MEDULLARY CARCINOMA OF THE THYROID GLAND

by

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INTRODUCTION
MEDULLARY carcinoma is an uncommon tumour of the thyroid gland which has been recognised only during the last 20 years. Between 1965 and 1978, 14 cases of medullary thyroid carcinoma have been diagnosed histologically in Northern Ireland. The purposes of this paper are to document the relevant details of these patients, to review the main clinical and pathological features of medullary carcinoma of the thyroid and to discuss some aspects of investigation and diagnosis of the condition.

CASE REPORTS
Five of the 14 cases referred to are described in some detail. Between them they demonstrate many of the typical features of medullary carcinoma and its associated phenomena. The main clinical aspects of all 14 cases are summarised in Tables I and II.

| Symptoms and signs in 14 patients with medullary carcinoma of the thyroid gland |
|---|---|---|---|---|---|---|
| Patients | Sex | Age | Duration of symptoms | Goitre | Palpable Nodes | Diarrhoea | Other features |
| J.D. | F | 28 | 2 years | Yes | Yes | Yes | No |
| R.K. | M | 62 | 7 years | Yes | Yes | No | No |
| F.O’N. | M | 65 | Unknown | Yes | Yes | No | Squamous Carcinoma lip |
| W.T. | M | 62 | 25 years | Yes | No | No | Left upper limb signs and Horner’s syndrome |
| E.U. | F | 40 | 6 months | Yes | No | No | No |
| M.P. | F | 51 | 1 month | Yes | No | No | No |
| M.Ra. | F | 55 | 15 months | Yes | No | No | Pain R. Neck |
| P.D. | M | 11 | 9 months | Yes | No | No | No |
| G.H. | F | 57 | 10 months | Yes | No | No | No |
| N.I. | F | 59 | Unknown | Yes | No | No | Pain left eye |
| M.Re. | F | 74 | 4 months | Yes | No | No | Weight loss, dysphagia |
| B.C. | M | 25 | 5 months | No | Yes | No | Marfanoid features, mucosal neuromata |
| J.S. | M | 59 | 1 year | Yes | Yes | Yes | No |
| P.M. | M | 39 | 5 years | No | Yes | Yes | Hoarseness, Marfanoid features |

* In these two patients the goitre was an incidental finding during admission for another reason. The age and duration of symptoms refer to time of diagnosis.
CASE I (R.K.)

A 62 year old male was referred to hospital with two lumps on the right side of his neck. The smaller swelling which had been present for six years was situated in the right lobe of the thyroid gland. The larger mass lay in the posterior triangle of the neck, partly covered by the sternomastoid muscle, and had appeared only three months prior to attendance. A clinical diagnosis of carcinoma of the thyroid with nodal metastases was made. Neck exploration was undertaken. A large hard tumour nodule was found at the lower pole of the right lobe of the thyroid gland. A clump of lymph nodes, obviously involved by tumour, was present at a higher level, deep to the sternomastoid muscle. A total right lobectomy and block dissection of the right side of the neck was performed. Histological examination revealed the presence of a primary medullary carcinoma of the thyroid with metastatic disease in the cervical nodes. A course of radiotherapy to the neck was given within eight weeks of surgery. Thyroxine was also prescribed in an attempt to maintain thyroid suppression. The patient remained well until four years after diagnosis, when he developed increasing weakness in both legs. A chest radiograph showed a discrete circular mass in the left lower lobe, where a myelogram revealed a complete block at the level of T9. Laminectomy was undertaken; the spinal cord and dura were being compressed anteriorly by a large tumour mass at the level of the radiological block. Palliative decompression was carried out. However, the patient's condition deteriorated and he died four days later. Post mortem examination revealed multiple metastases from the medullary thyroid carcinoma in both lungs, the liver and around the region of the spinal cord decompression.

CASE II (F.O'N.)

A 65 year old man was referred from the Northern Ireland Radiotherapy Centre, where he had been receiving treatment for carcinoma of the lower lip. Examination had revealed the presence of multiple discrete lymph nodes on the right side of the neck and in both supraclavicular fossae. There was no other significant symptomatology, but clinically the left lobe of the thyroid was enlarged and hard. Biopsy of the neck glands suggested a diagnosis of secondary medullary carcinoma of the thyroid. Formal exploration of the neck was undertaken. A large tumour in the left lobe of the thyroid gland was found. There was widespread involvement by tumour of the superficial and deep lymph nodes of the neck. A total left lobectomy was carried out along with removal of all accessible lymph nodes. It was recognised that a number of tumour nodes in the superior mediastinum were left behind. The pathology report confirmed the thyroid tumour as being medullary carcinoma, the malignant cells being dispersed in a matrix of amyloid. The postoperative course was uneventful and the patient was discharged five days after surgery on l-thyroxine. He remained well for two years but then began to experience diarrhoea which increased in intensity over a 12 month period. He developed hepatomegaly and a liver scan confirmed the presence of multiple metastases. He died three and a half years after diagnosis.

CASE III (P.D.)

An 11 year old boy was referred to hospital because of a swelling in the left anterior triangle of the neck which had been present for nine months. A clinical diagnosis of adenoma of the left lobe of the thyroid gland was made. At operation a 2 cm nodule was found in the left lobe of thyroid and a subtotal lobectomy performed. The pathology report suggested that the lesion was a "well encapsulated carcinoma". The patient was started on thyroxine as suppressant therapy. He remained well but at review three and a half years later he was found to have a swelling in the right lobe of his thyroid gland. At exploration this was seen to be a well circumscribed nodule within the lobe and total lobectomy was carried out. Histologically this nodule closely resembled that seen nearly four years earlier.
but on this occasion an unequivocal diagnosis of medullary carcinoma was made following the demonstration of amyloid in the stroma. Further exploration of the neck was undertaken when all remnants of the thyroid gland were removed. Nodules of carcinoma comparable to the previous tumour were seen microscopically. In the postoperative period tetany proved troublesome but gradually regressed with the commencement of calcium therapy. The patient is now aged 17 years and is alive and well six years after his initial operation, with no clinical evidence of tumour. His calcitonin level, however, is elevated at 4.2 ng/ml (normal 0.08 ng/ml) which may indicate the presence of residual recurrent disease.

CASE IV (B.C.)

A 25 year old male presented with a five month history of tiredness, lethargy and general malaise. On examination he was noted to be tall and thin with Marfanoid facies. Bilateral cervical and axillary lymphadenopathy were noted but no goitre could be palpated. His lips were thickened and his tongue had a serrated edge. He had attended the Plastic and Maxillo-Facial Unit eight years earlier because of his facial appearance and poor dental condition. Dental clearance and biopsy of 'nodular thickenings' of the tongue and lips had been carried out at that time. Histological examination of the nodules had shown them to be neuromata. Biopsy of the lymph nodes in the neck and the axillae was now performed. Microscopically the cervical node was replaced by secondary medullary thyroid carcinoma with large amounts of amyloid. The axillary nodes simply demonstrated reactive change. Thyroid function tests, serum calcium and phosphorus levels were normal. However, the urinary levels of both catecholamines and vannilyl mandelic acid (VMA) were grossly raised at 1742 μg/24 hours and 39 mg/24 hours respectively, the normal levels being less than 120 μg/24 hours and less than 9 mg/24 hours. An intravenous pyelogram demonstrated a normal urinary tract. Nevertheless, on the basis of the urinary investigations the presence of a phaeochromocytoma seemed certain. Confirmation of the diagnosis was achieved by renal and adrenal angiography when a tumour of the left adrenal gland was identified. Selective venous sampling revealed a forty-fold increase in catecholamine concentration in the blood draining from the left adrenal gland over that draining from the right. In addition, the fasting plasma calcitonin level was now estimated at 9.28 ng/ml.

Abdominal exploration revealed not only a large 5 to 6 cm tumour of the left adrenal gland but also a smaller phaeochromocytoma of the gland on the right side. Bilateral subtotal adrenalectomy was carried out (Professor R. B. Welbourn). Five weeks later total thyroidectomy was performed (Mr. S. Taylor). Both lobes were diffusely infiltrated with medullary carcinoma tissue. A number of lymph nodes, obviously involved in tumour, were also removed at operation but formal block dissection of the neck was not attempted. Three parathyroid glands were visualised and appeared normal macroscopically. Postoperatively, steroid and thyroid replacement therapy was commenced and the patient progressed without major complication. A course of radiotherapy was given to the neck three months following thyroidectomy because of persisting palpable lymph nodes. At present, now more than three years since his surgery, he is in good health and has returned to his former occupation as a merchant seaman. However, although there is no clinical or radiological evidence of metastatic disease at present, his plasma calcitonin levels have remained high, almost certainly indicating continued presence of malignant tissue at some site, presumably in his neck.

CASE V (P.M.)

A 39 year old male was admitted to hospital for investigation of hoarseness which had been present for six months. Systematic questioning revealed that for five years he had been experiencing watery diarrhoea. He often passed 8 to 12 motions per
TABLE II

Clinical details in 14 patients with medullary carcinoma in the thyroid gland

| Patient | Operation performed | Node metastasis | Current status | Years from diagnosis | Persisting or recurrent tumour | Calcitonin estimation (normal) |
|---------|---------------------|-----------------|---------------|----------------------|-------------------------------|------------------------------|
| J.D.    | Thyroid + node biopsy | Yes             | Dead          | 9                    | Radiological metastases       | 0.08 ng/ml                   |
| R.K.    | R. total lobectomy + block dissection | Yes | Dead | 4 2/12 | Metastases at post mortem + + + |                            |
| F.O’N.  | L. total lobectomy + accessible nodes | Yes | Dead | 3 6/12 | Hepatic metastases           |                            |
| W.T.    | L. total lobectomy | Yes             | Dead          | 12 days              | Metastases at post mortem + + + |                            |
| E.U.    | R. subtotal lobectomy | No              | Alive         | 9 | Yes – mass in neck         |                            |
| *M.P.   | R. subtotal lobectomy | No              | Dead          | Operative Death      | Multiple foci L lobe at post mortem |                            |
| M.Ra.   | Thyroid biopsy      | No              | Dead          | 3 4/12              | Mass in neck                  | 25 ng/ml                     |
| P.D.    | L. subtotal lobectomy | No | Alive | 6 | Only elevated calcitonin level | 4.1 ng/ml                   |
| G.H.    | R. subtotal lobectomy | No | Alive | 5 10/12 | No |                            |
| N.I.    | L. total lobectomy | No              | Alive         | 3 9/12              | No |                            |
| M.Re.   | L. total lobectomy | No              | Alive         | 3 8/12              | No |                            |
| †B.C.   | Total thyroidectomy | Yes             | Alive         | 3 6/12              | Only elevated calcitonin level | 9.28 ng/ml (pre-op) 6.56 ng/ml (2yr post-op) |
| J.S.    | Thyroid + node biopsy | Yes | Dead | 6/12 | Mass in neck                | 357 ng/ml                    |
| P.M.    | Node biopsy         | Yes             | Alive         | 11/12 | Mass in neck                | 115.9 ng/ml                  |

* The patient M.P. had a phaeochromocytoma of the right adrenal gland.
† The patient B.C. had bilateral phaeochromocytomata.

day, but at no time had he passed any blood per rectum. On examination he was tall and thin. A firm diffuse mass was palpable in the lower neck on the right side but was thought, clinically, not to be thyroid. Indirect laryngoscopy revealed a paralysed right vocal cord. Surgical exploration of the cervical mass showed it to be a cluster of matted malignant lymph nodes, several of which were removed for biopsy. Microscopically the nodes were replaced by metastatic medullary carcinoma of the thyroid gland. The plasma calcitonin level was grossly elevated at 115.9 ng/ml.

Further operation was performed with a view to carrying out a block dissection of the neck along with thyroidectomy. A 1 cm diameter nodule was present in the right lobe of the thyroid while the left lobe was quite normal. However, there were many tumour nodes surrounding the carotid sheath on the right side and extending deep into the neck. It was felt that these could not be removed successfully and so right total lobectomy alone was carried out. Histology con-
firmed that the nodule in the right lobe was a primary medullary thyroid carcinoma. In the 10 months since operation the patient's condition has remained fairly stable. He continues to experience intermittent diarrhoea, while a hard nodular mass persists on the right side of the neck. Plasma calcitonin levels remain very high.

HISTORICAL ASPECTS

Medullary carcinoma of the thyroid gland was described as a distinct clinical and pathological entity for the first time in 1959 (Hazard et al, 1959). It has been estimated as constituting approximately 7 to 10 per cent of all thyroid cancers (Hill et al, 1973) and as such is a relatively uncommon tumour. However, there is good evidence to suggest that it is a condition which has been significantly underdiagnosed and misdiagnosed in the past (Normann et al, 1976). Medullary carcinoma is a malignancy arising from the parafollicular or C-cells of the thyroid gland. These cells are thought to derive from neural crest ectoderm and to migrate at an early embryological stage into the primitive alimentary tract mucosa from whence they are carried to their final resting place in the thyroid, when this gland buds off the primitive foregut (Weichert, 1970). The C-cells in the mature gland lie outside the follicles in a parafollicular distribution and secrete the hormone calcitonin which plays a part in calcium homeostasis by lowering the plasma calcium level (Ganong, 1977).

In recent years interest in medullary carcinoma of the thyroid has grown significantly for a number of reasons. First, this type of tumour has shown itself to be biologically extremely active by producing, in different instances, a variety of hormones and enzymes including calcitonin and serotonin (Moertel, 1965; Williams, 1966), adrenocorticotropic hormone (Scott, 1977), histaminase (Baylin et al, 1970), and prostaglandins (Williams et al, 1968). Second, it has been recognised that certain other endocrine anomalies may co-exist. Phaeochromocytoma and parathyroid adenoma or hyperplasia are most frequently noted and together with medullary thyroid carcinoma constitute the syndrome of multiple endocrine neoplasia, type II or MEN II (Sipple, 1961; Williams, 1965; Steiner et al, 1968). The patient (M.P.) who presented simply because of thyroid enlargement was shown at post mortem examination to have a hitherto unsuspected phaeochromocytoma of her right adrenal gland. However, no parathyroid abnormality was detected. A subgroup of patients exists (MEN IIb) in which medullary thyroid carcinoma, alone or in association with the adrenal and parathyroid lesions alluded to, is seen in the presence of multiple small neuromata of the lips, tongue or eyelids, a high arched palate, Marfanoid facies and occasionally other skeletal abnormalities. The patient (B.C.) is thought to fall into this category.

58
The third, and perhaps, in the Northern Ireland context, the most important stimulus to increasing interest in the condition has been the recognition that in a significant number of cases, medullary carcinoma of the thyroid has a strong familial tendency (Melvin et al, 1972; Jackson et al, 1973; Sizemore et al, 1977). It is now thought probable that in affected families inheritance is on an autosomal dominant basis. Thus, about 50 per cent of the offspring of a patient known to have medullary carcinoma might be expected to develop the disease. This obviously has extremely important implications in terms of investigation and follow-up of ‘at risk’ family members.

PATHOLOGICAL CONSIDERATIONS

Hazard and his co-authors described the characteristic histological pattern of medullary thyroid carcinoma as consisting of solid sheets and cords of spindle shaped or polyhedral cells, broken up by a stroma containing amyloid (Hazard et al, 1959). They emphasise the importance of the absence of any tendency towards papillary or follicular formation. Amyloid was present in easily recognisable quantities in the stroma in all 21 cases described by Hazard and his colleagues, and they imply that the presence of amyloid is necessary for a diagnosis of medullary carcinoma to be made. Other pathologists have largely agreed with this view (Woolner et al, 1961; Williams et al, 1966), although Williams and his colleagues in their detailed studies of the pathological findings in medullary carcinoma, while excluding three cases from their review on the grounds that no amyloid could be identified microscopically, state that the absence of amyloid should not necessarily exclude the diagnosis of medullary carcinoma (Williams et al, 1966). This view has more recently been expressed with more conviction following the discovery that in some instances, although amyloid cannot be identified using the light microscope in what was thought to be a medullary carcinoma, electron microscopy reveals the presence of typical calcitonin secretory granules in the tumour cells (Normann et al, 1976). In all 14 cases reported here amyloid was identified histologically in the tumours. Electron microscopy was performed in only one instance (patient P.M.) where moderate numbers of densely staining secretory granules were visualised within the neoplastic C-cells.

CLINICAL FEATURES

Medullary thyroid carcinoma is less common in females relative to males than other thyroid cancers, resulting in a virtually equal sex incidence (Shapiro, 1976; Sizemore et al, 1977). Of these 14 cases, seven are male and seven female. Clinically the patient most commonly presents with a goitre or because of cervical lymphadenopathy. It can be seen that the majority of our patients (12 out of 14) had a palpable goitre at the time of presentation. Six patients, of whom two had no goitre, demonstrated cervical lymphadenopathy at initial examination (Table I). Less frequently diarrhoea may be the major presenting feature. The cause of the diarrhoea in such patients remains unknown although a number of
suggestions have been put forward and attempts made to incriminate several different agents, including calcitonin itself, serotonin and the prostaglandins $E_2$ and $F_2\alpha$ (Williams et al, 1968; Bernier et al, 1969; Steinfeld et al, 1973). Diarrhoea seems to be more prevalent in those patients who have extensive local disease or disseminated tumour and would, therefore, appear to be related to tumour bulk (Williams, 1966). This suggestion would be in keeping with the findings in our own group of patients, three of whom were experiencing diarrhoea at the time of presentation (Table I). A fourth patient (F.O’N.) developed severe diarrhoea approximately two years after he had been diagnosed, and this persisted until his death from hepatic metastases.

Occasionally, the presenting symptomatology may be related to associated pathology, particularly phaeochromocytoma, or to metastatic disease. The importance of excluding co-existing phaeochromocytoma in a patient with medullary carcinoma before embarking on thyroid surgery cannot be over-emphasised. The patient (M.P.) in the perioperative and immediate postoperative periods developed a series of unexplained cardiac arrhythmias and hypertension which resulted in acute cardiac failure and death. The latter was almost certainly due to excess circulating levels of catecholamines released from a phaeochromocytoma of the right adrenal gland, unsuspected clinically but discovered at post mortem examination.

The malignancy of medullary thyroid carcinoma is thought to be of intermediate grade, but while in some patients the presence of the tumour is compatible with good life expectancy, others die rapidly from widespread metastatic disease. This variation is reflected in our own series in which the survival time following diagnosis ranged from six months to nine years, if the two patients who died in the immediate postoperative period are excluded (Table II). Hill and his colleagues (1973) report a crude overall five year survival after diagnosis of 37 out of 72 cases (51 per cent). The corresponding 10 year survival rate is 29 per cent. The best prognosis is associated with complete surgical removal of the tumour.

**DIAGNOSIS**

Diagnosis of medullary carcinoma of the thyroid gland was, until comparatively recently, essentially a postoperative one, based on histological examination of the surgical specimen. However, in the late sixties it was recognised by a number of workers, including Cunliffe and his colleagues in Newcastle, that a hypocalcaemic agent was present in the plasma of patients with medullary carcinoma and also in the tumour itself (Cunliffe et al, 1968). The Newcastle group provided convincing evidence that this was calcitonin, elevated levels of which were identified in the plasma of their patient preoperatively. Further, all hypocalcaemic activity and detectable calcitonin disappeared from the circulation within hours of total thyroidectomy. It was, therefore, suggested that medullary carcinoma of the thyroid did in fact produce calcitonin and could be diagnosed preoperatively by measuring plasma calcitonin levels. It was also suggested that,
by carrying out serial plasma calcitonin estimations, tumour recurrence and metastases might be detected at an early stage (Cunliffe et al, 1968). These hypotheses have subsequently been shown to be correct (Deftos and Potts, 1970; Melvin et al, 1971; Deftos, 1974). Although elevated plasma levels of calcitonin have been demonstrated in a number of patients (Table II), these estimations were all carried out after the diagnosis of medullary carcinoma had been made histologically. As indicated in Table II, three patients had clinically evident disease at the time of the calcitonin measurement, while two others were free a palpable tumour. It remains to be seen how these latter two patients progress. One problem has been the fact that the radioimmunoassay necessary to measure plasma and tissue calcitonin levels is available in only a very few centres. However, such an assay is now being established in the University Department of Medicine, Belfast.

Since 1965 only the 14 cases of medullary thyroid carcinoma reported here have been positively diagnosed in Northern Ireland. It is, however, likely that during the past 25 years there have been other cases misdiagnosed, the clinicians and pathologists perhaps being unaware of the existence of the entity.

FUTURE MANAGEMENT

Medullary carcinoma of the thyroid gland while usually presenting in a sporadic manner, reveals a strong familial tendency. The more enthusiastically this familial tendency is sought, the more often it is found. Sizemore and his colleagues (1977) in a recent review of a five year experience of medullary carcinoma at the Mayo Clinic, suggest that at least 19 per cent of patients assumed to be suffering from the sporadic variant, in fact have familial disease. It would, therefore, seem to be extremely important to investigate 'at risk' first degree relatives of patients who have been identified as having medullary thyroid carcinoma. The main object of this is to identify those carrying the disease at as early a stage as possible so that appropriate treatment in the form of total thyroidectomy can be instituted. Basal plasma calcitonin levels in such patients may, however, be totally normal.

In recent years, however, it has been shown that the hyperplastic or neoplastic C-cell mass can be provoked or stimulated into producing elevated plasma levels of calcitonin by a number of different agents (Hennessy et al, 1973; Cohen et al, 1973). Calcium, pentagastrin, alcohol and glucagon are among those which have been utilised in different centres and with varying degrees of efficacy in calcitonin provocation tests (Hennessy et al, 1974; Wells et al, 1975; Sizemore and Go, 1975; Dymling et al, 1976). Patients with medullary carcinoma show an elevation in their plasma calcitonin level following administration of one or more of these agents while normal individuals fail to demonstrate any change. Several centres have now reported the use of calcitonin provocation tests in the investigation of appropriate patients who are at risk, in an attempt to diagnose preclinical, occult medullary thyroid carcinoma (Telenius-Berg et al, 1977; Starling et al, 1978; Hillyard et al, 1978; Lips et al, 1978). In many instances an
elevated plasma level of calcitonin under basal conditions or following administration of a reliable provocative agent has been accepted as the only criterion necessary to proceed to neck exploration. When this policy has been adopted it has now been clearly shown that in virtually 100 per cent of patients whose necks have been explored, and in whom total thyroidectomy has been performed, medullary carcinoma or its precursor state C-cell hyperplasia has been found (Wolfe et al, 1973; Wells et al, 1975; Leape et al, 1976; Verdy et al, 1978; Wells et al, 1978).

The importance of early operation before the tumour has extended locally or metastasised is obvious. Availability of a reliable provocation test coupled with an aggressive surgical approach in appropriate cases should allow for some improvement in the prognosis for these early cases. Follow-up of patients operated on for occult, asymptomatic medullary thyroid carcinoma is still very limited (less than five years in most instances). However, early results would suggest that total thyroidectomy has been 'curative', as judged by negative postoperative provocation tests, in more than 80 per cent of patients whose diagnosis was made on the basis of provocative testing alone (Wells et al, 1978). Encouraged by these results, active provocative testing of the first degree relatives of patients in Northern Ireland known to have had medullary carcinoma has now commenced. Other index cases and their families have yet to be traced. Only time will reveal the relevance of the exercise.

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