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Back Matter

Abstracts From the Fourth International Workshop on MEN

Reevaluation of Histologic Criteria for C-Cell Hyperplasia in MEN 2A Using Genetic Recombinant Markers

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In multiple endocrine neoplasia type 2A (MEN 2A), medullary thyroid carcinoma (MTC) is typically multicentric and bilateral. It is preceded by and arises in a background of C-cell proliferative changes histopathologically classified as diffuse and nodular C-cell hyperplasia (CCH). The localization of the MEN 2A gene to chromosome 10 now offers the opportunity to study the direct correlation of CCH with the genetic defect. Members of a kindred followed for 20 years and who underwent thyroidectomy with well-defined histopathologic C-cell proliferative changes ranging from mild diffuse CCH to MTC were studied using six different pericentromeric markers for chromosome 10. The probes used were 14,34, B14-34, MEN 203, TBQ 16, RBP9, and MEN 203W-1. Excellent correlation was found between C-cell proliferative abnormalities identified histopathologically and carrier state for this disorder detected by genetic linkage studies. However, in two cases with only mild diffuse CCH, the genetic linkage analyses were negative. Further studies are required to determine the significance of these findings.

The Clinical Implications of a Positive Calcitonin Test for C-Cell Hyperplasia in Genetically Unaffected Members of a Multiple Endocrine Neoplasia Type 2A Kindred

Rudy M. Landsvater,* Anne G. M. Rombouts, Gerard J. te Meerman, Joke M. Jansen, Marianne J. H. Berends, Rolf A. Geerdink, Albert Struyvenberg, Charles H. C. M. Buys, and Kees J. M. Lips (*Department of Internal Medicine, Utrecht University Hospital, Utrecht, the Netherlands)

Hyperplasia of the thyroidal C-cells precedes the development of medullary thyroid carcinoma (MTC) in multiple endocrine neoplasia type 2A (MEN 2A). The identification of an abnormal calcitonin (CT) level after a provocative stimulus has been widely used to diagnose this preneoplastic condition at an early stage in the evolution of MTC, when total thyroidectomy is likely to be curative.

In a large kindred at risk for the development of MEN 2A, with 23 proven gene carriers, we identified seven individuals with marked CT elevation after pentagastrin administration who were probably not gene carriers. Total thyroidectomy has been performed in five of these individuals and C-cell hyperplasia was found in each. Four were the offspring of a mother who is at risk for the development of MEN 2A but has normal C-cell provocation test results at age 64, making it unlikely that she is a gene carrier. Investigation of the father, who is not at risk, showed abnormal serum CT values after C-cell provocation testing over a period of 10 years without evidence of progressive elevation. None of the five individuals with proven C-cell hyperplasia developed other manifestations of MEN 2A. The application of genetic restriction fragment-length polymorphism testing utilizing DNA sequences closely linked to and flanking the MEN 2A gene demonstrated, with a greater than 99% likelihood, that none of the five patients from whom a blood sample was available was an MEN 2A gene carrier.

We conclude that C-cell hyperplasia due to some mechanism other than the presence of the MEN 2A gene can occur in MEN 2A kindreds. This finding will complicate diagnosis. Any subject unaffected by MEN 2A may have C-cell hyperplasia as a pathological or physiological condition and this condition may be hereditary in some cases. C-cell hyperplasia unrelated to MEN 2A may also predispose to MTC and may explain suggested nonlinkage with pericentromeric chromosome 10 markers in some MTC-only families. DNA analysis offers an important tool for distinguishing between MEN 2A gene carriers and unaffected individuals who may have a positive provocation test result.

Presymptomatic Screening of MEN 2A Families by DNA Analysis

L. Papi,* H. Telenius, M. A. Ponder, and B. A. J. Ponder (*CRC Human Cancer Genetics Group, Cambridge University, England)

The inherited cancer syndrome multiple endocrine neoplasia type 2A (MEN 2A) is transmitted as an autosomal dominant trait with incomplete penetrance. Because the gene of MEN 2A has been localized on chromosome 10 by genetic linkage, it is possible to use DNA analysis to identify gene carriers. We studied 15 MEN 2A families with seven different pericentromeric markers for chromosome 10 to predict the genetic status for MEN 2 of 59 members. Of these, 55 were informative for at least one marker and 11 were informative for flanking markers. We were not able to predict the genetic status for four individuals of two different families. In one family this was due to the unavailability of the DNA of the unaffected parent.

DNA analysis is a reliable test in the screening of MEN 2 families and offers several advantages to pentagastrin stimulus. However, since a small error rate in DNA analysis still exists, a combined application of biochemical and DNA screening is most accurate.

Mapping the Multiple Endocrine Neoplasia Type 2 Region: A Progress Report

Bruce Ponder,* Emily Gardner, Michael Jackson, Sara Mole, Julie Moore, Lois Mulligan, Laura Papi, Hakan Telenius, Alan Tunnacliffe, Doug Easton, Carol Jones, and Yusuke Nakamura (*CRC Human Cancer Genetic Research Group, Cambridge, England)

Because of the limited resolution of genetic linkage mapping in the multiple endocrine neoplasia type 2 (MEN 2) region, we have placed a major effort into the physical map and a search for deletions or rearrangements in germline and tumor DNA. Translocation chromosomes isolated in hybrids or by flow sorting have been used to assign DNA markers to five intervals in the pericentromeric region, and we are currently characterizing a large panel of radiation hybrids. Fifty-five cosmids (prepared from libraries from two earlier radiation hybrids selected to contain the pericentromeric region) and several genes have been assigned to these intervals, but mapping is complicated by diverged alphoid and satellite III repeats in the pericentromeric region. We are now attempting to make additional markers which map to the region so as to build a detailed map using yeast artificial chromosomes and pulsed field gel electrophoresis. None of the genes so far identified has proven to be the MEN 2 gene, nor have any abnormalities been detected in germline DNA or DNA from several tumors.

Identification and Characterization of a Gene at D10S94 in the Multiple Endocrine Neoplasia Type 2A Gene Region

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We have identified a candidate gene for multiple endocrine neoplasia type 2A (MEN 2A) at the D10S94 locus in proximal 10q11.2. D10S94 is tightly linked to the gene (MEN2A) and to date no recombinants between MEN2A and D10S94 have been observed. An evolutionarily conserved sequence from D10S94 was used as a probe to isolate cDNAs corresponding to a gene which we have termed AR1. The AR1 transcript is approximately 2.3 kb in length. The gene spans 11 kb and has at its 5′ end an unmethylated CpG island. It encodes a putative polypeptide of 416 amino acids with homology to nucleolin proteins. We have excluded AR1 as being the gene responsible for MEN 2A through sequence analysis of polymerase chain reaction-amplified exons from an MEN2A chromosome and its wild-type homologue from one MEN 2A patient. We are currently testing for sequence differences in AR1 which might be causally associated with two other dominantly inherited disorders, MEN 2B and medullary thyroid carcinoma (MTC) without pheochromocytomas. MEN 2B and MTC without pheochromocytomas share with MEN 2A the clinical feature of MTC and have been mapped to the same region of chromosome 10 as MEN 2A. Preliminary results suggest that MEN 2B and MTC without pheochromocytomas are not associated with mutations in AR1.

Management of Pheochromocytomas in the Pregnant MEN 2 Patient

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Adrenal pheochromocytomas are a variable expression of the multiple endocrine neoplasia type 2 syndrome. Although expressivity of this hormonal malignancy is usually consistent within kindreds, achieving the diagnosis can be difficult—especially in the pregnant patient. No matter how difficult, pre-term diagnosis of pheochromocytoma is important since it allows significant improvement in the maternal and fetal mortality rates—the maternal mortality drops from 58% to 12% and the fetal mortality rate drops from 50% to 40%. Major causes of mortality include the debilitating effects of long-term catecholamine excess prior to delivery and variable blood pressure response to the stress of pregnancy and, specifically, labor and delivery. In a recent attempt to improve outcome in a 29-year-old pregnant MEN 2A patient, an aggressive program was undertaken which included frequent prepartum assessments (including catecholamine testing), alpha adrenergic blockade, and elective caesarean section with bilateral adrenalectomy under continuous epidural analgesia. An uncomplicated pregnancy and operation yielded a healthy mother and child, both of whom were discharged home on the fourth postoperative day. The importance of frequent monitoring, alpha blockade, elective surgery, and epidural analgesia are stressed since all contribute to a positive result.

DMSA Versus Anti-CEA with the Avidin-Biotin System: Comparison Between Two Scintigraphic Methods for Early Diagnosis in Medullary Thyroid Carcinoma

G. Di Sacco, F. Muratori, U. Verga,* A. Grattieri, G. Paganelli, and A. Libroia (*Department of Endocrinology, Niguarda Hospital, Milan, Italy)

We studied medullary thyroid carcinoma (MTC) targeting in four patients with elevated basal and/or after stimulus serum calcitonin levels using anti-carcinoembryonic antigen (anti-CEA) immunoscintigraphy with the avidin-biotin system and (V)

dimercaptosuccinic acid (DMSA) scintigraphy. All patients showed normal serum CEA serum levels. Before thyroidectomy, an echotomography showed intrathyroidal nodules in three patients. Cytosmear of these nodes by fine needle aspiration was negative.

^{99m}Tc (V) DMSA scintigraphy gave negative responses in four patients. Anti-CEA scintigraphy gave positive responses in three of four cases. In two patients, the histologic study of the surgical specimen showed two intrathyroidal MTC foci (θ max 0.8 cm) plus C-cell hyperplasia (CCH). In the other two patients, the histologic diagnosis was CCH in one and colloid goiter in the other. A marked immunohistochemical positivity to CEA was found in the surgical specimen of the patients with MTC and CCH (negative in the patient with the colloid goiter which also had been negative to anti-CEA scintigraphy). Such data suggest that the anti-CEA immunoscintigraphy with the avidin-biotin system could have an important role in localizing MTC lesions.

Circulating Neuron-Specific Enolase in Patients with Medullary Thyroid Carcinoma

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Neuron-specific enolase (NSE) immunoreactivity has been reported as an additional marker for the immunocytochemical characterization of medullary thyroid carcinoma (MTC). We report the values of serum NSE levels in 46 patients at the primary diagnosis of MTC or at relapse. Mean values at first presentation were 19.9 ± 39.4 μg/L; in patients without neuroendocrine disease, the corresponding values averaged 8.2 ± 2.3 μg/L. Seventeen of 46 patients had NSE levels above the upper limits of normal (12.5 μg/L) at diagnosis. During the course of the disease, 24 patients were found to have NSE levels higher than those measured at the first analysis: 42.3 ± 60.9 μg/L. Eighteen of these 24 patients had levels above the upper limit. No relationship was found between the presence of multiple endocrine neoplasia type 2 or pure MTC and serum NSE levels, but a relationship was found between the highest NSE levels at any time during the course and a poor prognosis of the disease subsequently.

Regulation of Calcitonin Gene Transcription in Medullary Thyroid Carcinoma Cells

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The calcitonin (CT) gene is normally transcribed by thyroidal C-cells. The production of CT is enhanced in C-cell hyperplasia and in medullary thyroid carcinoma (MTC), whereas advanced stages of this tumor are often characterized by diminished CT production. We have studied transcriptional regulation of the CT gene by mapping functional cis-elements of transcription in the 5′ flanking DNA of the CT gene and examination of their activity by DNA transfer methods. Three elements of transcription were located between −1333 and −820 of the CT 5′ flanking DNA: a repressor at −1333 to −1090 and two enhancer elements at −1060 to −905. The enhancer elements were functional in the presence of repressor sequences in CT-positive MTC cell lines, but not in CT-negative cell lines. Removal of the repressor sequences revealed that the enhancer sequences were functional in a CT-negative metastatic MTC cell line; this modification failed to induce enhancer activity in nonendocrine, CT-negative cells. We hypothesize that CT gene transcription depends on the presence of a cell-specific transcription factor. The activity of this factor may be limited in metastatic MTC tumors, due to increased activity of a repressor protein.

Calcitonin Responses After Thyrotropin Releasing Hormone Injection in 14 Patients with Medullary Thyroid Carcinoma

F. Muratori, U. Verga,* G. Di Sacco, and A. Libroia (*Department of Endocrinology, Niguarda Hospital, Milan, Italy)

Medullary thyroid carcinoma (MTC) may occur as either sporadic or hereditary conditions and may be diagnosed using a specific and sensitive marker, calcitonin (CT). Not all the cases of MTC have elevated basal serum CT levels, but all exhibit an abnormally high level in response to a variety of secretagogues: pentagastrin (PG) and/or calcium infusion (Ca^{++}). Recently Nakamura et al have reported that thyrotropin releasing hormone (TRH) induced CT secretion in vitro and in vivo in two MTC patients. The present study was performed to assess the incidence of CT responsiveness to TRH in a group of 14 MTC patients, all PG and/or Ca^{++} responders. Eleven patients with multiple endocrine neoplasia type 2A (MEN 2A) (eight previously treated with total thyroidectomy and three untreated) and three affected by sporadic MTC were studied. TRH test (400 μg intravenously) was performed in all the patients and blood samples collected at 1, 2, 3, 5, 15, 30, and 60 minutes for CT radioimmunoassay measurements. An increase in plasma CT levels was observed in five patients with MEN 2A (three untreated and two after total thyroidectomy); 1st patient: CT basal versus peak, 50 to 187 pg/mL; 2nd patient: CT basal versus peak, 200 to 615 pg/mL; 3rd patient: CT basal versus peak, 162 to 486 pg/mL; 4th patient: CT basal versus peak, 6.8 to 31.1 pg/mL; 5th

patient: CT basal versus peak, 4.2 to 40 pg/mL. These results show that plasma CT increased after TRH in the three untreated MTC patients and in two of 11 patients with recurrences of MTC after total thyroidectomy and confirm that CT increases after TRH are frequent findings in untreated patients with MTC.

Haplotype Analysis of 24 French Families with MEN 2A

S. A. Narod,* M. F. Lavoue, C. Calmettes, K. Morgan, H. Sobol, P. Goodfellow, and G. M. Lenoir (*McGill University, Montreal, Canada)

Twenty-four families with origins in France with multiple cases of medullary thyroid carcinoma (MTC) or pheochromocytoma have been typed with nine polymorphic markers spanning the centromere of chromosome 10. No recombination was seen between the multiple endocrine neoplasia type 2A locus (MEN2A) and RBP3 (lod = 17.1), D10Z1 (lod = 12.5), MEN 203 (lod = 6.1), D10S94 (lod = 8.0), and TB14.34 (lod = 6.2). There was no evidence for genetic heterogeneity of MEN 2A in the French families. Haplotypes were constructed using the nine probes for the 24 chromosomes with MEN2A mutations and for 100 control chromosomes with MEN2A mutations and for 100 control chromosomes from unrelated individuals. One haplotype was seen in four families but in only one control ($P < 0.05$). Three additional families shared a segment of this haplotype near the MEN 2A gene; it is therefore likely that these seven families have an affected ancestor in common. Because the rate of pheochromocytoma varied in the seven families from 0% (0 of 9) to 80% (4 of 5), other genetic, epigenetic, or environmental factors may modify the expression of the MEN 2A gene. (See Am J Hum Genet 1992;51:469-77)

A French-Canadian Family with MEN 2A and MEN 2B Cosegregating with Chromosome 10 Markers

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A family in which multiple endocrine neoplasia (MEN) type 2A and type 2B coexist has been studied. The proband is a 32-year-old female who was found to have medullary thyroid carcinoma (MTC) at age 9; she has mucosal neuromas, typical facial features of the MEN 2B phenotype, megacolon, and adrenal medullary hyperplasia with hypertension. Her son, who has mucosal neuromas and mental retardation, was found to have MTC at age 22 months. The father of the proband, found to have MTC at age 52, has the MEN 2A phenotype. Six chromosome 10 centromeric markers at D10S34, FNRB, D10Z1, D10S94, RBP3, and D10S15 were tested in 15 members of the family. FNRB haplotypes were the only informative restriction fragment-length polymorphisms and were detected in BanII, KpnI, and HinfI digests. The alleles for individuals with either MEN 2A or MEN 2B phenotypes appear to be on chromosome 10 traveling with the FNRB haplotype A1B1C1. Four other members of the family at risk carry the same haplotype and have normal phenotypes. To date, one brother of the proband carrying the haplotype associated with the disease has mildly elevated calcitonin levels after pentagastrin stimulation for which surgery has been recommended. This family study suggests that MEN 2A and MEN 2B loci are closely related on chromosome 10 and that an additional mutation close to or in the MEN 2A locus can produce an MEN 2B phenotype.

The Natural History of the Multiple Endocrine Neoplasia Type 2B Syndrome: A Study of 18 Cases

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Multiple endocrine neoplasia type 2B (MEN 2B) is an autosomal dominantly-inherited disorder associated with medullary thyroid cancer (MTC), pheochromocytoma, and a characteristic phenotype. The present study was performed to investigate the natural history of the syndrome and to describe its expression. The data of 18 cases, seven males and 11 females, were collected. The information included age at diagnosis, expression of the disease, surgical findings, and the results of the postoperative calcitonin (CT) tests. The mean age at diagnosis of the MEN 2B syndrome was 18 years (range: 8 to 41 years). In all patients the presenting sign was a thyroid abnormality. Retrospectively, eight of the 18 patients had had neuromas since early childhood. All 18 patients had MTC. In three patients, MTC was diagnosed via screening. In two of these patients normalization of the CT value was found after thyroidectomy. One patient died of MTC metastases at the age of 20 years (mean follow-up of eight years). Eight of the 18 patients had a pheochromocytoma. All of our patients had neuromas, bumpy lips, and all but one had a marfanoid habitus. A large proportion of the patients had intestinal abnormalities (75%), thickened corneal nerves (69%), skeletal abnormalities (87%), and a delayed puberty (43%). From these findings the following conclusions were drawn: 1) despite the well-characterized phenotypic expression, the syndrome is usually not recognized; 2) the course of MTC in MEN 2B is not as aggressive as is generally thought; 3) periodic examination of relatives who are at risk may lead to early diagnosis and curative treatment; and 4) intestinal abnormalities, skeletal abnormalities, and a delayed puberty are major components of the syndrome.

Screening and Clinical Management of Familial Multiple Endocrine Neoplasia Type 1

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We have evaluated indices for their efficacy in screening for multiple endocrine neoplasia type 1 (MEN 1). Screening has been directed principally at endocrinopathy with the finding that calcium and parathyroid hormone (PTH) analyses had the highest cost-effectiveness. Neither testing for silent pituitary (with prolactin) or pancreatic disease (with gastrin, chromogranin A, or pancreatic polypeptide) nor testing for MEN 1 growth factor activity was effective. However, prolactin was effective in screening kindreds with the prolactinoma variant of MEN 1. DNA testing is now possible in kindreds; PYGM is the most tightly linked locus we have evaluated in typical MEN 1 as well as in the prolactinoma variant. We have not encountered any patient with obligate recombination between PYGM and MEN 1 or any monoclonal MEN 1 tumor with retained heterozygosity at this locus. Management of the endocrine complications of MEN 1 generally involves strategies to ameliorate but not cure a feature. In primary hyperparathyroidism we recommend delayed surgery and use of a fresh or cryopreserved autograft. In Zollinger-Ellison syndrome and in prolactinoma, we generally recommend pharmacotherapy alone. With decreasing morbidity from associated endocrinopathy, more attention will be directed at the possibilities for prevention and treatment of islet cancer in MEN 1.

Clinical Phenotype and Linkage Analysis of a Prolactinoma Variant of Multiple Endocrine Neoplasia Type 1 (MEN 1 BURIN)

J. S. Green,* A. E. Bale, S. J. Marx, and N. R. Farid (*Memorial University of Newfoundland, St. John's, NF, Canada)

Four presumably related multiple endocrine neoplasia type 1 (MEN 1) families from Newfoundland with more frequent and earlier onset prolactinomas than in typical MEN 1 were identified and described by Farid et al in 1980. A follow-up study was undertaken in 1989-1990 to further define the clinical phenotype of this prolactinoma variant of MEN 1 (MEN 1 BURIN) and to determine whether MEN 1 BURIN maps to chromosome 11q13 as does typical MEN 1. Pedigrees of all four families have been extended, records reviewed, and comprehensive screening initiated. Sixty-nine affected patients (ages 14 to 83 years) have now been identified. Hyperparathyroidism is definitely present in 93%, prolactinomas in 34%, pancreatic islet cell tumors (not identified in the earlier study) in at least 5%, and carcinoid tumors in 14%. DNA was obtained from members of one of the families for linkage studies with chromosome 11 markers known to be linked to typical MEN 1. Two-point analysis of data with the LINKAGE program gave the following maximum likelihood estimates: PYGM-Z = 3.27, theta = 0.0; PGA-Z = 1.50, theta = 0.0; D11S146-Z = 0.96, theta = 0.0; INT2-Z = 1.32, $\text{theta}_m = 0.0$; $\text{theta}_f = 0.09$. The clinical data support the conclusion that the phenotype of MEN 1 BURIN overlaps that of typical MEN 1, and the linkage data suggest that MEN 1 BURIN maps to the same locus as typical MEN 1.

Immunocytochemical Features of Islet Cell Tumors in Patients with Multiple Endocrine Neoplasia Type 1

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Twenty-three primary and five metastatic islet cell tumors from 10 patients with multiple endocrine neoplasia type 1 (MEN 1) were studied by immunocytochemical procedures using a battery of antibodies to insulin, glucagon, somatostatin, pancreatic polypeptide (PP), vasoactive pancreatic polypeptide (VIP), gastrin, and serotonin. Evidence of multiple polypeptide hormone production was found in 18 tumors (eight tumors produced two polypeptides, nine produced three, and one produced four). The remaining 10 tumors produced a single polypeptide. Insulin immunoreactivity, the most common hormone demonstrated, was observed in 16 tumors (57%), followed by glucagon in 15 (54%), PP in 12 (43%), VIP in five (18%), gastrin in four (14%), somatostatin in three (11%), and serotonin in three (11%).

Molecular Controls of Medullary Thyroid Carcinoma Differentiation

Barry D. Nelkin, Andree de Bustros, Douglas W. Ball, and Stephen B. Baylin* (*The Johns Hopkins Medical Institutions, Baltimore, MD)

We have used studies of the different stages of evolving medullary thyroid carcinoma (MTC) to outline molecular steps in the progression of this cancer. Increasing virulence of the tumor appears to involve loss of maturation features of the normal C-cells, especially as these involve expression of the gene for calcitonin (CT), the major peptide hormone for this cell type. Studies of cultured MTC cells have revealed that increased growth rate correlates with decreased CT gene transcription and mRNA splicing patterns different from those for normal C-cells. Insertion of the Harvey ras oncogene can restore mature

properties to cultured MTC, including decreased growth rate, increased CT gene transcription, altered splicing of the CT gene mRNA towards that of normal C-cells, and increased numbers of mature cytoplasmic neurosecretory granules. These overall ras gene-induced changes may be coordinated through increases in expression of the c-jun oncogene and, for the CT gene, specifically, by a series of transcription factors which bind to a 300 bp 5′ flanking region of the gene. This ras gene-induced model offers an excellent opportunity to define further the molecular steps involved in C-cell differentiation, MTC progression, and regulation of CT gene expression.

Detection of Tumor Suppressor Gene Abnormalities by Single Strand Conformation Polymorphism Analysis

Robert E. Sobol,* Barbra Blake, Michelle Tufo, and Leonard J. Deftos (*Department of Medicine and the Cancer Center, University of California at San Diego, CA)

Tumor suppressor (TS) gene mutations have been observed in a wide variety of cancers. These abnormalities are believed to contribute to tumorigenesis as the transfer of functional wild type TS genes reverses the malignant phenotype. Most TS gene abnormalities represent nonuniform point mutations in evolutionary conserved domains. These TS gene abnormalities are therefore difficult to detect by standard Southern, Northern, or polymerase chain reaction (PCR) analyses. Single strand conformation polymorphism (SSCP) analysis provides a simple and sensitive method to detect these point mutations. In this approach, genomic or cDNA sequences of interest are amplified by PCR and radiolabeled by incorporating ^{32}P dCTP in the reaction mixture. The amplified products are then denatured and run in a nondenaturing acrylamide gel. Changes in DNA sequences, including point mutations, result in different migration patterns which are detected by autoradiography. In preliminary studies, we have evaluated exon 5 of the TS gene p53 for abnormalities by SSCP analysis. One medullary thyroid carcinoma and two lung carcinoma cell lines had normal p53 configurations. This technique will prove useful in evaluating the relationships between TS gene abnormalities and tumorigenesis in multiple endocrine neoplasia.

CGRP Receptor Heterogeneity

J. A. Fischer,* D. Stangl, H. Henke, and C. Beglinger (*Research Laboratory for Calcium Metabolism, University of Zurich, Switzerland)

The human CGRP I and II (or alpha and beta) are encoded by two different genes, but they have 34 of the 37 amino acid residues in common. Widespread distribution of CGRP-specific high affinity binding sites has been recognized throughout the central nervous system and among peripheral organs (heart, spleen, blood vessels, lung, liver, and kidney) as well as in neuroblastoma cell lines. In the human cerebellum, solubilization with CHAPS and subsequent cross-linking of ^{125}I human CGRP I (1-37) and (8-37) and CGRP III (1-37) revealed the same binding proteins with apparent molecular weights of 95, 60, 54, and 17 kD. The 60 and 54 kD components are N-glycosylated. However, using receptor autoradiography, subtle differences in the regional distribution of ^{125}I-CGRP I and II binding have been visualized (e.g., in the human ventromedial hypothalamus). In peripheral organs and in neuroblastoma cell lines, CGRP receptors are linked to cyclic AMP production. Human CGRP I more potently stimulated blood flow through the skin and carotid artery ($P < 0.01$), the heart rate ($P < 0.05$), and plasma renin activity and aldosterone secretion ($P < 0.02$) in normal human subjects than did human CGRP II. Inhibition of pentagastrin-stimulated gastric acid output, on the other hand, was only obtained with CGRP II. The separate effects of human CGRP I and II on the cardiovascular and gastric systems may be mediated by different receptors or receptor pathways so far not recognized at the level of receptor binding proteins.

Genetic Events in Multiple Endocrine Neoplasia Type 2 Tumorigenesis and Progression

L. M. Mulligan,* E. Gardner, B. A. Smith, C. G. P. Mathew, and B. A. J. Ponder (*CRC Human Cancer Genetics Group, Cambridge, England)

Genetic mapping of the multiple endocrine neoplasia type 2 (MEN 2) gene (MEN2) is reaching the limits of resolution possible for genetic linkage. The location of the gene locus may be signaled by deletions or rearrangements in the germline or in the DNA of the associated tumors. We have examined a panel of 52 paired normal and tumor samples from patients with MEN 2-type tumors (pheochromocytomas and medullary thyroid carcinoma) using markers for the pericentromeric region of chromosome 10. We have been unable to detect altered restriction patterns in any of the examined tumors in a panel of 73 unrelated MEN 2 individuals examined by pulsed field gel electrophoresis for germline mutations. These data suggest that rearrangement or deletion of sequences which include loci genetically close to MEN2 is not a frequent accompaniment to tumorigenesis.

In addition, to characterize the contribution to progression of MEN 2 type tumors made by mutation at other loci, we have examined marker loci on each chromosomal arm for allele loss. Losses occurred most frequently at loci on chromosome 1p,

3p, 11p, 13q, 17p, and 22q. In each case a shortest region of overlap was confined to regions suggested to include tumor suppressor genes from allele loss studies in other tumor types.

The Multiple Endocrine Neoplasia Type 1 Adrenal Cortex

B. Skogseid,* C. Larsson, and K. Oberg (*Department of Internal Medicine, University Hospital, Uppsala, Sweden)

In multiple endocrine neoplasia type 1 (MEN 1), benign enlargement of the adrenal cortex has been found in about one-third of necropsy cases. To elucidate the clinical and genetic characteristics of the MEN 1 adrenal lesion, we have investigated 33 MEN 1 patients. Twelve individuals (37%) demonstrated adrenal enlargement which was bilateral in seven. Histopathology revealed diffuse and nodular cortical hyperplasia, adenomas, and a single case of adrenocortical carcinoma. The apparently benign adrenal enlargements were not associated with biochemical disturbances in the hypothalamic-pituitary-adrenocortical axis and were without radiological signs of progression during follow-up. The individual developing unilateral adrenocortical carcinoma showed rapid adrenal expansion, femininization, and an abnormal urinary steroid profile after four years of observation for bilateral minor adrenal enlargements. Pancreatic endocrine tumors were significantly overrepresented and present in all the MEN 1 individuals with adrenal involvement. In agreement with findings in sporadic cases, the MEN 1 adrenocortical carcinoma genome showed loss of constitutional heterozygosity for alleles at 17p, 13q, 11p, and 11q. The benign adrenal lesions retained heterozygosity for the MEN 1 locus at chromosome 11q13. Despite its prevalence and malignant potential, the pituitary-independent adrenocortical proliferation does not appear to be a primary lesion in MEN 1, but might represent a secondary phenomenon, perhaps related to the pancreatic endocrine tumor. *(J Clin Endocrinol Metab [in press])*

Future Meetings

Continuing Medical Education

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February 15-19, 1993

Location: Big Sky, Montana

Program Directors: Daniel Anbe, MD, Sidney Goldstein, MD, Philip Hill, MD, and Howard Rosman, MD

This five-day program will present a comprehensive overview of current problems in cardiology combined with practical workshops in electrocardiography and echocardiography. The program will enable participants to interact with the faculty in an informal and stimulating atmosphere.

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Other Educational Programs

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Tuesdays 8:00-9:00 AM (a case presentation conference)
Contact: Dr. Jan Rival (876-1895)

Bone & Mineral Conference
Tuesdays 2:00-3:00 PM (research seminar); 3:00-4:00 PM (clinical cases)
Contact: Dr. Michael Kleerekoper (876-2365)

Basic Rheumatology Conference
Wednesdays 8:00-9:00 AM
Contact: Dr. Howard Duncan (876-2643)

Cardiology Conference
Wednesdays 4:30-5:30 PM
Contact: Dr. Howard Rosman (876-2871)

Cardiosurgical Conference
Mondays 4:00-5:00 PM
Contact: Dr. Fareed Khaja (876-2760)

CICU Morbidity Mortality Conference
Mondays 8:00-9:00 AM
Contact: Dr. Steven Borzak (876-9406)

Clinical Cardiology Conference
Wednesdays 8:00-9:00 AM
Contact: Dr. Paul Stein (876-3221)

Endocrinology and Metabolism Conference
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Contact: Dr. Fred Whitehouse (876-2131)

Referring Physician Office

Henry Ford Hospital's Referring Physician Office has a 24-hour Consult Line (1-800-999-4340). Physicians can call toll-free to discuss a possible referral, arrange medically supervised transportation, or obtain general information about Henry Ford Hospital's wide range of services.

Readers of the *Henry Ford Hospital Medical Journal* are hereby notified that Volume 40, Numbers 3 & 4, 1992, will be their last issue received until further notice. Please see the Editor's Note in this issue on page 157 for additional information regarding plans for the restructuring of the *Journal*.

Henry Ford Hospital

Detroit, Michigan 48202

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