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Diagnosis, Management, and Pathogenetic Studies in Medullary Thyroid Carcinoma Syndrome

Naguib A. Samaan,* Kuo-Pao Paul Yang,* Pamela Schultz,* and R.C. Hickey†

A retrospective study of 224 patients with medullary thyroid carcinoma (MTC) diagnosed between 1963 and 1988 was performed to 1) establish the diagnosis of MTC in early childhood, 2) establish the role of prophylactic regional lymphadenectomy in patients with MTC, 3) study the effect of chemotherapy on MTC patients with metastatic disease, 4) study the effect of somatostatin analog 201-995 (Sandoz Pharmaceuticals) on the frequency of diarrhea in MTC, and 5) locate the common region(s) of gene deletion on chromosome 1 and examine the loss of heterozygosity on chromosome 10 in tumors. Our data indicated that a progressive rise of serum calcitonin in early childhood (rather than the expected fall with age seen in normal subjects) is diagnostic of MTC. No differences in clinical course or prognosis were observed between patients with MTC localized to the thyroid who had prophylactic neck node dissection and those who did not. Conventional chemotherapy had no significant benefit in the treatment of patients with metastatic disease. The somatostatin analog was found to be an effective drug in the treatment of diarrhea associated with MTC. Allelic losses were frequently found in MTCs and pheochromocytomas, and the loss of DNA sequences in these tumors appeared to involve the distal third of the short arm of chromosome 1, with a common breakpoint at 1p32. (Henry Ford Hosp Med J 1989;37:132-7)

Over the last two decades much progress has been made in our understanding of the medullary thyroid carcinoma (MTC), both the hereditary and sporadic forms. However, many questions remain unanswered. This study addresses the following five areas:

1. We showed in 1973 (1,2) that serum calcitonin (CT) is elevated at birth (Figs 1 and 2) and gradually decreases over time (3), and we proposed that high CT during intrauterine fetal life may be important for bone development. These findings have been confirmed by others (4,5). The question raised by these observations is how to establish the diagnosis of MTC at an early age when CT is physiologically elevated.

2. Another important question is how much nodal dissection, if any, is needed when the disease is localized to the thyroid gland.

3. Although we have shown that ¹³¹I therapy for ablation therapy of MTC is ineffective (6) and that radiotherapy post-operatively is not beneficial (7), the role of various chemotherapeutic agents in advanced disease has not been thoroughly discussed because the number of patients reported in the literature is too small to reach a significant conclusion.

4. A disabling diarrhea can be the presenting manifestation in 30% of patients with MTC (8). However, various drugs have been used without success. We examined the possible benefits of the somatostatin (SMS) analog 201-995 (Sandoz Pharmaceuticals) in MTC patients.

5. We tested the hypothesis of suppressor gene inactivation in MTC and searched for the common region(s) of gene deletion on

chromosome 1 and examined tumors also for loss of heterozygosity for chromosome 10.

Diagnosis of MTC at an Early Age

An infant was born with skeletal deformities in the form of clubbed feet and gastrointestinal signs of partial obstruction. A biopsy from the rectum showed neuromata similar to that seen in multiple endocrine neoplasia type 2B (MEN 2B), but the lips, tongue, and eyelids showed no neuromata. There was no family history of MTC or thyroid disease. Eye examination showed thickening of the corneal nerves. MTC was suspected, but the thyroid gland was clinically normal. Serum CT was measured basally and after pentagastrin stimulation (Nichols Laboratory, San Juan Capistrano, CA). The basal CT level was 84 pg/mL with a peak of 200 pg/mL two minutes after intravenous administration of pentagastrin, which was considered to be within the normal range for infants of that age in that laboratory. Since we have observed previously in our laboratory that serum CT is high at birth and decreases with age in normal children, we elected to

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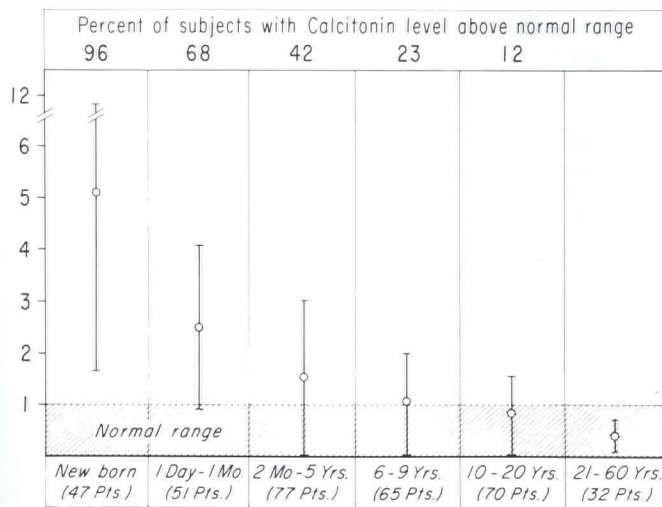


Fig 1—Serum calcitonin levels in different age groups showing progressive decrease with age. (From Samaan NA, Anderson CD, Adam-Mayne ME. Immunoreactive calcitonin in the mother, neonate, child, and adult. *Am J Obstet Gynecol* 1975;121:622-5. Reprinted with permission.)

wait six months and repeat the pentagastrin stimulation test, particularly since the infant was marasmic due to difficulties in feeding.

At the age of 14 months, serum CT was again measured during pentagastrin stimulation in the same laboratory. The CT level showed an increase both at basal and after pentagastrin stimulation, which is contrary to what we observed in normal subjects with progress of age (3). The basal CT level was 107 pg/mL with a peak of 312 at 2 minutes. Total thyroidectomy revealed marked nodular C-cell hyperplasia in the isthmus region. CT was again measured 16 months following surgery and the basal level was 14 pg/mL with no rise after stimulation with pentagastrin. The patient is currently in good health on thyroid replacement.

MTC Localized to the Thyroid Gland: Indications for Nodal Dissection

In the 224 patients diagnosed with MTC at The University of Texas M.D. Anderson Cancer Center from 1944 to 1988, the mean \pm standard deviation of age at diagnosis was 43.0 ± 15.1 years. The males comprise 46% of the population. Total thyroidectomy had been performed in 75% of the patients. At the time of diagnosis the disease involved the thyroid gland and regional lymph nodes in 36% and the thyroid gland alone in 35%. External radiotherapy as an initial treatment had been performed in 28% and radioactive iodine has been given to 10% of the patients. MEN 2 had been identified in 24% of the patients. Local recurrence in the neck had occurred in 30% and distant metastases have been documented in 37% of the patients. A total of 33% had died of MTC (Table 1). To determine if prophylactic neck dissection was beneficial to the patients' outcome, those patients who presented with disease to the thyroid gland only and who had neck dissection with negative lymph nodes (15 patients)

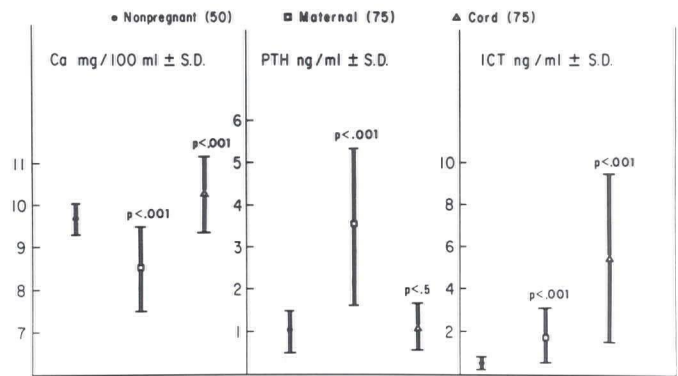


Fig 2—Serum calcium (Ca), parathyroid hormone (PTH), and calcitonin (CT) in nonpregnant, maternal, and cord blood. Cord blood showed high serum calcium and CT and low PTH, whereas maternal blood showed subnormal calcium levels and high PTH and CT. (From Samaan NA, Wigoda C, Castillo SG. Human serum calcitonin and parathyroid hormone levels in the maternal, umbilical cord blood and postpartum. In: *Endocrinology 1973. Proceedings of the Fourth International Symposium*. London: William Heinemann Medical Books, Ltd, 1974:368. Reprinted with permission.)

Table 1
Population Characteristics of MTC Patients at The University of M.D. Anderson Cancer Center (1944-1988) and Localization of MTC at Presentation

Population Characteristics	Localization of MTC at Presentation
Males: 103 (46%)	Thyroid gland: 79 (35%)
Mean Age (years) \pm SD: 45.5 ± 15.4	Thyroid gland and nodes: 81 (36%)
Females: 121 (54%)	Thyroid gland, nodes, and soft tissue: 42 (22%)
Mean Age (years) \pm SD: 40.8 ± 14.6	Thyroid gland, nodes, soft tissue, and distant metastasis: 18 (7%)
Hereditary Cases: 24%	

were compared with those who had involvement of the thyroid gland only and no neck dissection performed (43 patients). When these two groups of patients were analyzed according to age, sex, surgery, radiotherapy, radioactive iodine, MEN 2 syndrome, recurrence, and survival, no differences between the groups were found (Table 2).

Radioactive Iodine, Radiotherapy, and Chemotherapy in the Treatment of MTC

To determine the value of adjunct ^{131}I therapy in MTC, two groups of patients with histologically proven MTC with localized disease to the thyroid gland only were studied. Group A consisted of 11 patients (six men and five women) treated by surgery followed by an ablative dose of ^{131}I , and group B included 46 patients (20 men and 26 women) treated by surgery alone. Patients in group A were followed for 1.5 to 14 years (median follow-up 53 months), and those in group B were followed for one to 27 years (median follow-up 75 months). We found no dif-

Table 2
Effect of Node Dissection of MTC Patients with Localized Disease to the Thyroid (58 Patients)

	Node dissection	No node dissection
Number of patients	15	43
Mean age (years) ± SD	37.5 ± 15.6	39.4 ± 14.5
Males	4 (27%)	11 (26%)
Females	11 (73%)	32 (74%)
Total thyroidectomy	12 (80%)	35 (81%)
< Total thyroidectomy	3 (20%)	8 (19%)
X-ray treatment	none	none
MEN 2	6 (40%)	15 (35%)
Recurrence	6 (40%)	9 (21%)*
Died	1 (7%)	6 (14%)*
Mean follow-up (years)	11.9 ± 5.2	6.9 ± 5.1

*P>0.1.

ference in the two groups in the rate of recurrence, metastasis, or survival (Fig 3). We also saw no significant difference in the level of CT between the two groups (6).

We found that when patients who received radiotherapy were matched for age, extent of disease, and surgery with patients who had had no radiotherapy, the *untreated* group was found to live significantly longer (7) ($P < 0.05$) (Fig 4).

Twenty-three patients with metastatic MTC were treated by various chemotherapeutic agents and 45 observations were recorded (some of the patients received more than one regimen) (Table 3). The drugs used were adriamycin alone, adriamycin plus cisplatin, MeCCNU, and VP-16, as well as other miscellaneous drugs such as DTIC, vincristine, bleomycin, etc. The results were disappointing. None of the patients had complete remission and few had partial or minor response. Complete remission was defined as disappearance of all evidence of tumor for at least four weeks and the patient being free of all symptoms of cancer. Partial response was defined as 50% or greater decrease in the products of the diameter of all measured lesions for at least four weeks without increase in the size of any other lesions or appearance of new lesions. Minor response was defined as a decrease in a measurable lesion which is too small to qualify as a partial response, and failure indicated an increase in tumor size of at least 25% or appearance of new lesions (Table 3).

Effect of SMS 201-995 on Diarrhea of MTC

Two patients with severe diarrhea were also studied. A 39-year-old white male who had MTC with lymph node and soft tissue involvement had surgery followed by radiotherapy to the neck. Over the last year he noticed severe diarrhea which increased up to 35 stools per day. His CT was markedly elevated (> 500 ng/mL; normal: 0 to 1 ng/mL) and his carcinoembryonic antigen (CEA) was also elevated (76 ng/mL; normal: 0 to 6 ng/mL). He was given various drugs for diarrhea including lomotil, emodium, and paragoric with no significant beneficial effect. He was then given SMS 201-995, 100 µg subcutaneously twice daily, and two drops of tincture of opium three times daily. His diarrhea decreased to 2 to 4 stools per day, and he gained 7.6 kg

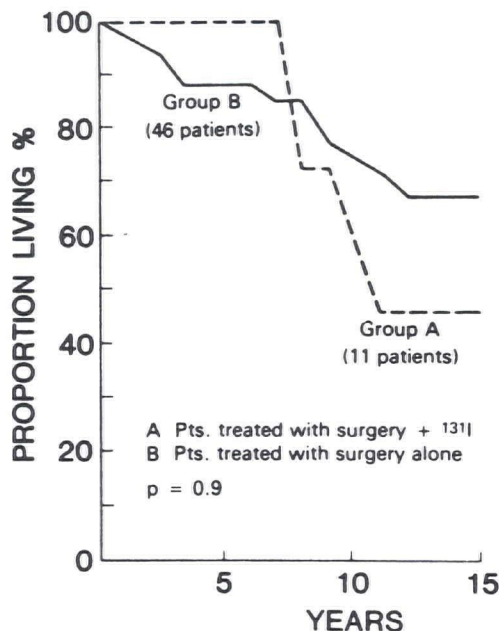


Fig 3—Actuarial survival curves of patients with localized disease in both groups, showing no therapeutic effect of ¹³¹I in survival of patients with MTC. (From Saad MF, Guido JJ, Samaan NA. Radioactive iodine in the treatment of medullary carcinoma of the thyroid. *J Clin Endocrinol Metab* 1983;57:124:8. Reprinted with permission.)

(17 lb) over a three-month period. The CT remained elevated (> 500 ng/mL) as did the CEA (79 ng/mL).

The second patient was a young, white female with MTC with metastases to the bone and skin. She had diarrhea with 15 to 20 stools per day and had lost a considerable amount of weight. She could not tolerate small amounts of food and felt nauseated and frequently vomited after meals. She was treated with SMS 201-995, 100 µg twice daily, and two drops of tincture of opium three times daily. She was no longer nauseated, had a good appetite, and gained 8.1 kg (18 lb) in three months. Her CT and CEA levels were elevated at 190 ng/mL and 587 ng/mL, respectively, before SMS 201-995 therapy and remained elevated at 220 ng/mL and 603 ng/mL, respectively, after three months of therapy.

Both patients also showed normal 5-hydroxyindoleacetic acid (5HIAA) and serotonin before and after treatment with no change during therapy. The second patient took the tincture of opium less frequently and irregularly without an increase in the frequency of diarrhea.

Molecular Analysis for Losses of DNA Sequences on Chromosomes 10 and 1p

Hsu et al (9) reported cytogenetic studies suggesting that MEN 2 patients exhibit some degree of chromosome instability. Hsu et al (10) also showed that cultures of peripheral lymphocytes from patients with MEN 2 were more susceptible than normal individuals to mutagen-induced chromosomal breakage, with the frequent involvement of chromosomes 1 and 4. The

Table 3
Effects of Chemotherapy in Medullary Thyroid Carcinoma
in 23 Patients and 45 Observations

Agents	Number	Complete Response	Partial Response	Minimal Response	Failure
Adriamycin	10	0	2	2	6
Adriamycin + cisplatin	10	0	2	2	6
Me CC Nu	3	0	0	0	3
VP-16	2	0	0	1	1
Miscellaneous	20	0	0	0	20

higher frequency of spontaneous and induced chromosome aberrations in these patients would conceivably increase the probability of acquiring mutations at the target gene(s). However, in studies of 25 members of four MEN 2A families, Ferrell et al (11) failed to find evidence favoring linkage between the MEN 2A mutation and genetic markers assigned to chromosomes 1 and 4.

Recent linkage studies (12,13) have assigned the predisposing gene for MEN 2A to chromosome 10. Since this predisposing mutation would most likely be expressed by loss of the homologous normal allele as suggested by Knudson in his two-hit model for carcinogenesis (14), we tested the hypothesis that the genetic etiology for MEN 2A is analogous to that for such childhood tumors as retinoblastoma and Wilms tumor. We examined the genotypes in constitutive and tumor cells from patients with MEN 2A at the interstitial retinol-binding protein (RBP3) locus which has been shown to link to MEN 2A (12,13,15).

DNAs from eight patients with hereditary/sporadic MTC or pheochromocytoma were examined for the loss of heterozygosity at the RBP3 locus by the Southern blot technique. However, none of the eight patients' genotypes were heterozygous for the marker, and we were unable to assess whether or not one of the parental alleles of this chromosome 10 gene is lost in their tumors. Flejter et al (16) recently reviewed high-resolution chromosome preparations from 23 MEN 2 families and found no apparent abnormalities involving chromosome 10. Landsvater et al (17) and Nelkin et al (18) reported that the incidence of reduction to homozygosity for chromosome 10 DNA markers in tumor DNA from MEN 2 patients was uncommon. Nevertheless, the possibility remains that submicroscopic deletion or point mutation may exist in the chromosome 10 loci in these tumor DNAs and may have escaped detection by these studies. Therefore, the nature of mechanisms involving chromosomes 10 in MEN 2 which result in the second mutational event remains unclear.

Mathew et al (19) reported that loss of heterozygosity on chromosome 1p was detectable in seven of 14 informative patients with MTC or pheochromocytoma from both hereditary and sporadic cases. Similar mutations at chromosome 1p were also frequently detectable in neuroblastomas (20), a tumor which is derived from the same embryonic origin as MEN 2. In other types of tumors such as colorectal tumors and small cell carcinomas of the lung, multiple mutations involving different chromosomes have been implicated as the genetic mechanisms for tumor initiation and progression (21-23). In light of these findings, we performed molecular analysis aimed at determin-

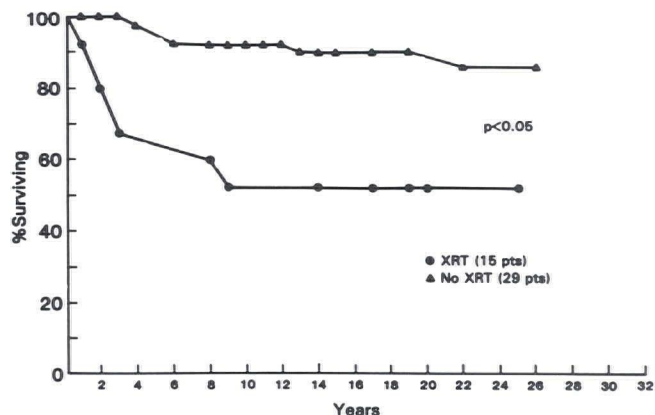


Fig 4—Comparison of survival in MTC patients matched for age, extent of disease, and surgery. External radiation showed no benefit, and those who received radiotherapy had shorter survival than those who did not. (From Samaan NA, Schultz PN, Hickey RC. Medullary thyroid carcinoma: Prognosis of familial versus sporadic disease and the role of radiotherapy. *J Clin Endocrinol Metab* 1988;67:801-5. Reprinted with permission.)

ing the region on chromosome 1p that may represent a common deletion in MEN 2A in order to locate the potential tumor suppressor gene whose mutation is involved in the processes of tumorigenesis.

Five polymorphic DNA probes (PND, FUCA1, DIS57, L-myc, and NGFB) that detect various chromosome 1p loci plus a 1q marker (AT3) were used to examine allelic deletions for chromosome 1. Among the eight patients, allelic deletion at the L-myc locus was clearly demonstrated by the loss of heterozygosity in two patients (Fig 5, cases 3 and 5) and by the reduction of about 50% of the gene copies in another two patients (Fig 5, cases 2 and 4) whose constitutional alleles were homozygous at this locus. In the remaining four patients, whose constitutional DNAs were homozygous to this marker, the status of gene deletion/inactivation at this locus could not be assessed. Patient 2's tumor DNA also had multiple deletions at four loci between 1p32 and 1p36, suggesting deletion of the distal third of 1p. Tumor DNAs from four patients (cases 3, 4, 5, and 6) lost heterozygosity at one or two loci within the distal third of 1p, suggesting interstitial deletions. Tumor DNA from patient 1 showed abnormal band patterns in regions of DIS57 and FUCA1 loci, suggesting gene rearrangement in the distal third of 1p of this tumor. The common region of gene deletion on chromosome 1p in these eight MEN 2A-associated tumors was determined to be 1p32 (Fig 6).

Discussion

We have previously shown that CT is elevated in infants at birth as well as in the pregnant mother. We suggested that the high CT in the presence of high serum calcium during intrauterine fetal life may play a role in the bone formation of the fetus. We also suggested that the high CT in the mother may play

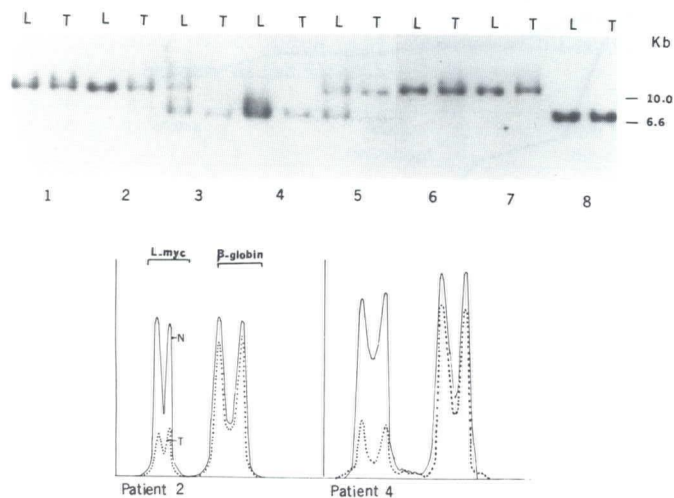


Fig 5—Allelic deletion (patients 2, 3, 4, and 5) at locus *Ip32* in eight cases of MTC and pheochromocytoma. DNAs were digested with *EcoRI*. Upper panel: Southern hybridization patterns of the ³²P-labeled *L-myc* probe to DNAs from peripheral blood leukocytes (L) and tumor cells (T) from each patient. Patient numbers are indicated below the blots. Numbers to the right of autoradiographs indicate the molecular size of the two polymorphic alleles in kilobases. Lower panel: Densitometric scans of Southern hybridizations with ³²P-labeled *L-myc* probe in cells from patients 2 and 4. Solid lines represent the readings for leukocyte DNA, and dotted lines represent those for tumor DNA. A β -globin gene probe serves as a control for normalization of the hybridization intensity.

a role in inhibiting the bone resorption in the presence of high maternal parathyroid hormone which increases the absorption of serum calcium from the gastrointestinal tract and reabsorption of the calcium from the renal tubules, and thus calcium will be available to the fetus (1,2). We have also shown that CT levels decrease with age (3). These observations were confirmed by others (4,5). However, the presence of elevated CT levels in childhood presents major problems for diagnosis of MTC early in life. We propose that if MTC or C-cell hyperplasia is suspected in early life, such as in our described patient, or in other MEN 2 family members, the measurement of CT at various intervals in early life and the finding of the progressive rise in CT rather than the expected fall may provide a diagnosis. This proposition is confirmed in the patient described.

The extent of surgery which is indicated in the treatment of MTC localized to the thyroid gland has been controversial (24-26). Our data suggest that if the lymph node sampling shows the middle compartment of the neck to be free of disease, no lymph node dissection is necessary. We suggest that other centers should examine their findings in this regard.

We previously reported that radioactive ablation for patients with MTC failed to affect the remission or survival rate (6). We also reported that when patients who received radiotherapy after surgery for MTC were matched for age, extent of disease, and

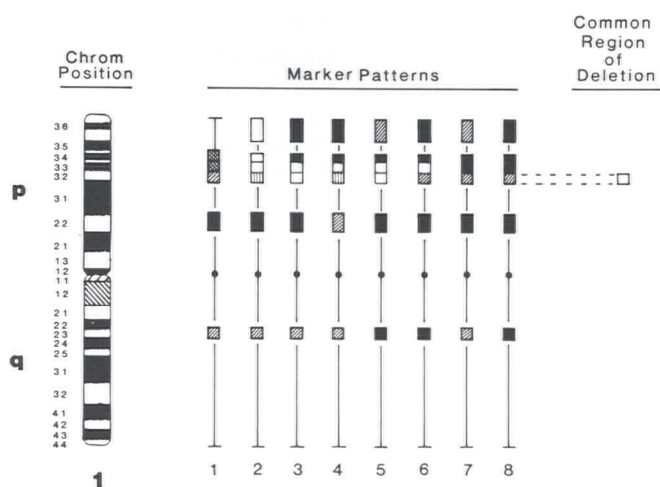


Fig 6—A summary of the allelic deletion on chromosome *1p* in the eight cases of MTC and pheochromocytomas studied. Open boxes represent regions where patients' leukocyte DNA was heterozygous and tumor DNA showed loss of an allele; boxes with vertical lines represent areas where patients' leukocyte DNA was homozygous and tumor DNA showed an approximately 50% reduction in band intensity; solid boxes represent areas where constitutional heterozygosity was retained in the tumors; boxes with unidirectional diagonal lines represent regions where patients' leukocyte DNA was homozygous and therefore allelic deletion could not be assessed; boxes with crossed diagonal lines represent regions where patients' tumor DNA revealed abnormal or new restriction fragments. The solid lines represent areas that we have not yet examined.

surgery with patients who had no radiotherapy, the untreated group was found to live significantly longer (7). We also showed that adriamycin, cisplatin, and bleomycin had little tumoricidal effects when administered as a single agent to cultured human MTC cells (27,28). Our present findings also indicate that the chemotherapy (such as adriamycin alone or in combination with cisplatin or other drugs such as bleomycin, vincristine, 5-fluorouracil, and methotrexate) has no measurable beneficial effect.

Diarrhea in MTC may be the presenting symptom in 30% of patients (8) and can be disabling. Our results in two patients suggest that SMS 201-995 either alone or with tincture of opium is effective in the treatment of diarrhea of MTC. The mechanism of action is unclear since there was no significant change in the CT level before and after treatment as well as no change in CEA, serotonin, or the 24-hour urinary 5HIAA. The somatostatin analog may act on the peripheral tissue or through an inhibition of a hormone, the nature of which is unknown.

The present study on pathogenetic mechanisms in MEN 2A suggests that a tumor suppressor gene for MTC and pheochromocytoma might be located at the distal third of *1p* (most likely at *Ip32*) where mutant alleles seem to be involved in the initiation and/or progression of these tumors. However, in view of the evidence reported by others (21-23) suggesting that several tumor suppressor genes on different chromosomes may be

involved in suppressing the malignant phenotype in similar but distinct tumor types, it is possible that heterozygosity might be lost frequently at other chromosomal loci also.

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