequency of benign growth. (These findings are very similar to those of Taylor and Wilkinson (1935), Pember-ton, and Black.) If we admit that in the first two decades of life two types of thyroid hyperplasia may be met—namely, the atoxic and the toxic—we should add a third type which might be called "malignant hyperplasia," and, according to our figures, the chances of each up to the age of 20 years would be: atoxic parenchymatous hyperplasia, 8.6%; toxic hyperplasia and toxic goitre, 6.1%; so-called malignant hyperplasia, 4.3%.

Clinical History.

—Having witnessed the slow evolution of most of the orthoplastic

Morris, Dubnik, and Dalton (1946), as well as Gorbman (1946), have found metastases of normal thyroid tissue after a long treatment with thiourea and thiouracil. In spite of the benign pattern of these formations, here is thyroid hyperplasia with blood-stream invasion. Is it really malignant? This is the general problem of the so-called benign metastatic adenoma.

Our opinion is that such growths are already malignant, and are not adenomas. They are malignant nodules as different from true adenomas as are colloid lobulated nodules. This has been well emphasized by Warren (1947). Clinical facts such as the case report by Payne, Crane, and Price (1947) of a malignant process arising in a patient with Graves's disease during treatment with thiouracil are as valuable as experimental results.

In brief, we think that somehow a previously healthy thyroid parenchyma, with or without an old benign adenoma which is the sign of a previous wave of benign hyperplasia, undergoes a special type of hyperplasia when treated with thiourea and carcinogen, or perhaps even with a thio- compound alone. We suggest it should be called malignant hyperplasia. The simplest form is perhaps the so-called benign metastatic adenoma which Bérard and Dunet named appropriately "adenomorphous carcinoma."

Adenocarcinomatous papillary, follicular, and even trabecular nodules seeming to arise in a foetal adenoma are a lobulating form of this hyperplasia. The most severe form is the anaplastic. In all these cases the rupture through the capsule—well shown in Goetsch's (1940) photomicrographs—and invasion of blood or lymphatic vessels are the first two signs of the malignant nature of the growths (Graham, 1924).

Pathological Studies

In several cases we found entirely independent adenomatous and carcinomatous lesions. Autoradiographic plates, obtained after administration of I^{131} in unpublished recent cases, show the accuracy of such a distinction.

A. The Boundary Between Adenoma and Cancer

Case 1.—A man aged 32, suffering from goitre since the age of 30. Pain in the neck, hardening and increasing volume of goitre, voice becoming hoarse; wasting and fever appeared three months before. Physical examination showed a hard mass in the right pole of the thyroid. Straightforward thyroidectomy under local analgesia. It was obvious, however, that a part of the growth passed down into the mediastinum along the internal jugular vein. Post-operative x-ray treatment, 6,000 r. Death occurred six months later from acute dyspnoea caused by mediastinal metastasis. Pathological examination showed a well-encapsulated, lighter-tinted, softer nodule the size of an apricot, lying in the centre of a diffuse carcinoma, from which it was separable with the finger. Microscopically, there was centrally a small- to medium-sized follicular adenoma with endotheliform epithelium, some follicles being empty, some

FIG. 3.—The borderline between an anaplastic cancer and an adenoma. The malignant growth has invaded the capsule from outside.

filled with more or less eosinophilic colloid. A definite boundary could be made out between these adenomatous follicles and the atypical carcinoma surrounding it and distorting the capsule at some points without involving it. The connective tissue all round the adenoma was scarlike, invaded by isolated or grouped neoplastic cells (Fig. 3).

Case 2.—A woman aged 78 had had a small "adenoma" for a very long time, with a severe illness recalling thyroiditis in the last month. Examination showed the same pattern as in Case 1. The adenoma was calcareous in the centre and rubber-like more peripherally; atypical carcinoma had developed all around it (Fig. 4).

FIG. 4.

Case 3.—A woman aged 57 with no history of goitre. Interference by a thyroid tumour, with dyspnoea and increasing hoarseness of the voice, in the last two months. Physical examination showed great respiratory distress, and a large hard adherent left thyroid swelling with an extensive superficial venous network. Radiography revealed a cervico-mediastinal tumour with calcareous spots. At operation under local analgesia the subthyroid muscles were cut and a biopsy taken of the scirrhous growth. The right lobe was healthy. In spite of immediate x-ray therapy and tracheotomy the patient died after 10 days. At necropsy a large mass was found around the trachea like a ring, lying mostly in front of the trachea and behind the sternal manubrium; an old small calcified goitre was separable from the growth. Histologically the adenoma was medium-sized, with large follicles, and covered by an intact capsule. The cancer was trabecular at some points, anaplastic at others.

Case 4.—A woman aged 63 with no history of goitre. Pain in the right capsule for four months, and loss of weight for four years. A thyroid swelling appeared four months previously, medial, hard, and deep in the neck. Radiography showed a subcoracoid metastasis in the right scapular region. A total enlarged thyroidectomy was performed. X-ray treatment was impossible because of severe anaemia, and the patient died three months later. Pathological examination showed a hard white tumour containing three little pink encapsulated nodules the size of a cherry. Microscopically it was mostly anaplastic epithelium simulating sarcoma, in some places involving a goitre with very small and medium-sized follicles the fibrous walls of which had collapsed with the rush of neoplastic elements.

These four cases show clearly that carcinoma may arise around the capsule of an adenoma, which can be considered as a scar, and that even if the boundary is broken cancer grows from the outside but does not seem to arise in the adenoma.

B. Diffuse Goitre and Cancer

Case 5.—A woman aged 74 with a goitre for the past 22 years, painful and suddenly increasing in size in the last few weeks. A hard mass could be felt in the left lobe and be moved in the tissue planes. Total thyroidectomy was performed on the left, and subtotal on the right, which was healthy. Pathological examination showed two parts—the first an irregular-walled haematocoele, the second a white and rather hard mass. Microscopically, adenomatous tissue with large and small follicles, with a flat epithelium and dense colloid, was seen in some parts and in others a trabecular epithelioma with considerable follicular differentiation and cylindro-cubic, rather regular eosinophilic cells. Capillaries were full of neoplastic nodules. Contiguity of these two areas was obvious and the border-line sinuous. The large follicle of a parenchymatous goitre lying in adenomatous and haemorrhagic tissue was quite different from any neoplastic structure, and at some points

a malignant "feeler" pushed forward this border-line without invading it (Fig. 5). Degeneration of goitre into carcinoma was not seen anywhere.

FIG. 5.—The borderline between a diffuse colloid goitre and a trabeculo-follicular carcinoma.

C. Cancer Developing in Benign Tissue

Case 6.—This patient was operated on elsewhere and the specimen sent to our department. At one point trabeculo-follicular malignant structures were found surrounded by adenomatous tissue with inactive follicles. When looking closely at the so-called capsule of the malignant nodule we could clearly see a vascular lumen filled with a neoplastic thrombus and masses of erythrocytes. A well-defined endothelium was spread out all round the growth. Thus what seemed to be a carcinoma arising in the centre of an adenoma was in fact an embolus in the lumen of a vessel in the adenoma (Fig. 6).

FIG. 6.—A malignant embolus in the vessel of an adenoma.

D. Adenoma as a New Growth in the Evolution of Cancer

Two cases lead us to suppose that an adenoma can form during or after the development of a cancer.

Case 7.—A man aged 39, with a very old goitre; he had had several crises of dyspnoea without any particular increase in its size. He had had paraplegia for two months. Examination showed a hard mobile tumour of the right lobe with a metastasis in the fourth thoracic vertebra. A right lobectomy with block dissection of the neck was performed and 4,500 r x-ray therapy given to the spine. One year afterwards a new growth appeared in the medial part of the neck, of the size of a small cherry, and a soft separable nodule connected with the left lobe was excised. Microscopical examination of a specimen from the first operation showed a polymorphic malignant lesion with follicles and trabeculae at some points, and here and there an anaplastic structure with isolated cells (Fig. 7). Sections of the so-called relapsed tumour (second operation) showed the small and medium-sized follicles of an adenoma in all parts, with

no sign of malignancy (Fig. 8). Death occurred five years later from the paraplegia, which had improved during the first two years. There was no recurrence in the thyroid area.

Case 8.—A woman aged 45, with a goitre for seven years previously; improved during the first four years with iodine, but got worse in the last two years, with a progressive increase in volume. Right extracapsular lobectomy and left subtotal thyroidectomy were performed. Four months later a small growth appeared on the right of the scar. A small, soft, separable growth was excised for biopsy and x-ray therapy was given. The first operative specimen showed trabeculae and follicles with an adenomatous stroma, and the second included two well-defined parts. The first part was a predominantly microfollicular epithelioma separated by a well-formed capsule from the second part, an adenoma with large follicles and flat epithelium and a big histiocytic reaction in the stroma.

These two cases show clearly that a benign process can appear concurrently with a malignant recurrence, or can occur by itself in the remaining healthy parenchyma after removal of the cancer. We have shown elsewhere that a benign thyroid growth may appear while another carcinoma arises in different parts of the body. In our view, and that

FIG. 8.—Histological structure of a so-called recurrence in the isthmus. (On several sections this pattern of benign adenoma was found repeated.) (Case 7.)

of several workers, a thyroid hyperplasia may arise as a safeguard against malignancy. Perhaps the thyroid may show such a reaction to its own carcinoma. Both are quite independent anatomically. The high frequency of severe anaplastic forms after the age of 60—that is, when thyroid secretion has stopped—is another argument in favour of this hypothesis.

Discussion

It appears that a patient with a well-defined adenoma may go on to have a cancer. Two types of lesion may be noted: (1) the well-encapsulated adenoma which may be benign indefinitely alongside the cancer, as shown in some case reports above. (2) The improperly called "malignant adenoma," which is a carcinoma from the first. Careful examination of such nodules, even when macroscopically they appear to be separable, always shows a gap in the capsule at one point and an invasion of capillaries by a mass of thyroid tissue.

These facts, well emphasized by Graham, gave us reason to consider as malignant a thyroid adenoma of our group associated with a sacro-lumbar metastasis. While some sections showed an apparently benign tumour in some areas, a neoplastic embolus in the blood vessels emphasized malignancy in others (Fig. 9).

The term "adenomorphous carcinoma" seems suitable in general, and, in accord with recent work using radio-iodine, we also call it a malignant lobulating hyperplasia.

This discussion is not academic. Even if it is not always in conformity with the exact and true description of the early stages of cancer and benign goitre, reported data are numerous enough to lead to the following practical conclusions:

1. Use of anti-thyroid drugs such as thiouracil in a patient suffering from an apparently benign adenoma or toxic goitre may be dangerous, as it may turn a hyperplastic parenchyma to malignancy.
2. Enucleation of a so-called adenoma, even if apparently well isolated, does not prevent the appearance of carcinoma, because the malignant process can develop in the surrounding tissue, or because, the adenoma being already cancerous, the operation was obviously an unsatisfactory treatment.

Summary

The view that thyroid carcinoma may arise in a pre-existing adenoma is challenged.

Evidence from the relative incidence of adenoma and cancer in the two sexes and at different ages is against it. It is suggested that any adenoma which seems to turn malignant in less than ten years from its initial appearance was in reality malignant from the first.

Histological sections are presented to show that adenoma and carcinoma may coexist, and that adenoma may follow cancer, which can also develop in a diffuse goitre or from normal tissue.

The significance of these observations for practical therapy is discussed.

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FIG. 9.—Malignant growth in a vessel of a so-called benign adenoma with bone metastases.