Virchows Arch. A Path. Anat. and Histol. 381, 179–187 (1979)

Virchows Archiv A

Pituitary Adenoma, Primary Parathyroid Hyperplasia and Papillary (Non-Medullary) Thyroid Carcinoma

A Case of Multiple Endocrine Neoplasia (MEN)

H. Dralle and E. Altenähr

Institute of Pathology (Director: Prof. Dr. G. Seifert), University of Hamburg, Martinistr. 52, D-2000 Hamburg 20, Federal Republic of Germany

Summary. An acidophilic pituitary adenoma associated with primary nodular parathyroid hyperplasia and a small papillary thyroid carcinoma was discovered at the autopsy of a 44 year old female acromegalic. The thyroid carcinoma showed evidence of lymphatic spread. Several etiopathogenetic mechanisms for the non-medullary thyroid carcinomata associated with Multiple Endocrine Neoplasia (MEN) have been postulated, since the follicular epithelium of the thyroid does not belong to the neural ectoderm derivates unlike the C-cells of the thyroid, the adenohypophysis and probably the parathyroid glands. Apart from genetic influence, or coincidence, one has to rule out carcinogenic exposure or hormonal influence. Clinically speaking, one should always consider whether malignant thyroid disease coexists with hyperplastic or neoplastic parathyroid tissue.

Key words: Multiple Endocrine Neoplasia (MEN) – Pituitary Adenoma – Parathyroid Hyperplasia – Non-Medullary Thyroid Carcinoma.

Introduction

Multiple Endocrine Neoplasia (MEN) is a usually hereditary, neoplastic entity of the neuroendocrine system, which involves neoplastic changes in several endocrine glands and/or neuro-ectodermal tissues (Weichert, 1970; Bolande, 1974; Pearse and Takor, 1976; Schimke, 1976; Kracht and Altenähr, 1977; Pearse, 1977). Histopathologically MEN involves (adenomatous) hyperplasia, adenomas or carcinomas (Welbourne, 1977).

Three neoplastic syndromes can be differentiated (Table 1):

1. Multiple Endocrine Neoplasia I (MEN I, Wermer's syndrome) with tumors of the parathyroid glands, the pancreatic islets, the pituitary gland and other endocrine and non-endocrine organs (Erdheim, 1903; Underdahl et al., 1953; Wermer, 1954 and 1963; Croisier et al., 1971; Harrison and Thompson, 1975; Champault et al., 1976).

2. Multiple Endocrine Neoplasia II (MEN II, Sipple's syndrome) with phaeochromocytoma, medullary thyroid carcinoma, parathyroid adenoma and other apudomas (Sipple, 1961; Cushman, 1962; Ballard et al., 1964; Steiner

0340-1227/79/0381/0179/$01.80

et al., 1968; Gorlin et al., 1971; Catalona et al., 1971; Keiser et al., 1973; Ingbar and Woeber, 1974; Robertson and Sizemore, 1975; Bartley et al., 1976).

3. Steiner et al. (1968) proposed a third group: Multiple Endocrine Neoplasia III (MEN III) with non-medullary thyroid carcinoma and parathyroid neoplasia.

The following case report deals with the autopsy findings of a 44 year old woman, who died after a pituitary tumor operation. The autopsy revealed: 1. acidophilic adenoma of the pituitary gland, 2. primary nodular hyperplasia of the parathyroid glands and 3. papillary (non-medullary) thyroid carcinoma.

Case Report

Autopsy was performed on a 44 year old female demonstrating the clinical signs of acromegaly which had existed for the past eight years. Familial and personal histories did not suggest a specific metabolic or tumor developing predisposition. Preoperative labatory tests demonstrated a 20-fold rise in growth hormone level, with normal serum concentrations of the other pituitary hormones (LH, TSH). In addition, the levels of T_3, T_4 and the 17-OH-Ketosteroids remained within normal limits. Calcium and phosphate levels were also normal. IgG was clearly below normal, the erythrocyte sedimentation rate was increased. All other estimations (electrolytes, transaminases, proteins and creatinine) proved to be within normal limits. Florid diabetes mellitus had existed for the past three years. The patient suffered from a bitemporal hemianopsia due to compression of the optic chiasm by the suprasellar neoplasm.[1]

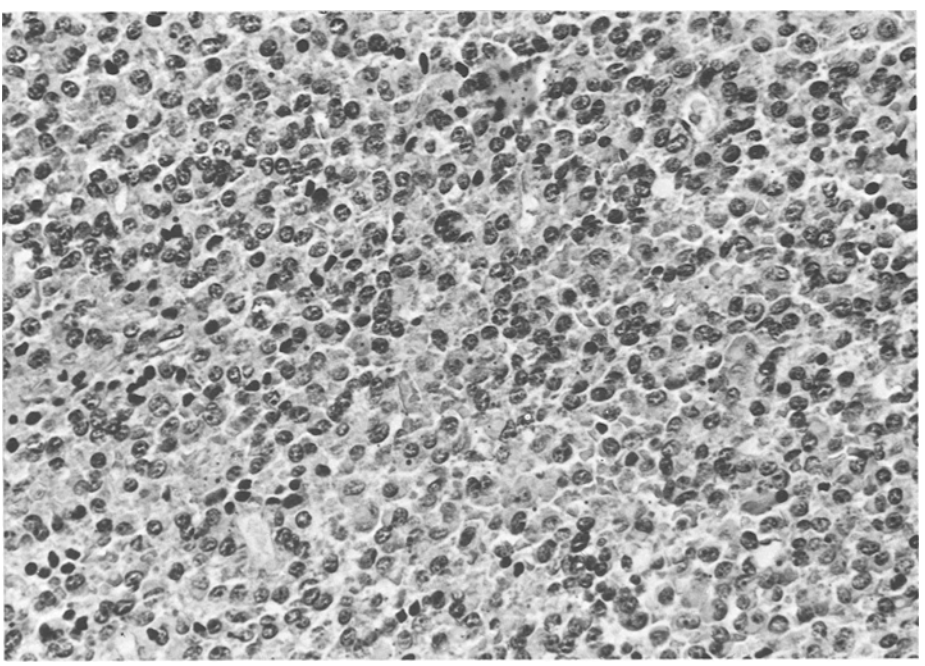

Fig. 1. Undifferentiated acidophil adenoma of the pituitary gland. Loss of the normal gland architecture. Tumor cells are poorly demarcated from each other and are weakly granulated. × 100

[1] We would like to gratefully acknowledge Prof. Dr. Kautzky, Director of Neurosurgery, University of Hamburg, for providing clinical data

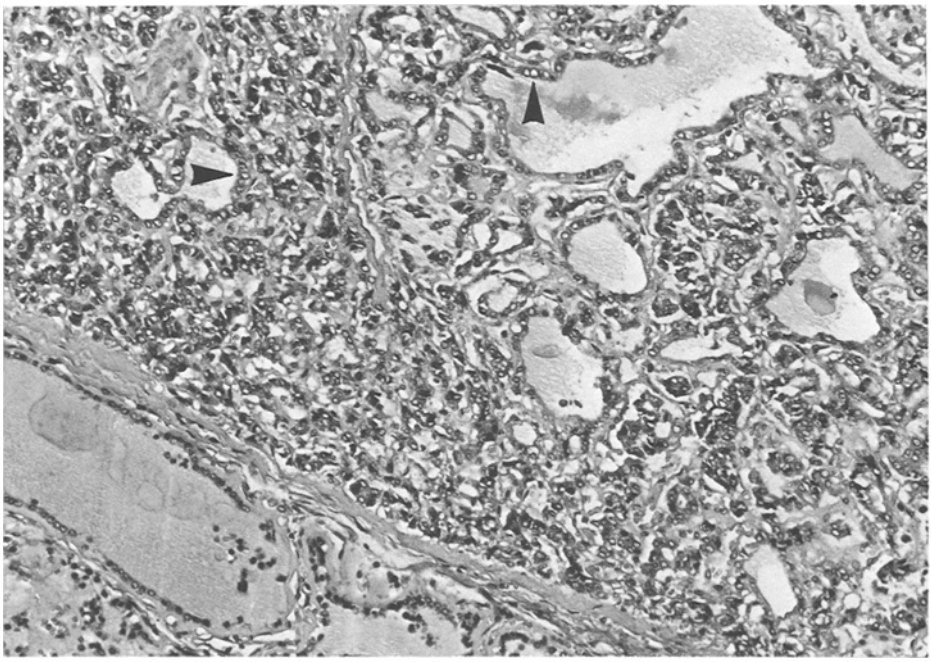

Fig. 2. Papillary thyroid carcinoma. Mixed papillary-follicular structure. Nuclei of the tumor cells have a "ground glass" appearance (*arrows*). Below, normal thyroid tissue. × 100

The operatively resected pituitary tissue weighed 0.5 gm. It consisted mainly of tumor, but included some normal anterior and posterior pituitary gland and parts of its capsule. Histologically it could be classified as an undifferentiated, acidophilic adenoma of the pituitary gland (J.No. 34863/77). The tumor cells appeared weakly granulated, indicating endocrine activity (Fig. 1) (Saeger, 1977).

The autopsy (S.No. 1493/77) revealed features of acromegaly and visceromegaly: enlargement of the mandibula and its alveoli; appositional growth of the supraorbital and maxillary bones; thickening of the lips; enlargement of the hands and feet and of all soft tissues.

Local findings including the changes to be expected following transnasal hypophysectomy were present. Two small tumor remnants were located in the supra- and parasellar region. The thyroid gland appeared enlarged and histologically resembled a diffuse nontoxic goitre. The enlarged thyroid lobules consisted of distended colloid-filled follicles, lined predominantly by flat epithelial and some cuboidal cells. Nodular aggregations of follicles were also present. Within the thyroid parenchyma a yellow-white non-encapsulated nodule, measuring 0.6 × 0.25 cm was found, displaying a mixed papillary and follicular structure (Fig. 2). The large nuclei of the tumor cells were surrounded by a narrow zone of eosinophilic cytoplasm and showed a characteristic "ground glass" appearance. No interstitial fibrosis or lymphoplasmocytic infiltration was seen. The rest of the parenchyma contained histologically similar tumor foci. The lesion was considered to be a clinically occult, papillary thyroid carcinoma, with intraglandular and lymphatic metastases.

The four parathyroid glands were also enlarged. They weighed 560 mg (normal weight: 120–140 mg). Histologically they consisted of nodular parenchyma, deprived of fat cells, made up of solidly packed chief cells and focal oxyphilic cell complexes (Fig. 3). These findings are consistent with nodular parathyroid hyperplasia.

Carefully examination of the pancreas, adrenal glands, ovaries, and uterus failed to reveal any hyper- or neoplastic changes. All other parenchymal organs, except the heart, were enlarged: liver −3360 g; spleen −480 g; kidneys −510 g; heart −390 g (TBW − 84 kg). No histological abnormalities were found. Both lungs showed signs of severe shock with intraalveolar oedema and microthrombi. The cause of death was considered to be central cardio-vascular failure.

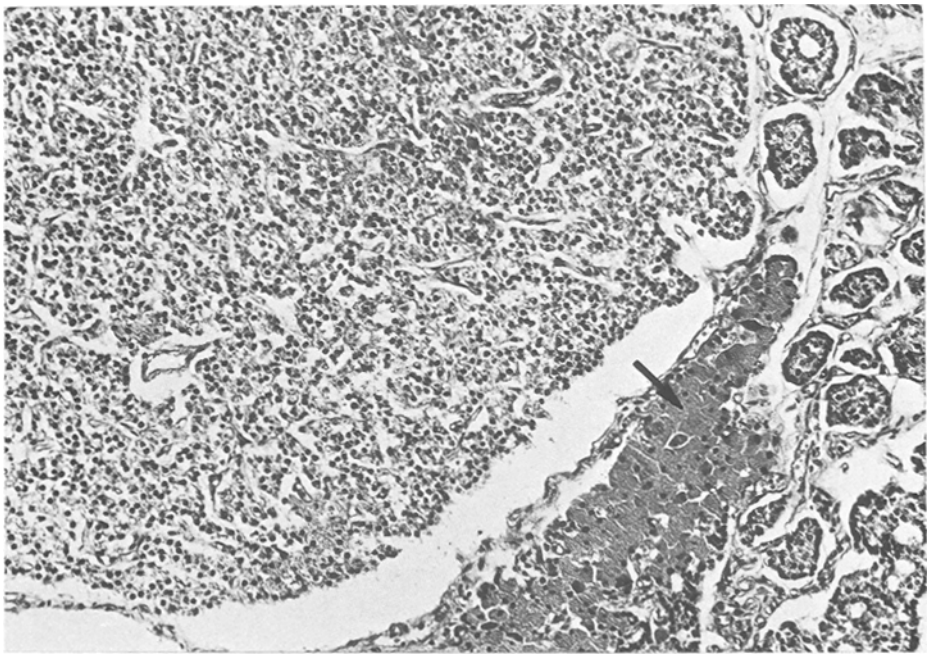

Fig. 3. Nodular parathyroid hyperplasia. On the left solidly packed chief cells, on the right oxyphil cell complexes (*arrow*). × 100

Discussion

In this 44 year old female with acidophilic adenoma of the pituitary gland, primary nodular parathyroid hyperplasia and papillary thyroid carcinoma, we are dealing with a case of Multiple Endocrine Neoplasia I, associated with a non-medullary thyroid carcinoma. Follicular cell tumors of the thyroid are not considered to be apudomas and not of neural crest origin. In contrast to these the tumors of the parathyroid and pituitary gland are supposed to be tumors of neural ectoderm origin (Pearse and Takor, 1976). Their association is rare. In order to establish this coincidence as a syndrome, several authors have proposed an additional MEN group: MEN III (Steiner et al., 1968; LiVolsi and Feind, 1976) (Table 1). It is not clear however, whether we are dealing with a real syndrome or a coincidental finding.

In the literature we were able to find only one case report of an association of an adenoma of the pituitary gland with a parathyroid neoplasm and a non-medullary thyroid carcinoma (Ries, 1974). The association of a non-medullary thyroid carcinoma with a parathyroid hyper- or neoplasia has been described on several occasions and a total of 77 instances (6%) in 1236 cases of parathyroid adenomas and hyperplasias has been published (Table 2). A further 26% of cases had thyroid adenomas and other benign lesions of the thyroid gland. A papillary thyroid carcinoma was found in 82% of the 77 mentioned cases as in our patient (Table 3). This is a very high percentage indeed, compared to the 35 to 60% of thyroid carcinomas which are considered to be papillary in most large series (Franssila, 1973; Lietz, 1974; Neracher and Hedinger, 1975).

Table 1. Classification of Multiple Endocrine Neoplasia (MEN). (Numerical order according to their prevalence)

MEN I	1. Parathyroid gland hyper/neoplasia 2. Pancreatic islet-cell tumors 3. Pituitary gland adenoma 4. Other endocrine tumors 5. Non-endocrine Tumors
MEN IIa	1. Medullary thyroid carcinoma 2. Parathyroid gland hyper/neoplasia 3. Phaeochromocytoma
MEN IIb	1. Medullary thyroid carcinoma 2. Phaeochromocytoma 3. Multiple mucosal neuromas and/ or corneal nerve hyperplasia and marfanoid habitus 4. Parathyroid gland hyper/neoplasia
MEN III	1. Parathyroid gland hyper/neoplasia 2. Non-medullary thyroid carcinoma 3. Other tumors of neuroectodermal origin

Table 2. Coincidence of non-medullary thyroid carcinoma, thyroid adenoma and benign thyroid lesions with primary parathyroid gland hyper/neoplasia

Author	Number	Parathyroid gland hyper/ neoplasia	Non-medullary thyroid carcinoma	Thyroid adenoma	Other thyroid lesions (toxic and non-toxic goitre)
Ogburn und Block, 1956	230	230	4		
Ellenberg et al., 1962	65	65	7	32	3
Fields et al., 1964	1	1	1		
Laing et al., 1969	72	72	3		25
Heimann, 1970	160	160	4	4	50
Krementz et al., 1971	96	96	5	3	16
Kaplan et al., 1971	166	166	9		
Trout et al., 1972	30	30	3	4	
Hajjar und Salti, 1973	1	1	1		
Malette et al., 1974	57	57	1	15	
Petro et al., 1975	56	56	5		
Uehlinger, 1975	1	1	1		
Kairaluoma et al., 1976	29	29	2		
LiVolsi et al., 1976	272	272	31	10	127
	1236	1236	77(=6%)	53 (=4%)	273 (=22%)

The following possibly causal relationships between adenomas of the pituitary gland, parathyroid adenomas and non-medullary thyroid carcinomas should be discussed:

1. One cannot exclude the possibility that we are dealing with a coincidental finding. The prevalence of thyroid carcinomas depends on geographic factors (Cuello et al., 1969; Hakama, 1969; Fukunaga and Yatani, 1975), and at autopsy Mortensen (USA, 1955) and Kind (Switzerland, 1966) found 2.1 and 0.3%

Table 3. Histological types of non-medullary thyroid carcinoma present in cases of primary parathyroid gland hyper/neoplasia (compare with Table 1)

Author	Papillary	Follicular	Clear cells	Oncocytic
Ogburn and Block, 1956	4			
Ellenberg et al., 1962	6	1		
Fields et al., 1964	1			
Laing et al., 1969	1			2
Heimann, 1970	4			
Krementz et al., 1971	3	1		1
Trout et al., 1972		3		
Hajjar and Salti, 1973	1			
Malette et al., 1974	1			
Petro and Hardy, 1975	4	1		
Uehlinger, 1975	1			
Kairaluoma et al., 1976	2			
LiVolsi et al., 1976	26	2	1	
	54 (=82%)	8 (=12%)	1 (=2%)	3 (5%)

of thyroid carcinomas respectively. Medullary thyroid carcinomas amounted for 6% of cases in Woolner et al.'s (1961) study.

2. A common genetic predisposition could account for the occurence of papillary thyroid carcinoma together with parathyroid adenoma/hyperplasia and adenoma of the pituitary gland, justifying the creation of the MEN III group. A familial non-medullary thyroid carcinoma has recently been described by Nemec et al. (1975), but in our case no familial factors could be discovered.

3. Exposure to exogenous carcinogenic stimuli could account for the non-medullary thyroid carcinomas. The following carcinogens have been described (Money and Rawson, 1968):

a) 131-I in animals (Lindsay, 1966) and man (Creutzig and Hundeshagen, 1977).

b) N-Nitroso compounds in animals (Thomas et al., 1975).

c) Iodine-poor diets, or goitrogens, leading to chronically increased TSH-stimulation (Matovinovic et al., 1968; Heinze and Pichlmaier, 1972; DeGroot, 1975).

d) Local irradiation (mostly children) (André, 1966; Hempelmann, 1969; Favus, 1976; Spitalnik and Strauss II, 1978; Schneider et al., 1978).

None of the aforementioned carcinogens were involved in our case.

4. Although the influence of a hypercalcaemic metabolism on the follicular epithelium of the thyroid has been discussed frequently (Ellenberg et al., 1962; Kaplan et al., 1971; Hajjar and Salti, 1973; Harrison and Thompson, 1975; Petro and Hardy, 1975; Uehlinger, 1975; LiVolsi and Feind, 1976), it has not been shown to play a role in the genesis of tumors in man.

5. The influence of growth hormone (GH) on neoplasms is unknown (Daughaday, 1974). To our knowledge GH-induced tumors have not yet been reported in man. In animal experiments, GH has induced an increased number of neoplastic changes in the adrenal medulla and lungs in rats (Moon et al., 1950). Nodular

and diffuse nontoxic goitres occur in 25 to 50% of acromegalic patients (Cushing and Davidoff, 1927; Davies, 1941; Hamwi et al., 1960; Gordon et al., 1962). If no latent goitrogenic factors are present, one may assume the goitre to be the result of GH-controlled anabolic metabolism (Siebenmann et al., 1971; Daughaday, 1974) and a direct, biochemical goitrogenic effect of GH has been discussed (Chandola, 1972; Mukhtar, 1971). A relationship between excess serum GH and parathyroid changes has not been investigated in detail. Altenähr and Kampf (1976) discovered that in light- and electronmicroscopic animal experiments, GH resulted in parathyroid inactivation; Lancer et al. (1976), however, described increasing PTH secretion and parathyroid gland weight. From a clinical point of view one should consider the possibility of the presence of a medullary and/or a non-medullary thyroid carcinoma in all cases of parathyroid hyper- or neoplasia.

References

Altenähr, E., Kampf, E.: Parathyroid function in rats treated with growth hormone. Virchows Arch. A Path. Anat. and Histol. **371**, 363–371 (1976)

André, P.: Postirradiation thyroid cancers. In: Tumors of the thyroid gland, (Appaix, A., Ed.), pp. 299–313. Basel, New York: Karger 1966

Ballard, H.S., Frame, B., Hartsock, R.J.: Familial multiple endocrine adenoma-peptic ulcer complex. Medicine **43**, 481–516 (1964)

Bartley, P.C., Lloyd, H.M., Aitken, R.E.: Medullary carcinoma of the thyroid, multiple pheochromocytomas, mucosal neuromas, marfanoid habitus and other abnormalities (Sipple's syndrome). Med. J. Aust. **2**, 173–176 (1976)

Catalona, W.J., Engelman, K., Ketcham, A.S., Hammond, W.G.: Familial medullary thyroid carcinoma, pheochromocytoma, and parathroid adenoma (Sipple's syndrome). Cancer **28**, 1245–1254 (1971)

Champault, G., Chapuis, Y., Patel, J.C., Louvel, A., Ghozian, R., Cachin, M., Leger, L.: Syndrome de Zollinger-Ellison et adénome parathyroidien. J. Chir. (Paris) **112**, 131–144 (1976)

Chandola, A., Thapliyal, J.P.: Effect of growth hormone and prolactin on the body weight and thyroid activity of spotted munia. Ann. d'Endocrinologie (Paris) **33**, 583–591 (1972)

Creutzig, H., Hundeshagen, H.: Schilddrüsenkarzinom nach Radiojodtherapie. Med. Klin. **72**, 855–857 (1977)

Croisier, J.C., Azerad, E., Lubetzki, J.: L'adénomatose polyendocrinienne (Syndrome de Wermer). Sem. Hôp. Paris **47**, 494–525 (1971)

Cuello, C., Correa, P., Eisenberg, H.: Geographic pathology of thyroid carcinoma. Cancer **23**, 230–239 (1969)

Cushing, H., Davidoff, L.M.: Studies in acromegaly. Arch. Intern. Med. **39**, 673–697 (1927)

Cushman, P.: Familial endocrine tumors. Report of two unrelated kindreds affected with pheochromocytomas, one also with multiple thyroid carcinomas. Am. J. Med. **32**, 352–360 (1962)

Davies, A.C.: The thyroid gland in cases of acromegaly. J. Clin. Endocrinol. Metab. **1**, 445–449 (1941)

Daughaday, W.H.: The adenohypophysis. In: Textbook of Endocrinology. Williams, R.H., Ed., pp. 31–79, Philadelphia, London, Toronto: Saunders 1974

DeGroot, L.J.: Thyroid carcinoma. Med. Clin. N.A. **59**, 1233–1246 (1975)

Ellenberg, A.H., Goldman, L., Gordan, G.S., Lindsay, St.: Thyroid carcinoma in patients with hyperparathyroidism. Surg. **51**, 708–717 (1962)

Erdheim, J.: Zur normalen und pathologischen Histologie der Glandula thyreoidea, parathyreoidea und Hypophysis. Beitr. pathol. Anat. allg. Pathol. **33**, 158–236 (1903)

Favus, M.J., Schneider, A.B., Stachura, M.E., Arnold, J.E., Ryo, U.Y., Pinsky, St.M., Colmann, M., Arnold, M.J., Frohman, L.A.: Thyroid cancer occurring as a late consequence of head- and neck irradiation. Evaluation of 1056 patients. New Engl. J. Med. **294**, 1019–1025 (1976)

Franssila, K.O.: Is the differentiation between papillary and follicular thyroid carcinoma valid? Cancer **32**, 853–864 (1973)

Fukunaga, F.H., Yatani, R.: Geographic pathology of occult thyroid carcinomas. Cancer **36**, 1095–1099 (1975)

Gordon, D.A., Hill, F.M., Ezrin, C.: Acromegaly: a review of 100 cases. Canad. Med. Ass. J. **87**, 1106–1109 (1962)

Gorlin, R.J., Vickers, R.A.: Multiple mucosal neuromas, phaeochromocytoma, medullary carcinoma of the thyroid and marfanoid body build with muscle wasting: reexanimation of a syndrome of neural crest malmigration. Birth Defects **7**, 69–71 (1971)

Hajjar, E.T., Salti, I.S.: The co-existence of parathyroid and thyroid disease. I. Primary hyperparathyroidism and thyroid carcinoma. Leb. Med. J. **26**, 241–245 (1973)

Hakama, M.: Different world thyroid cancer rates. In: Thyroid cancer. UICC Monograph Series, Vol. 12. Hedinger, Ch.E., Ed. pp. 66–71, Berlin, Heidelberg, New York: Springer 1969

Hamwi, G.J., Skillman, Th.G., Tufts, K.C.: Acromegaly. Am. J. Med. **29**, 690–699 (1960)

Harrison, T.S., Thompson, N.W.: Multiple endocrine adenomatosis I and II. Curr. problems in surgery. Chicago: The University of Chicago Press 1975

Heimann, P., Nilsson, O., Hansson, G.: Parathyroid and thyroid disease. II. Thyroid disease connected with hyperparathyroidism. Acta Chir. Scand. **135**, 143–146 (1970)

Heinze, H.G., Pichlmaier, H.: Diagnostik und Therapie der Struma maligna. Internist **13**, 148–159 (1972)

Hempelmann, L.H.: Radiation exposure and thyroid cancer in man. In: Thyroid cancer. UICC Monograph Series, Vol. 12. (Hedinger, Ch.E., Ed.) Berlin, Heidelberg, New York: Springer 1969

Ingbar, S.H., Woeber, K.A.: The thyroid gland. In: Textbook of Endocrinology. (Williams, R.H., Ed.), pp. 95–233. Philadelphia, London, Toronto: Saunders 1974

Kairaluoma, M.I., Heikkinen, E., Mokka, R., Huttunen, R., Larmi, T.K.I.: Non-medullary thyroid carcinoma in patients with parathyroid adenoma. Acta Chir. Scand. **142**, 447–449 (1976)

Kaplan, L., Katz, A.D., Ben-Isaac, C., Massry, Sh.G.: Malignant neoplasms and parathyroid adenoma. Cancer **28**, 401–407 (1971)

Keiser, H.R., Beaven, M.A., Doppman, J., Wells, S., Buja, L.M.: Sipple's syndrome: medullary thyroid carcinoma, phaeochromocytoma, and parathyroid disease. Ann. Intern. Med. **78**, 561–579 (1973)

Kind, H.P.: Die Häufigkeit der Struma maligna im Sektions- und Operationsgut des Pathologischen Instituts der Universität Zürich von 1900 bis Mitte 1964. Schweiz. Med. Wschr. **96**, 560–568 (1966)

Kracht, J., Altenähr, E.: Peripheres, disseminiertes endokrines Zellsystem (APUD-System) und Schilddrüse. Deutsch. Med. Wschr. **102**, 1196–1200 (1977)

Krementz, E.T., Yeager, R., Hawley, W., Weichert, R.: The first 100 cases of parathyroid tumors from Charity Hospital of Louisiana. Ann. Surg. **173**, 872–883 (1971)

Laing, V.O., Frame, B., Block, M.A.: Associated primary hyperparathyroidism and thyroid lesions. Arch. Surg. **98**, 709–712 (1969)

Lancer, St. R., Bowser, E.N., Hargis, G.K., Williams, G.A.: The effects of growth hormone on parathyroid function in rats. Endocrinol. **98**, 1289–1293 (1976)

Lietz, H.: Pathologische Anatomie der Schilddrüsentumoren. In: Schilddrüse 1973 (Schleusener, H., Weinheimer, B., eds.) pp. 60–69, Stuttgart: Thieme 1974

Lindsay, St., Nichols, C.W., Chaikoff, I.L.: Induction of benign and malignant thyroid neoplasma in the rat. Arch. Path. **81**, 308–316 (1966)

LiVolsi, V.A., Feind, C.R.: Parathyroid adenoma and nonmedullary thyroid carcinoma. Cancer **38**, 1391–1393 (1976)

Malette, L.E., Bilezikian, J.P., Heath, D.A., Aurbach, G.D.: Primary hyperparathyroidism: clinical and biochemical features. Medicine **53**, 127–146 (1974)

Matovinovic, J., Leahy, M.S., Armstrong, W.F., Hill, H.C.: The effect of environment on the growth and function of rat thyroid transplant tumors. In: Thyroid neoplasia. (Young, St., Inman, D.R., eds.) pp. 211–248, London, New York: (1968)

Melicow, M.M.: One hundred cases of pheochromocytoma at the Columbia – Presbyterian Medical Center, 1926 – 1976. Cancer **40**, 1987–2004 (1977)

Money, W.L., Rawson, R.W.: Factors influencing malignancy versus benignancy of thyroid neoplasms in man and experimental animals II – experimental animals. In: Thyroid neoplasia. (Young, St., Inman, D.R., eds.), pp. 179–199, London, New York: 1968

Moon, H.D., Simpson, M.E., Li Ch.H., Evans, H.M.: Neoplasms in rats treated with pituitary growth hormone. Cancer Res. **10**, 364–370 (1950)
Moon, H.D., Simpson, M.E., Li Ch.H., Evans, H.M.: Neoplasms in rats treated with pituitary growth hormone. I. Pulmonary and lymphatic tissue. Cancer Res. **10**, 297–308 (1950)
Mortensen, J.D., Woolner, L.B., Bennett, W.A.: Gross and microscopic findings in clinically normal thyroid glands. J. Clin. Endocrinol. Metab. **15**, 1270–1280 (1955)
Mukhtar, E.D., Alexander, L., Wilkinson, R., Appleton, D., Hall, R.: Thyroid function in acromegaly. Lancet **2**, 279–283 (1971)
Nemec, J., Soumar, J., Zamrezil, V., Pohunkova, D., Motlik, K., Mirejovsky, P.: Familial occurrence of differentiated (non-medullary) thyroid cancer. Oncology **32**, 151–157 (1975)
Neracher, H., Hedinger, Ch.: Klassifizierung der Schilddrüsenmalignome nach der Nomenklatur der WHO 1974. Schweiz. Med. Wschr. **105**, 1000–1006 and 1052–1056 (1975)
Ogburn, P.L., Black, B.M.: Primary hyperparathyroidism and papillary adenocarcinoma of the thyroid: report of four cases. Proc. Staff Meet. Mayo Clin. **31**, 295–298 (1956)
Pearse, A.G.E.: The diffuse endocrine (paracrine) systeme: Feyrter's concept and its modern history. Verh. dtsch. Ges. Path. **61**, 2–6 (1977)
Pearse, A.G.E., Takor, T.T.: Neuroendocrine embryology and the APUD concept. Clin. Endocrinol. **5** Suppl., 229s–244s (1976)
Petro, A.B., Hardy, J.D.: The association of parathyroid adenoma and non-medullary carcinoma of the thyroid. Ann. Surg. **181**, 118–119 (1975)
Ries, P.: Eine Kasuistik zum Wermer-Syndrom. Polyadenomatose des Endokriniums. Verh. dtsch. Ges. Path. **58**, 569 (1974)
Robertson, D.M., Sizemore, G.W.: Thickened corneal nerves as a manifestation of multiple endocrine neoplasia. Trans. Am. Acad. Ophtalmol. Otolaryngol. **79**, OP 772–787 (1975)
Saeger, W.: Die Hypophysentumoren. Stuttgart, New York: Fischer, 1977
Schimke, R.N.: Multiple endocrine adenomatosis syndromes. Adv. Intern. Med. **21**, 249–265 (1976)
Schneider, A.B., Favus, M.J., Stachura, M.E., Arnold, J., Arnold, M.J., Frohman, L.A.: Incidence, prevalence and characteristics of radiation-induced thyroid tumors. Am. J. Med. **64**, 243–252 (1978)
Siebenmann, R.E., Steiner, H., Uehlinger, E.: Die pathologische Morphologie der endokrinen Regulationsstörungen. In: Handbuch der allgemeinen Pathologie. Endokrine Regulationsstörungen. (Altmann, H.W., Ed.), Vol. 8. Berlin, Heidelberg, New York: Springer 1971
Sipple, J.H.: The association of phaeochromocytoma with carcinoma of the thyroid. Am. J. Med. **31**, 163–166 (1961)
Spitalnik, P.F., Strauss II, F.H.: Patterns of human thyroid parenchymal reaction following low-dose childhood irradiation. Cancer **41**, 1098–1105 (1978)
Steiner, A.L., Goorman, A.D., Powers, S.R.: Study of a kindred with phaeochromocytoma, medullary thyroid carcinoma, hyperparathyroidism and Cushing's disease: multiple endocrine neoplasia, Type 2. Medicine **47**, 371–409 (1968)
Thomas, C., Bollmann, R., Christov, K.: Pathogenese und Morphologie der Schilddrüsentumoren bei der Ratte. In: Handbuch der allgemeinen Pathologie. (Altmann, H.W., Ed.), Vol. 6, pp. 769–837. Berlin, Heidelberg, New York: Springer 1975
Trout, H.H., Mulder, D.G.: Surgery for parathyroid adenoma. Arch. Surg. **105**, 67–70 (1972)
Uehlinger, M.: Primärer Hyperparathyreoidismus und papilläres Schilddrüsencarcinom. Schweiz. Med. Wschr. **105**, 1547–1552 (1975)
Underdahl, L.O., Woolner, L.B., Black, B.M.: Multiple endocrine adenomas: report of 8 cases in which the parathyroids, pituitary and pancreatic islets were involved. J. Clin. Endocrinol. Metab. **13**, 20–47 (1953)
Weichert, R.F.: The neural ectodermal origin of the peptide-secreting endocrine glands. Am. J. Med. **49**, 232–241 (1970)
Welbourne, R.B.: Current status of the apudomas. Ann. Surg. **185**, 1–12 (1977)
Wermer, P.: Genetic aspects of adenomatosis of endocrine glands. Am. J. Med. **16**, 363–371 (1954)
Wermer, P.: Endocrine adenomatosis and peptic ulcer in a large kindred. Am. J. Med. **35**, 205–212 (1963)
Woolner, L.B., Beahrs, O.H., Black, B.M., McConahey, W.M., Keating, F.R.: Classification and prognosis of thyroid carcinoma. Am. J. Surg. **102**, 354–387 (1961)

Received July 17, 1978