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THYROID NEOPLASMS FOLLOWING IRRADIATION*

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Animal experiments and clinical observations have demonstrated that carcinoma of the thyroid may follow irradiation of the gland. In rats, thyroid carcinomas with metastases have been produced by the administration of ^{131}I (Goldberg and Chaikoff, 1952). If the radioactive iodine or x -irradiation is given with a goitrogen, the tumours are more readily produced and a smaller dose of irradiation is effective (Doniach, 1958).

Exposure of the human thyroid gland to ionizing radiation has become increasingly frequent. The isotopes ^{131}I and ^{132}I are widely used in the diagnosis of thyroid disorders, and the former is also employed extensively in the treatment of thyrotoxicosis. In the past, before radioiodine was available, this condition was sometimes treated by x -irradiation. Treatment of cutaneous lesions in the neck with radium or x rays may lead to some incidental irradiation of the thyroid gland. In some centres it was the practice to irradiate enlarged thymus glands in infancy, and this procedure also inevitably involved the thyroid gland.

There are several reports of carcinoma of the thyroid in man developing after irradiation. It has only rarely been reported after the treatment of thyrotoxicosis by x -irradiation (Quimby and Werner, 1949). The findings in children have been of greater significance, and there is now a well-recognized association between irradiation of the cervical and upper thoracic region in infancy and the subsequent appearance of a carcinoma of the thyroid (Duffy and Fitzgerald, 1950; Clark, 1955; Fetterman, 1956; Simpson and Hempelmann, 1957).

In view of the increasing use of radioactive materials, information regarding the development of carcinoma of the thyroid gland following irradiation, either deliberate or accidental, is clearly important. In a previous report three patients who developed carcinomas in these circumstances were briefly described (Kilpatrick, Blomfield, Neal, and Wilson, 1957). Six further patients have now come under observation; in four the diagnosis of carcinoma was clearly established, and in two there was an adenomatous condition of the thyroid presenting some neoplastic features, though a firm diagnosis of carcinoma was not possible. These cases are now reported in detail.

Thyroid Carcinomas Following Irradiation

A definite carcinoma of the thyroid has been observed in seven patients following irradiation. Cases 1, 5, and 6 were mentioned briefly in the previous report (Kilpatrick *et al.*, 1957). The doses in these patients have been re-examined. In particular, in Case 5 further information regarding the relative position of the thyroid and radium has resulted in a recalculation which shows a higher dose to the gland than originally reported. The details regarding irradiation dose, latent period, and nature of the neoplasm are summarized in the Table (see next page).

In six patients the irradiation was given in infancy or childhood for the treatment of cutaneous lesions in the neck region, and the details of the original treatment are available. Except in Case 6, the site of irradiation is known from the position of the scar of the original lesion. A calculation of the amount of irradiation received by the thyroid gland has been attempted, and the assumptions on which this has been based are described in the case reports. In three patients (Cases 1, 2, and 6) this did not exceed 300 r.

The interval between the irradiation and the observation of a swelling in the thyroid probably affords the best indication of the latent period, as there was usually a considerable delay before the diagnosis was finally established by surgical exploration and histological examination. In the patients receiving irradiation in the first year of life and subsequently developing a carcinoma the latent period in three (Cases 1, 2, and 4) was under 10 years, but in Case 3 the swelling was apparently not observed until she was 18 years old. In Cases 5 and 6 the irradiation was given in adolescence, and the latent periods were 8 and 17 years. In all these patients irradiated in childhood the carcinoma was predominantly papillary in type, though some follicular arrangement was apparent in Case 4. In four (Cases 1, 2, 4, and 5) the skin lesion was localized on one side of the neck, and in them the thyroid swelling first appeared and the spread of malignant tissue was most extensive in the lobe of the gland immediately adjacent to the irradiated area. In one patient (Case 3) the cutaneous lesion was in the midline and the carcinomatous nodule was situated behind the scar. Case 6 had extensive irradiation of the front of the neck and there was involvement of both sides.

*Based on the opening paper delivered by G.M.W. to the Section of Pathology at the Annual Meeting of the B.M.A., in Birmingham, July, 1958.

Details of Cases

Case	Sex	Age at Time of Irradiation	Diagnosis and Site of Irradiation	Method of Irradiation	Estimated Maximum Dose to Thyroid	Age at Surgical Biopsy of Thyroid	Interval Between Irradiation and First Sign of Goitre	Type of Neoplasm
1	F	2 months	Naevus on right mandible	Radium	130 r	10 years	9 years	Papillary carcinoma
2	F	3 "	Naevus on right side of neck	X-ray	100 r	12 "	8 "	" "
3	F	2 years	"	"	160 r	"	"	"
4	F	5 months	Naevus on front of neck	Radium	2,700 r	19 "	18 "	" "
5	F	3 "	Naevus on left side of neck	"	1,400 r	22 "	25 "	Papillary and follicular carcinoma
6	F	6 "	"	"	1,300 r	"	"	"
7	M	12 years	Keloid on right side of neck	"	1,000 r	25 "	8 "	Papillary carcinoma
8	M	13 "	"	"	1,700 r	"	"	"
9	F	14 "	Eczema of neck	X-ray	150 r	31 "	17 "	" "
10	F	16 "	"	"	150 r	"	"	"
11	F	26 "	Thyrotoxicosis	"	? > 2,000 r	63 "	37 "	Anaplastic carcinoma
12	F	3 months	Naevus on left side of neck	Radium	? > 1,000 r	27 "	17 "	Papillary adenoma
13	F	21 years	Thyrotoxicosis	X-ray	? > 2,000 r	43 "	22 "	Adenoma

The seventh patient with a carcinoma differed greatly from the others. She was irradiated in adult life for the treatment of thyrotoxicosis, and 37 years later developed an anaplastic carcinoma in contrast to the predominantly papillary type seen in the younger patients.

The available details regarding the irradiation of the initial lesion, and the operative findings and histological features leading to the diagnosis of carcinoma, are described in the following case reports. Treatment has been surgical resection whenever possible, followed in some cases by radiotherapy. In some of the younger patients thyroxine has been given post-operatively to act as a pituitary suppressant, as there is evidence that reduction of thyrotrophin may check the growth of some thyroid carcinomas (Crile, 1956; Thomas, 1957).

Case 1

Female born on March 10, 1938. Treatment with radium was given to a capillary naevus overlying the right mandible, beginning on May 4, 1938, and extending over a period of a year. On each of five occasions irradiation was given with five 5-mg. needles; total radium, 25 mg. for 30 minutes. The needles were applied close to the skin, but the size of the treated area is not precisely known. It is assumed that the area was 4 sq. cm. and the distance of the needles from the skin 0.5 cm. It is thought that the nearest part of the thyroid lay between 1.5 cm. and 3 cm. from the treated area. Assuming average size and development during the first year of life, the naevus received approximately 400 r and the thyroid between 50 and 130 r.

Nine years later, in January, 1947, a swelling in the neck was noted by her mother. On August 24, 1948, a surgical exploration was carried out. The left lobe of the thyroid appeared normal. The right lobe was hard and irregular, and contained a fairly well circumscribed nodule about 1 cm. in diameter. There was some enlargement of the cervical lymph nodes on the right side, and several were removed. Histologically there was a papillary carcinoma of the thyroid with metastases in the lymph nodes.

Deep x-ray therapy up to 3,100 r was given to the neck between September 13 and October 15. Several enlarged lymph nodes were present after treatment, but they remained constant in size until 1952, when they began to enlarge. Block dissection of the left side of the neck was carried out on April 8, 1953, and of the right side on June 23. Enlarged lymph nodes on both sides contained papillary carcinomatous metastases.

When she was last seen on July 25, 1957, she was well, with no signs of recurrence.

Case 2

Female born on May 29, 1944. A small naevus was present on the lower part of the right side of the neck (Fig. 1), and this was treated on two occasions by x-irradiation.

On August 22 the naevus was treated with 400 r, 4 cm. focus skin distance, 45 kV, 1 mm. Al filter, 2.5 cm. diameter. Treatment was repeated on August 21, 1946, when the naevus received 400 r, 15 cm. focus skin distance, 100 kV, 1 mm. Al filter, 3 cm. diameter. Assuming that the nearest part of the thyroid was 2 cm. distant from the point of application of the beam, it is possible that a small fraction of the right lobe received a dose of as much as 260 r, made up of 100 r from the first treatment and 160 r from the second. Some of the rest of the thyroid, including the posterior part of the left lobe, may have received a dose of up to 200 r, made up of 80 r from the first treatment and 120 r from the second, but the majority of the gland probably received a dose of less than 100 r.

In 1952 a swelling in the region of the thyroid was noted by her mother, and this slowly increased in size, particularly on the right side. Some tracheal compression was evident on x-ray examination. At operation in November, 1956, the sternothyroid was adherent and bound to a nodular fixed thyroid. The nodules were vascular and hard, and spread extensively into the surrounding structures, especially on the right side. Two biopsies of the gland were carried out, but extensive excision was not possible. The microscopical appearance of both nodules was that of a carcinoma, predominantly of papillary type but showing also some more solid areas of compact acini of thyroid epithelium enclosing no colloid. The larger nodule (right lobe) was almost wholly papillary in structure and had very little capsule of fibrous or normal thyroid tissue. The smaller nodule (left lobe) was enclosed by a fibrous capsule, but there was a definite invasion of the capsule by epithelial growth and

FIG. 1.—Case 2. Showing scar of the small naevus on neck, and the thyroid swelling.

possibly invasion of venules. Mitotic figures, though present, were not very frequently seen.

After operation she was given laevothyroxine sodium, 0.1 mg. twice daily, and this was subsequently increased to thrice daily without the development of any signs of hyperthyroidism. The thyroid swelling decreased considerably in size and has become much softer. A repeat x-ray examination has shown disappearance of the tracheal narrowing. She was last seen on May 21, 1958, when she was in excellent general health and there was no evidence of any extension of the tumour.

Case 3

Female born on October 20, 1938. A large naevus on the front of the neck, measuring approximately 5.5 cm. in diameter, was treated with radium. On March 18, 1939, 10 1-mg. needles were inserted for 72 hours. The radium plane consisted of an ellipse 5 by 4 cm., seven needles being placed in an outer ring and three in an inner ring. The radium probably covered most of the neck between the jaw and the upper border of the clavicles. Assuming some of the thyroid tissue was in a plane 0.5 cm. below the radium plane and the area was 15 sq. cm., the dose in 72 hours on a basis of 302 mg. hr./1,000 r was approximately 2,300 r. At 1 cm. deep to the radium plane on a basis of 546 mg. hr./1,000 r, the dose was approximately 1,300 r. The irradiation scar in the patient was over and below the thyroid swelling. The dose at the upper limit of the ring of radium needles and 1 cm. deep to the skin may have been 20% greater than quoted above. It may be assumed that the dose on the anterior part of the gland was between 1,300 and 2,700 r.

A swelling was noted in the thyroid in 1956. At operation on May 12, 1957, a round nodular swelling about 3 cm. in diameter was excised from the isthmus and right lobe of the thyroid. Section revealed a pale, fleshy tumour with a few areas of recent haemorrhage. On histological examination there was a fairly well circumscribed papillary adenocarcinoma of the thyroid (Fig. 2). The epithelial cells were mainly cuboidal, but a certain amount of pleomorphism was evident. They formed a single layer around the vesicles and fronds, but in places they were heaped and occasional mitoses were seen. Colloid was restricted to the

FIG. 2.—Case 3. This shows a well-differentiated carcinoma, mainly of the papillary type. (H. and E. $\times 116$.)

marginal areas of the tumour. There had been some haemorrhage. The capsule consisted of fibrous tissue and compressed normal gland.

Following operation she was treated with laevothyroxine sodium and has remained in excellent health, and when last seen on April 23, 1958, there was no sign of any recurrence.

Case 4

Female born on June 1, 1935. A large naevus was present on the left side of the neck, measuring approximately 7 by 3 cm. (Fig. 3). Two treatments with radium were given.

On August 27, 1935, radium needles were inserted—six 2-mg. and two 1-mg.; total radium, 14 mg. for 36.5 hours. The area of implant was 20 sq. cm. The following estimates and assumptions have been made. (1) The distance from the affected skin to the main mass of the left

FIG. 3.—Case 4. Showing the considerable scarring following irradiation of the naevus and the underlying thyroid enlargement.

lobe of thyroid was 8 mm. and to the extreme edge of the right lobe 22 mm. (2) The needles lay within 5 mm. of the left lobe and were 8 mm. distant from the main mass of the lobe. On this basis the estimated dose to the nearest point of the left thyroid lobe was 1,400 r, to the main mass of the lobe 1,000 r, and to the extreme edge of the gland 400 r.

On December 19, 1936, radium needles were again inserted—eight 2-mg. and three 1-mg.; total radium, 19 mg. for 42.5 hours. The area of implant was 32 sq. cm. It is estimated that on this occasion the nearest part of the left thyroid lobe was 8 mm., the main mass 10 mm., and the extreme edge of the right lobe 40 mm. from the needles. The estimated dose to the nearest point of the left thyroid lobe was 1,300 r, to the mass of the lobe 970 r, and to the extreme edge of the right lobe 230 r.

The total doses from the two exposures to irradiation therefore probably lay in the following range—left lobe 2,000–2,700 r, and right lobe 600–700 r.

A swelling in the left lobe of her thyroid gland was noted in early childhood, probably during the period 1941–3, though no precise date can be given. There was a slow increase in the size of the swelling, particularly during 1957. At operation on September 25, 1957, a hard nodular irregular swelling was present in the left lobe of the thyroid gland and was closely adherent to the strap muscles on the left side of the neck. Metastases were present in the lymph nodes in the left supraclavicular fossa. The tissue was friable and covered with numerous thin-walled vessels. As much as possible was removed, but dissection beneath the strap muscles was extremely difficult, and was abandoned. The right lobe appeared essentially normal.

Histologically there was a mixture of follicular and papillary highly cellular thyroid tissue. A small proportion of the acini contained densely staining colloid, but the cell pattern was highly irregular and many mitotic figures were present. The appearances were those of a fairly well differentiated adenocarcinoma, and the neoplasm merged with a thin peripheral rim of normal thyroid tissue.

Immediately after operation she was given triiodothyronine, 0.02 mg. four times a day, and a week later this was changed to laevothyroxine sodium, 0.1 mg. twice daily and later thrice daily. When last seen, on May 21, 1958, she was in good general health and there was no evidence of further extension of the growth.

Case 5

Male born on June 5, 1923. He was burnt on the right side of the neck when 3 years old and the resultant keloid scar was excised in 1932 and again in 1935. This second excision was followed by radium therapy. Two applications were made externally in sorbo-rubber tubes. On August 1, 1935, 41.5 mg. was applied for 15 hours, and on March 17, 1936, 79 mg. for 13 hours. Assuming the near lobe of the thyroid lay 1 cm. beneath the skin at the point of application of the radium, the right lobe received approximately 1,000 r on the first occasion and 1,700 r on the second. The left lobe received 150 r and 250 r respectively.

A swelling was noted on the right side of the neck in 1944, but this was left undisturbed for four years. On September 21, 1948, a lymph node deep to the right sternomastoid was excised; histology showed a papillary carcinomatous metastasis from the thyroid. On October 6, 1948, a right hemithyroidectomy was carried out together with removal of three more slightly enlarged lymph nodes on the right side of the neck. A nodule about 2 cm. in diameter was embedded in the right lobe of the thyroid gland, and histologically this was a papillary carcinoma. In November, 1948, a course of deep x-ray therapy was given to the neck. In 1957 he was well, with no signs of recurrence.

Case 6

Female born on April 26, 1922. On April 8, 1936, she was treated by x rays for eczema of the neck, and this was repeated on June 9, 1938. On each occasion the total dose was 300 r by unfiltered x rays of 75 kV. It is estimated that the anterior surface of the thyroid received approximately 150 r on each occasion and that the dose to the thyroid tissue 2 cm. from its anterior surface was 60 r.

In 1950 she noticed a swelling in the region of the thyroid gland and was given methylthiouracil for about five months. In November, 1952, this swelling increased in size; she developed some prominence of the eyes and had symptoms suggestive of hyperthyroidism. The swelling on both sides of the neck continued to enlarge. On April 7, 1953, a biopsy of a lymph node from the right side of the neck revealed a papillary carcinoma. At operation on July 1, 1953, the thyroid gland felt extremely hard throughout. The left lobe was removed apart from a thin slice posteriorly. The right lobe was very irregular and was attached to the trachea. The whole right lobe was removed together with a chain of enlarged lymph nodes. Histologically the right lobe contained a papillary carcinoma and the lymph nodes were replaced by this tumour. The left lobe was partially replaced by a papillary carcinoma.

In July, 1954, a swelling of a left supraclavicular gland was discovered, and this continued to enlarge. In November, 1954, 6,000 r was given by cobalt beam to the left supraclavicular region. The gland subsided but later began to enlarge again. On February 18, 1955, several enlarged lymph nodes were excised from the left side of the neck; histologically all contained papillary carcinoma.

When last seen in 1957 she was well, with no signs of any further recurrence.

Case 7

Female born on April 4, 1893. During the period 1918-22 repeated x-ray therapy was given to the thyroid for the treatment of thyrotoxicosis. No details of dosage are available, but gross atrophy, scarring, and telangiectasia of skin of neck was produced, particularly over the thyroid isthmus. From what is known of current practice at that time and from the conspicuous cutaneous reaction it is probable that the thyroid gland received more than 2,000 r.

Thereafter she remained well but with some residual enlargement of the gland until 1955, when she noticed an increase in the swelling on the right side. On examination there was a hard nodular enlargement of the isthmus and right lobe. At operation on April 15, 1956, the right lobe of the thyroid was enlarged and adherent to surrounding structures. The left lobe appeared normal. The whole

thyroid was removed with the exception of some tissue firmly adherent to the carotid sheath. Histologically there was an undifferentiated anaplastic carcinoma with striking pleomorphism of cells and very numerous mitoses. In May, 1956, there was a recurrence of the swelling on the right side and front of neck, and she was given x-ray therapy. She died on November 24, 1956, after continued enlargement of the recurrence in the neck.

Thyroid Adenomas Following Irradiation

In two patients (Cases 8 and 9, in Table I) an adenomatous enlargement of the thyroid was discovered many years after exposure to irradiation. Though an actively hyperplastic condition was present in the glands, there was insufficient evidence to justify a diagnosis of carcinoma. Mitoses were seen in the epithelial cells, but there was no spread outside the capsule of the thyroid or invasion of veins. In Case 8 irradiation of a naevus overlying the left sternomastoid tendon was carried out in early infancy, and subsequently enlargement of the isthmus and right lobe of the thyroid developed. In Case 9 thyrotoxicosis was treated by x-irradiation in early adult life and a hard nodular goitre developed 22 years later. The details of these cases are as follows.

Case 8

Female born on August 4, 1930. When aged 3 months she had treatment with radium needles for a naevus overlying the tendinous head of the left sternomastoid muscle. The needles were left in for 36 hours, but other details of the treatment are not available. There is a conspicuous

FIG. 4.—Case 8. This part of one adenoma consists of small irregular follicles, lined by cells with large vesicular nuclei and prominent nucleoli. There are occasional mitotic figures. (H. and E. $\times 200$.)

FIG. 5.—Case 8. This is another part of the adenoma seen in Fig. 4. A papillary structure is present. The follicles are distorted and the epithelial cells are moderately pleomorphic. (H. and E. $\times 185$.)

irradiation scar, and comparison with the other similar cases suggests that the thyroid received at least 1,000 r. When aged about 17 years a goitre was noted by her doctor. This slowly increased in size. In December, 1957, a large irregular swelling was present in the isthmus and right lobe of her thyroid gland. At operation on December 19, 1957, the strap muscles and fascia of the neck stripped clearly, revealing the right lobe to be three or four times normal size, soft but not cystic in consistency, and with a normal vascular supply. This enlargement included the isthmus and ended abruptly at the junction with the left lobe. The right lobe and isthmus were excised.

On section of the excised tissue two fleshy nodules were seen, the larger 3 cm. and the smaller 2 cm. in diameter. On histological examination two adenomatous areas were seen compressing the surrounding thyroid tissue and possessing rudimentary and incomplete fibrous capsules. Their structure was that of actively hyperplastic thyroid tissue: the epithelium was cuboidal and surrounded colloid-filled vesicles of the normal range of size. Infolds of epithelium were occasionally seen. A microfollicular structure predominated in parts (Fig. 4). Mitoses in the epithelial cells were fairly frequent. A papillary pattern of growth was seen in some parts of both adenomas (Fig. 5), but the papillary processes usually enclosed colloid vesicles and were invested with a single layer of regular and uniform cells. The thyroid tissue outside the adenomas was more normal, but here, too, mitotic figures were usually frequent in the epithelial cells. A marginal area in one of the sections showed intermingling of thyroid acini, fibrous tissue, and striped muscle, but this probably did not indicate neoplastic invasion. The general features and the absence of anaplasia, vascular invasion, and infiltration of the surrounding tissues preclude a definite histological diagnosis of carcinoma, but the process does seem to be an adenomatous neoplastic condition rather than a simple goitre.

Since operation she has been given laevothyroxine sodium 0.1 mg. thrice daily. When last seen on May 5, 1958, she was well, with no sign of any recurrence of thyroid enlargement.

Case 9

Female born in 1914. She developed a thyroid swelling when she was about 15 years old. When 21 years of age she became unduly nervous, lost weight, and had a rapid pulse rate. A diagnosis of thyrotoxicosis was made, and in 1935 she received about four treatments with x rays to the neck. Unfortunately it has not been possible to trace the records of this treatment, and the dose is not known. From what is known of practice at the time it probably exceeded 2,000 r.

In 1955 a lump was noted in the right side of the neck which gradually increased in size. In October, 1957, there

was a hard enlargement of the right lobe of the thyroid, narrowing the trachea and displacing it to the left. There was no clinical evidence of hyperthyroidism, and a ^{131}I tracer test showed normal thyroid function.

At operation on October 23, 1957, the strap muscles and fascial layers stripped easily off the underlying thyroid. The left lobe was approximately of normal size and texture; the right lobe was enlarged four or five times, with a particularly exaggerated upper pole. It was elastic to palpation, with average-sized vessels and without evidence of an extra-capsular spread. At its lower pole was a cyst about 1 cm. in diameter. Following ligation of the superior and inferior thyroid arteries a right hemithyroidectomy was performed. The left lobe was left undisturbed. On section the resected portion of the right lobe consisted of several ovoid or spherical masses from 0.5 to 3 cm. in diameter. These were surrounded by a fibrous capsule, sometimes fairly dense; in several parts, however, the capsule consisted only of compressed but otherwise normal-looking thyroid tissue. The structure of the nodules varied greatly, ranging from relatively solid masses of polyhedral cells (Fig. 6) to large colloid-filled follicles lined by cuboidal or slightly flattened epithelial cells. Colloid was relatively scanty in the follicles and in the stroma. The epithelial cells in the nodules had large nuclei, often with prominent nucleoli, and pyknosis was widespread. Mitoses were not infrequent, particularly in the parts where the follicles were small or where the cells formed solid columns. Few intrafollicular projections were present, and scalloping of the colloid was confined to a few follicles. Several large scars and deposits of calcium were present in the stroma.

Though no pathological features were found to suggest that the condition was definitely carcinomatous, the adenomata showed a fairly active hyperplasia. When she was last seen on May 9, 1958, there was no evidence of any local recurrence or metastatic spread.

Discussion

The development of a carcinoma of the thyroid many years after exposure to ionizing radiation constitutes no evidence of a causal relationship; this must be sought on other lines. Most evidence is available with regard to the association between irradiation in childhood and the development of a neoplasm in the thyroid. In reviewing all cases since 1946 of proved carcinoma of the thyroid at the hospitals in Sheffield from which our cases have been drawn, we have found 12 patients developing the condition while under 35 years of age. In six a history of ionizing irradiation of the neck region in childhood was obtained. There is no available information regarding the frequency of exposure of the neck region to irradiation in the general public, but it seems highly improbable that it reaches the level of 50%. In attempting to obtain the past history it is most important that the parents should be interviewed, as the patient may be unaware of previous therapy if it was given in early life for a condition leaving no scar. One patient included in the non-irradiated group developed a thyroid carcinoma when 29 years of age. He gave a history of treatment with "rays" for swollen glands in the neck while in Holland 16 years previously. No details have been traced, but the description of the apparatus given by the parents suggested that the treatment was by ultra-violet rather than x-irradiation. A similar high incidence of previous exposure to ionizing radiation among younger patients with thyroid carcinoma has been reported by others (Duffy and Fitzgerald, 1950; Clark, 1955; Fetterman, 1956).

A further indication of a possible association between the irradiation and the development of the carcinoma is that in the five patients with a localized cutaneous lesion the site of the initial and maximal development of the carcinoma was invariably in the underlying part of the thyroid receiving the greatest exposure. In Case 8 the thyroid nodules were situated in the isthmus and right lobe, while the naevus overlay the tendinous head of the left sternomastoid. As,

FIG. 6.—Case 9. This is a more cellular part of an adenoma. Only a few small follicles are present. The cells are large and show slight nuclear pleomorphism and sometimes hyperchromatism. Some mitotic figures are evident. (H. and E. $\times 137$.)

however, the disposition of the radium needles is not known, no calculation of the exposure of different parts of the thyroid to radiation has been possible in this patient.

More definite evidence has been obtained by following the subsequent medical history of infants subjected to x-irradiation of the thymus. Simpson and Hempelmann (1957) found 10 cases of thyroid carcinoma and 7 cases of thyroid adenoma among 1,502 irradiated children, while in 1,933 untreated siblings there was no carcinoma and only one with an adenoma. Their study thus provided strong circumstantial evidence that irradiation in infancy may be an aetiological factor in the pathogenesis of thyroid cancer. Their cases were irradiated for supposed enlargement of the thymus, ours chiefly for skin disorders, particularly naevi. It is, of course, remotely possible, though highly improbable, that the various conditions for which the irradiation was given are all associated directly with an increased liability to develop cancer.

Two further points are noteworthy in our cases of carcinoma following irradiation in childhood. Firstly, the calculated dose to the thyroid gland was low and in three cases did not exceed 300 r. In Case 1 the dose was slightly below the minimum of 180 r reported by Simpson and Hempelmann (1957). Secondly, the latent period in the children is frequently shorter than that seen in carcinoma following irradiation in adult life (Medical Research Council, 1956).

In contrast to the information now available concerning children there is little to suggest that irradiation of the thyroid in adult life may lead to the development of a carcinoma. Indeed, in Case 7 the irradiation for thyrotoxicosis in 1919 and the anaplastic thyroid carcinoma in 1956 might be regarded as fortuitous. Although x-irradiation was a recognized method of treating thyrotoxicosis over 40 years ago, reports of cases of thyroid carcinoma following this procedure are remarkably few (Quimby and Werner, 1949). No accurate information is available regarding the frequency of the use of this method of treatment of thyrotoxicosis. In Sheffield it was employed particularly during the years 1931-43, and 99 patients were treated. The latent period for the development of a carcinoma following irradiation in adult life is at least 20 years (Medical Research Council, 1956), and the available evidence in the case of the adult thyroid suggests that it may be much longer. It is thus possible that an association may be noted more often in future years.

The two patients (Cases 8 and 9) presenting nodular adenomas in the thyroid following irradiation are of considerable interest. The histological features suggested considerable cellular hyperplasia: mitosis was frequently seen. However, in the absence of local invasion and metastases the histological appearances alone did not justify a diagnosis of carcinoma. Nevertheless more innocent-looking thyroid adenomas have often been the origin of distant metastases. It is clear from Simpson and Hempelmann's (1957) study that there is an increase in the incidence of thyroid adenomas as well as carcinomas following irradiation. The histology of the two adenomas reported certainly suggests that they should be regarded as premalignant conditions.

It is clearly important to review present practice with regard to exposure of the thyroid to ionizing radiation. It is evident that the increased risk incurred by any individual patient as a result of exposure is very small. It is apparent only when a large survey of irradiated individuals is carried out or when actual cases of carcinoma in younger patients are studied. Doses apparently sufficient to induce neoplastic change are surprisingly small and may be exceeded in certain diagnostic and therapeutic procedures in childhood. On the average, a test dose of ^{131}I resulting in an uptake of 15 microcuries distributed evenly throughout a gland weighing 15 g. or less would deliver a dose to the thyroid of at least 100 r. As, however, the distribution is probably irregular, certain regions would receive a dose considerably in excess of this amount. ^{132}I , with its shorter half-life, delivers a much lower dose. However, the development of satisfactory

chemical methods for the measurement of blood iodine (Acland, 1958) should greatly decrease the necessity of using radioactive iodine isotopes. Certainly, in children the use of ^{131}I is only justifiable in exceptional circumstances. Paediatricians, dermatologists, and radiotherapists should appreciate that exposure of the infant thyroid to irradiation may occasionally be followed by the development of a carcinoma. In adults this sequence is apparently less common even though much larger doses are used for therapeutic purposes; but, as the latent period may increase with irradiation in later life, the full effect of increasing use of procedures involving the use of ionizing radiation is not yet apparent. Thyroid carcinoma is a rare condition and accounts for only 0.4% of all deaths from malignant disease (Registrar General's Report, 1954). In cases in later adult life, irradiation is not at present a factor of importance (Kilpatrick *et al.*, 1957). While it is essential to keep the incidence under close observation in order that the precise risks may be more clearly defined, the danger of the use of ^{131}I for the treatment of thyrotoxicosis being followed by a carcinoma of the thyroid appears small and remote.

Summary

Nine cases of thyroid neoplasms are described. In all of them the thyroid gland had been exposed several years previously to ionizing radiation.

In seven patients indisputable histological evidence of carcinoma of the thyroid was present, and in six infiltration outside the gland or metastases had occurred. In six patients the thyroid had been incidentally exposed to irradiation in infancy or childhood during the treatment of cutaneous lesions by radium or x-irradiation. In them the dose to the thyroid varied from 130 r to 2,700 r and the latent period from 5 to 18 years. The carcinoma developed in the part of the thyroid exposed to the greatest irradiation. The seventh patient was irradiated for the treatment of thyrotoxicosis when she was 26 years old and had an anaplastic thyroid carcinoma 37 years later.

In two patients a nodular enlargement of the thyroid developed after irradiation. Histologically, hyperplastic adenomatous areas and mitotic figures were seen, but in the absence of local invasion and metastases the histological features alone did not justify a diagnosis of carcinoma. They were regarded as premalignant conditions.

The evidence regarding an association between exposure to ionizing radiation and the subsequent development of a carcinoma is reviewed. Exposure in childhood predisposes to the appearance of thyroid neoplasms. The association following irradiation in adult life is less certain.

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