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Abstracts From the Third International Workshop on MEN 2

Diagnostic Relevance of Calcitonin Gene Products in Medullary Thyroid Carcinoma Patients

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Protein products of the calcitonin (CT) and CT gene-related peptide (CGRP) have been examined in the circulation of normal subjects and medullary thyroid carcinoma (MTC) patients. Non-cross-reacting antibodies raised to the human amino-terminal flanking peptide of the CT gene, PAS-57, to CT and to CGRP were used to characterize and quantify the circulating peptides in normal subjects. Serum was obtained before and 1.5 minutes after 1-minute intravenous calcium infusions (2 mg/kg body weight). PAS-57 was identified for the first time in the serum of normal subjects and MTC patients. On high-performance liquid chromatography, a major peak of PAS-57 eluted with the retention time of synthetic human PAS (1-57). Molecular components of circulating CGRP and of CT in normal subjects had the same retention times as synthetic human CGRP (1-37) and CT (1-32) and of large molecular weight precursor proteins. In normal men basal levels of PAS-57 (194 ± 27 pgeq/mL [mean ± SEM]) and of CT (26.4 ± 5.0 pgeq/mL) were higher than in normal women (PAS-57: 102 ± 10 pgeq/mL; CT: 17.0 ± 3.2 pgeq/mL). In response to intravenous calcium, PAS-57 and CT increased fourfold in normal men and twofold in normal women ($P < 0.01$). Circulating levels of CGRP were 9.5 ± 1.6 pgeq/mL in normal male subjects and were 5.5 ± 0.9 pgeq/mL in normal females but did not increase after intravenous calcium. In MTC patients with raised CT levels (3.54 ± 1.66 ngeq/mL), the ratio of circulating PAS-57 and CT (25.0 ± 2.5) was fourfold higher than in normal subjects (both intravenous calcium and pentagastrin-stimulated PAS-57 and CT levels). CGRP was rarely increased in MTC patients.

In conclusion, PAS-57 represents the predominant CT/CGRP gene-derived product in the circulation of normal subjects and of MTC patients. Much like CT, PAS-57 and CGRP are higher in normal men than in women, and unlike CGRP, PAS-57 and CT levels are stimulated by intravenous calcium in normal subjects as well as in MTC patients.

Note: We are indebted to J.J. Body (Free University, Brussels, Belgium), C. Calmettes (University of Paris, France), M.A. Dambacher (University of Zurich, Switzerland), C.J.M. Lips (University of Utrecht, The Netherlands), and F. Raue (University of Heidelberg, West Germany) for samples from MTC patients.

Chromogranin A in Familial Pheochromocytoma

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Incidence of pheochromocytoma is clearly elevated in multiple endocrine neoplasia type 2A (MEN 2A) and the von Hippel-Lindau syndrome (HLS), both autosomal-dominantly inherited disorders. Until recently there has been no simple screening test with high sensitivity and specificity. We studied a large family with HLS including 23 descendants, measuring plasma chromogranin A and comparing the results with other tests. The results are as follows:

Test	Sensitivity	Specificity
Chromogranin A	100% (5/5)	100% (12/12)
Urinary norepinephrine	100% (5/5)	100% (9/9)
Urinary epinephrine	20% (1/5)	100% (9/9)
Urinary vanillylmandelic acid	40% (2/5)	100% (7/7)
Ultrasound	100% (5/5)	82% (9/11)
Computed tomography	100% (5/5)	—
Magnetic resonance imaging	100% (5/5)	—
Meta-iodo-benzylguanidine	100% (5/5)	100% (3/3)

Note: Normal ranges are 15 to 50 ng/mL for chromogranin A, <80 μg/d for norepinephrine, <20 μg/d for epinephrine, and <8 mg/d for vanillylmandelic acid.

The fractions in parentheses indicate number of subjects.

In this kindred elevations of chromogranin A were sensitive and specific in detecting familial pheochromocytoma, with diagnostic values as good as or better than those achieved by urinary catecholamines or their metabolites, or imaging methods. Cooperation is offered for measuring chromogranin A in MEN 2A families. In subjects found to have elevated chromogranin A, medullary thyroid cancer must be excluded since it can also cause chromogranin A elevations (1).

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Pentagastrin Test in Sporadic Pheochromocytoma Compared with Pheochromocytoma in MEN 2 Syndrome

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Raue (1979) and Cordes (1982) have shown that calcitonin (CT), carcinoembryonic antigen, and other substances found in pheochromocytomas can be detected both immunohistochemically and biochemically. The question arises as to whether the CT from pheochromocytomas is secreted into serum in measurable amounts and whether this process can be stimulated.

We performed a pentagastrin test preoperatively in 11 patients with sporadic pheochromocytoma and in two patients with sporadic adrenal hyperplasia and compared the results with 11 patients with multiple endocrine neoplasia type 2 (MEN 2) before and after adrenalectomy. In none of the first group could the base value be stimulated. The values were lower than 0.1 ng/mL in 11 of the 13 patients. In six cases of the MEN 2 group, the medullary thyroid carcinoma (MTC) was resected at the same time as the pheochromocytoma. In these cases it could not be decided whether the CT arose from MTC only or also from pheochromocytoma as well. In the five other patients, CT was significantly elevated before adrenalectomy and did not decrease postoperatively. In only one case was the postoperative stimulated CT slightly reduced, but the pentagastrin test did not become negative.

These data suggest that in cases of sporadic pheochromocytoma serum CT cannot be increased by pentagastrin stimulation and that in the MEN 2 syndrome a positive pentagastrin test results from the thyroid tumor and not the pheochromocytoma.

Diagnostic Performance of an Immunoradiometric Assay for Calcitonin

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We have used a monoclonal immunoradiometric "sandwich" type assay (IRMA) for the measurement of monomeric calcitonin (mCT) in serum of patients with medullary thyroid carcinoma (MTC). The assay, a modification of a commercial kit (CIS, Saclay, France) using sequential incubation, has a sensitivity of 0.5 pg/mL, and the results correlate highly with data obtained after extraction of serum mCT on C18 silica cartridges. Reference values were < 6 pg/mL (95th percentile). Of 11 patients with surgically proven MTC, five had normal postoperative serum levels of mCT (range < 0.5 to 3.8 pg/mL) and six had elevated levels (range 44 to > 270 pg/mL). With a conventional competitive radioimmunoassay (INC, Stillwater, MN; reference range < 100 pg/mL), seven patients had normal levels (range 22 to 75 pg/mL) and four had elevated levels (range 132 to $> 1{,}000$ pg/mL). Stimulation with pentagastrin led to similar increases in both assays. One patient showed a decrease from 85.1 to 56.5 pg/mL one month after surgical removal of bilateral pheochromocytoma. The adrenal surgery was performed six years after total thyroidectomy for MTC. We conclude that basal levels of mCT by IRMA have predictive value for the follow-up of MTC patients.

Molecular Genetics of MEN 2A

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Multipoint analysis in our multiple endocrine neoplasia type 2A (MEN 2A) families provides strong support for the order TB10.34-MEN 2A-(RBP3, MCK2)-TBQ16 across the centromeric region of chromosome 10, where the distance TB14.34-RBP3 is F 8cM, M 0cM; F = M 3cM. Somatic cell hybrids containing 10q only (64034p6), 10pter-q11.2 (TG3), and 10q 11.2-qter (TK2) assign TB14.34 to 10p and RBP3 to 10q below the q11.2 breakpoint. Recombinants with these flanking markers are all either nonrecombinant or uninformative with the centromere probe p α 10RP8, so we cannot assign MEN 2A unequivocally to the long or short arm. We have made cosmid libraries from irradiation hybrids containing fragments of chromosome 10 and are mapping these cosmids by linkage and in somatic cell hybrids. One cosmid, MEN 203, which maps below the q11.2 breakpoint but between RBP3 and TB14.34 by linkage, shows no recombinants so far in our families. Current two-point lod scores between MEN2A and pericentromeric markers in our family set are: RBP3 28.51 $\theta m = 0$, $\theta f = 0.03$; MCK2 29.43 $\theta m = 0$, $\theta f = 0.02$; TB14.34 9.86 $\theta m = 0$, $\theta f = 0.08$; MEN 203 12.45 $\theta m = 0$, $\theta f = 0$; TBQ16 8.35 $\theta m = 0$, $\theta f = 0$. Only one of 42 tumors so far shows allele loss on chromosome 10; there were ten of 27 losses on 1p, two of 11 on 13q (one of two sporadic pheochromocytomas; one of six medullary thyroid carcinoma [MTC] in MEN 2A) and three of 13 on 22q (two of three pheochromocytomas, one sporadic, one MEN 2A; and one of nine MTC in MEN 2A). The genetic mechanism of tumor development in MEN 2A may be more complex than that proposed for retinoblastoma.

Tight Linkage Between Chromosome 10 Alpha Satellite DNA and the Gene for Multiple Endocrine Neoplasia Type 2A

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Since the locus for multiple endocrine neoplasia type 2A (MEN 2A) was mapped to the chromosome 10 pericentromeric region, extensive research efforts have been directed to the genetic and physical mapping of this region. We recently constructed a 10-locus

fine resolution linkage map of the chromosome 10 pericentromeric region (1). This map, covering a region of 70 cM in length and extending from D10S24 (at 10p12.2-13) to D10S3 (at 10q21-23) with the majority of its interlocus intervals being no more than 7% recombination units apart, has provided a fine framework to localize more precisely the MEN 2A gene to a small region (10 cM) in the vicinity of the centromere bounded by FNRB and RBP3 on either side (2,3). Several restriction fragment length polymorphisms (RFLPs) revealed by a chromosome 10 alpha satellite DNA probe (pα10RP8) have been characterized which can be unambiguously scored and serve as excellent genetic markers for the D10Z1 locus in the centromeric region (4). Pairwise linkage analyses in six MEN 2A kindreds demonstrated tight linkage between the chromosome 10 alpha satellite RFLPs and the MEN 2A gene; peak lod score of 12.02 being found at $\theta = 0$ and one lod unit support interval being 0 to 4 cM. Close linkage between D10Z1 and other chromosome 10 pericentromeric markers was also demonstrated by significantly positive lod scores. This highly polymorphic marker should facilitate further efforts for more detailed molecular studies of the MEN 2A gene and should prove valuable for genetic counseling and carrier status determination in MEN 2A families (5).

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Nuclear DNA Content of Medullary Thyroid Carcinoma in a Large Family with the MEN 2A Syndrome

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DNA aneuploidy has been associated with metastatic tumors and found to be an independent risk factor in medullary thyroid carcinoma (MTC). DNA content of MTC in the multiple endocrine neoplasia type 2A (MEN 2A) syndrome is most often found to be diploid. Flow cytometry of MTC was performed in a large family with the MEN 2A syndrome. Six of eight siblings of the index case and eight of nine members of the next generation had MTC. Five patients (aged 10 to 27 years) were without detectable lymph node metastases. After total thyroidectomy, plus excision of affected lymph nodes, all patients received an ablative dose of ^{131}I. Eight years after thyroidectomy all patients are alive and free of signs and symptoms of MTC. Six patients had a normal pentagastrin (PG) test after operation; five of them still have normal PG tests. In the index patient the postoperative calcitonin levels gradually decreased and have remained in the normal range, even after PG stimulation, for five years. Flow cytometry of paraffin-embedded tissue could be performed in 12 of the 15 patients. The majority of all tumors (nine) showed a rather broad unimodal G1 peak ($CV > 5.5$) which was classified as peridiploid. Only two MTCs were clearly aneuploid (DNA index = 1.20). In one patient (index case) the tumor was diploid with polyploidization. These results indicate that the majority of the MTC patients in this family with the MEN 2A syndrome have no or limited ploidy aberrations in their tumors, which correlates well with the favorable prognosis of hereditary MTC.

Registry of Medullary Thyroid Carcinoma (MTC) in Germany: The German MTC Study Group

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A registry for medullary thyroid carcinoma (MTC) in Germany was set up by the German MTC Study Group in 1988. Reliable screening tests exist for the hereditary varieties of MTC (multiple endocrine neoplasia [MEN] types 2A and 2B), and if the disease is detected by family screening in an early stage, curative surgery is possible.

Presently 424 patients (246 females and 178 males) with MTC have been reported by 17 cooperative centers. The mean age at diagnosis was 45.8 years, and 25% (n = 108) had hereditary forms, most of them MEN 2A (n = 77). Thirteen are MEN 2B and 18 belong to the hereditary variety with other endocrinopathies. The mean ages at diagnosis for MEN 2A and MEN 2B were 36.6 and 26.9 years, respectively. As 34 patients have been diagnosed annually since 1982, nearly 25% of all expected cases of MTC in Germany have been diagnosed. A total of 293 patients were followed for a period of 0.1 to 20.5 years (median 3.9 years). The five- and ten-year survival rates were 79.2% and 55.2% for all patients, 91.2% and 80.2% for MEN 2A patients, 70.0% and 46.7% for MEN 2B patients, and 65.0% and 27.2% for sporadic cases, respectively. Women had a significantly better prognosis than men ($P < 0.005$), and sporadic MTC had a worse prognosis than inherited MTC ($P < 0.03$). A total of 217 patients are still alive, 77 were cured with normal serum calcitonin levels, 58 are living with pathologically elevated calcitonin levels but no evidence of disease, 56 are living with clinical evidence of tumor, and 76 patients died (57 deaths from MTC, seven deaths from other causes, 12 unknown). This registry will provide a basis for further collaborative diagnostic or therapeutic studies.

Thyrotropin-Releasing Hormone Enhances Calcitonin Secretion in Medullary Thyroid Carcinoma

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Calcitonin (CT) is a crucial tumor marker in medullary thyroid carcinoma (MTC) and multiple endocrine neoplasia type 2 (MEN 2). Various tests are in use for provocation of CT secretion in occult MTC. Increased CT secretion after administration of thyrotropin-releasing hormone (TRH) was reported recently in two patients (1).

Eleven patients with known MTC and elevated serum CT levels (four of 11 of MEN 2 families, one of four prior to surgery for pheochromocytoma) received increasing doses of 20, 50, 100, 200, 500, and 1,000 μg TRH intravenously in 2-minute intervals. Thyrotropin-stimulating hormone (TSH) and CT levels were measured at 2-minute intervals and at 30 minutes after the last injection.

Basal serum CT ranged from 0.66 to 80.4 (mean 15.8) ng/mL. In all six patients with basal values above 2 ng/mL, CT increased by a factor of 1.4 to 3.6 (mean 2.1) of baseline. In five of these the maximal CT value was reached within eight minutes (350 μg total dose of TRH). Five patients with basal CT below 2 ng/mL had no significant response. These two groups did not differ regarding occurrence of MEN 2, concentration of carcinoembryonic antigen, or TSH response to TRH (suppressed in nine patients due to concomitant thyroxine medication). In normal controls CT was unchanged in the normal range. TRH exhibits a TSH-independent, probably direct effect on CT secretion in MTC patients, particularly in those with higher basal values. Further research is needed to evaluate the pathophysiological and prognostic significance of this finding.

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DNA Linkage Analysis for Early Diagnosis of Multiple Endocrine Neoplasia Type 2A

H.P.H. Neumann,* O.A. Muller, B.A.J. Ponder, C.G.P. Mathew, and H. Telenius (*Medical Clinic, University of Freiburg, West Germany)

The gene causing multiple endocrine neoplasia type 2A (MEN 2A) has recently been assigned to the pericentromeric region of chromosome 10. We performed linkage analysis using DNA markers closely related to the locus on chromosome 10: MCK2 (1), retinol binding protein cDNA (2), and cIBIRBP-9 (Mathew et al, unpublished data). Available for the study were EDTA blood samples from two families. The analysis was positive in the two asymptomatic offspring in one family whereas the markers were not informative in the other family. Genetic distance between the informative marker of the first family and the MEN 2A gene is 2 cM, ie, a likelihood of 98% for the gene carrier status of the two children aged 11 and 7 years. Clinical investigations (including pentagastrin test, plasma catecholamines, and 24-hour urine catecholamines and parathormone) of these children have been negative so far.

We recommend early linkage analysis for establishing the genetic status in offspring of MEN 2A families to focus further screening on those who are predicted to be gene carriers.

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Cytogenetic Characterization of Two Human and Three Rat Medullary Thyroid Carcinoma Cell Lines

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Cytogenetic studies of hereditary tumors, eg, retinoblastoma, have been used to localize the gene(s) responsible for the phenotypic effect. Once localized, molecular characterization of the gene(s) can contribute to understanding the underlying disease mechanism.

Cytogenetic characterization of two human medullary thyroid carcinoma (MTC) cell lines and three rat MTC cell lines has been accomplished. The human cell lines studied were the TT cell line, previously reported, and an unpublished cell line, MZ-CRC-1, derived from a malignant pleural effusion from a patient with metastatic MTC. The sporadic or hereditary nature of this latter tumor is unknown. Analysis of the cytogenetic changes present in these cell lines showed both human cell lines to contain abnormalities of chromosomes 1p, 3p, 5q, 7q, 9p, 10 (pericentromeric), and 11p. The rat MTC cell lines characterized cytogenetically were the CA-77, 6-23C_6, and the 44-2 cell lines. Karyotypically, the 6-23C_6 and 44-2 cell lines are related. Common to the two unrelated lines (the CA-77 and the 6-23C_6/44-2 cell lines) are abnormalities of chromosomes 3 and 7. Comparison of human and rodent gene maps should help determine the common gene changes present in the medullary thyroid cancer cell lines of these species.

Combination Chemotherapy of Advanced Medullary Thyroid Carcinoma

H. Scherubl,* F. Raue, and R. Ziegler (*Department of Internal Medicine, University of Heidelberg, West Germany)

Medullary thyroid carcinoma (MTC) generally has a good prognosis unless the disease is far advanced and there are distant metastases. We evaluated the effectiveness and toxicity of doxorubicin (50 mg/m^2), cisplatin (60 mg/m^2), and vindesine (3 mg/m^2), repeated every three weeks, in patients with advanced MTC.

Ten patients, in whom the conventional treatment modalities (surgery including reoperation and in some instances radiotherapy) had been exhausted and who suffered from progressive disease, were included in the study. The median age at the start of the chemotherapy was 43.5 years (range 18 to 58 years). The male:female ratio was 7:3. Survival was measured from the beginning of chemotherapy. Only one partial remission (PR), which lasted for 15 months, was seen. Three patients had progressive disease (PD) and seven had no change (NC) in their condition. At the time of this analysis the median survival was 16 months (range 5 to 28 months) for the patients with PD and 37 months (range 4 to 90 months) for the patients with NC; the one patient with PR died 24 months after the start of chemotherapy. The tumor markers calcitonin and carcinoembryonic antigen proved to be valuable parameters for assessing response. Toxicity was considerable. Nausea and vomiting occurred in virtually all patients, and myelodepression and alopecia occurred in the majority of patients. Thus the described combination chemotherapy failed to be superior to the usually applied doxorubicin monotherapy in patients with advanced MTC.

Receptors and Actions of Sex-Steroid Hormones in Human Medullary Thyroid Carcinoma

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Several lines of evidence point to a possible relationship between sex-steroid hormones (SSH) and medullary thyroid carcinoma (MTC). On one hand, for a given MTC stage, the prognosis is worse for males than for females; on the other hand, estradiol (E_2)-specific receptors (R) have been found in the human MTC cell line TT. This study was undertaken to analyze further the relationship of E_2, progesterone (Pg), and dihydrotestosterone (DHT) with human MTC. In MTC obtained from one female and one male patient at surgery SSH-R was analyzed by the following methods: steroid binding analysis (SBA) of E_2, Pg, and DHT; enzyme immunoassay (EIA) for E_2 and Pg; and immunocytoanalysis (ICA) for the detection of nuclear receptors of E_2 and Pg. The TT cell line was also used to study the in vitro effects of the SSH on calcitonin (CT) secretion by the culture cells. High affinity (Kd = 1×10^{-10}M) E_2R were found by SBA although in low concentrations (7 fm/mg protein and 5 fm/mg protein, by SBA and EIA, respectively). Nuclear E_2R were not found (by ICA) in any of the studied tissues. PgR (Kd = 1.5×10^{-9}M) were found in higher concentrations in female than in male tissue (117 fm/mg protein and 107 fm/mg protein versus 33 fm/mg protein and 13 fm/mg protein, by SBA and EIA, respectively). Both tissues had nuclear PgR by ICA. DHT receptors were also positive by SBA in both tissues (Kd = 0.88×10^{-9}M and B max 4-10 fmol/mg protein). Addition of physiological and supraphysiological concentrations of the three SSH (10^{-11} to 10^{-7}M) to cultured TT cells in RPMI media devoid of phenol-red produced a significant stimulation of the CT secretion by the cells to the culture media. These results support the hypothesis that MTC is a target tissue for SSH, E_2, Pg, and DHT.

Clinical, Histological, and Immunocytochemical Findings in Pheochromocytoma

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Adrenalectomy specimens containing normal (n = 3), hyperplastic (n = 4), or neoplastic (n = 55) medullary tissue were investigated by conventional histology and immunocytochemistry. Morphologic findings were compared with preoperative symptoms and follow-up data. Of 55 pheochromocytomas, 14 were neoplasms inherited in the multiple endocrine neoplasia type 2 setting. Five of the sporadic pheochromocytomas followed a malignant course. Three benign and three malignant pheochromocytomas lacked endocrine activity.

Tumor weights of more than 100 g were recorded for each of the malignant pheochromocytomas but only for five of 50 clinically benign pheochromocytomas. Except for three malignant neoplasms, all tumors exhibited the characteristic cellular and structural pattern of adrenal paragangliomas. Increased mitotic activity was observed with seven benign lesions and with each of the malignant lesions. Three malignant pheochromocytomas could not be distinguished histologically from adrenocortical carcinoma. However, immunocytochemistry using neuroendocrine markers (NSE, Chr A, synaptophysin, etc) resulted in definite typing of all pheochromocytoma cases. Regarding the detection of S-100-protein positive sustentacular cells and the expression of intermediate filament proteins and of various polypeptide hormones (calcitonin, CGRP a-hCG), no differences were seen between sporadic and hereditary or between benign and malignant tumors. Positivity for tyrosine hydroxylase was strictly correlated to the presence of endocrine symptoms. Neither conventional histologic nor immunocytochemical studies allowed definite conclusions on the genetic background or the malignant potential of an individual pheochromocytoma.

Imaging Techniques in Patients with MEN 2

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In patients with multiple endocrine neoplasia type 2, imaging procedures are needed to detect neoplasias, ie, medullary thyroid cancer (MTC), pheochromocytoma, hyperparathyroidism (HPT), as well as organ involvement in intestinal ganglioneuromatosis. Hormone determinations in serum, which serve as screening procedures for MTC, pheochromocytomas, and HPT, are generally more sensitive for primary diagnosis than are imaging techniques. However, because prognosis depends on early surgical intervention, suspected tumors need to be localized as precisely as possible.

Imaging techniques are categorized into morphological methods (such as sonography, conventional x-ray, computed tomography, magnetic resonance imaging [MRI]) and scintigraphic methods with different tracers to image tumor blood flow or metabolism. For primary diagnosis, sonography is best suited to localize neck lesions in suspected MTC and HPT. In the case of lymph node involvement of MTC, sonography should be combined with computed tomography or MRI to detect mediastinal lesions. To localize pheochromocytomas, the ^{123}I meta-iodo-benzylguanidine (MIBG) scintigraphic method seems to be at least as sensitive as computed tomography or MRI.

In follow-up of MTC, residual or recurrent tumor and/or lymph nodes in the neck as well as distant metastases need to be detected as early as possible. A variety of radiopharmaceuticals such as ^{99m}Tc phosphonates, ^{201}Tl, ^{99m}Tc (V) dimercaptosuccinic acid (DMSA), ^{123}I MIBG, and radiolabeled antibodies against calcitonin or carcinoembryonic antigen (CEA) have been proposed for this difficult task. Today, ^{99m}Tc (V) DMSA and anti-CEA antibodies seem to be the most promising scintigraphic methods. However, these methods for functional imaging only supplement sonography, which is best suited for routine follow-up. For recurrent or metastatic pheochromocytomas, ^{123}I MIBG may be the scintigraphic method of choice.

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^{99m}Tc-Methoxyisobutyl Isonitrile (^{99m}Tc-Sestamibi) Uptake by Metastases from Medullary Thyroid Carcinoma

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^{99m}Tc-Sestamibi is a new radiopharmaceutical which is mainly used in nuclear cardiology for detection of ischemic heart disease. Tissue uptake of this agent is related to the blood flow. Increased ^{99m}Tc-Sestamibi uptake by some tumors has previously been reported. Five patients who have had total thyroidectomy for medullary thyroid carcinoma (MTC) were prospectively studied with ^{99m}Tc-Sestamibi scan. These patients were referred because of abnormally increased plasma calcitonin levels postoperatively. Anterior cervico-thoracic views were obtained using a planar gamma camera at 5, 60, and 120 minutes after intravenous injection of 10 to 15 mCi of ^{99m}Tc-Sestamibi. Abnormal ^{99m}Tc-Sestamibi uptake was found in three of five patients. One patient had a focal increased uptake in the right cervical area. A lymph node invaded by MTC was located behind the right primitive carotid at surgery. In two other patients, abnormal uptake was seen on the left side of the trachea and in the mediastinum, respectively. Ultrasound study showed solid masses, and malignant cells were found on cytopuncture. In the remaining two patients, ^{99m}Tc-Sestamibi scan and other noninvasive imaging procedures were normal.

Accordingly, in three of five patients, metastases from MTC were localized with ^{99m}Tc-Sestamibi scan. It is possible that the uptake could be related to the vascularity of the tumor. More fundamental studies are needed, but these preliminary clinical data suggest that ^{99m}Tc-Sestamibi imaging can be useful in the evaluation of patients with MTC.

Surgical Aspects of MEN 2A

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Surgical management of patients with suspected or proven multiple endocrine neoplasia type 2 (MEN 2) syndrome comprises the following aspects: 1) preoperative diagnostic procedures, 2) surgical strategy in MEN 2-medullary thyroid carcinoma (MTC) and in MEN 2-pheochromocytomas, and 3) indications and operative procedure for one- or two-stage operations in patients with synchronous occurrence of MTC and pheochromocytoma. Eighteen patients with MEN 2A from six unrelated kindreds were surgically treated at our institution from 1976 to 1989. One young male patient (index case) died two years after thyroidectomy from metastasizing MTC. Two female patients are living with asymptomatic liver metastases of MTC 15 and 13 years after thyroidectomy; all other patients are living without clinically apparent metastases of MTC and without recurrence of surgically treated pheochromocytomas. No patient had evidence of malignant pheochromocytomas.

Our current surgical strategy in MEN 2A-MTC is total thyroidectomy and systematic central lymphadenectomy with bilateral systematic lymphadenectomy of the lateral cervical lymph node compartment. Mediastinal lymph nodes are dissected in patients with extensive neck disease and/or lymph node involvement of the mediastinum. Regarding pheochromocytomas, to avoid the need for adrenal cortex replacement therapy we prefer unilateral adrenalectomy compared to bilateral total adrenalectomy in cases of unilateral gland involvement. In patients with bilateral involvement of benign pheochromocytomas, alternative surgical procedures to bilateral total adrenalectomy such as unilateral total adrenalectomy combined with contralateral subtotal adrenalectomy or bilateral total adrenalectomy with autologous adrenal cortex transplantation have been applied. In three young patients with simultaneous manifestations of MTC and pheochromocytoma, one-stage operation without morbidity or mortality has been performed. Three additional patients were surgically treated in a two-stage operation because of advanced age and reduced general physical conditions.
