Medullary Thyroid Carcinoma:

Relationship of Method of Diagnosis to Pathologic Staging

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Medullary thyroid carcinoma (MTC) develops in virtually all patients affected with multiple endocrine neoplasia type II (MEN II), a disease inherited as an autosomal dominant trait. The thyroid tumor cells secrete calcitonin (CT) and the detection of elevated plasma levels (>300 pg/ml) of this hormone in MEN II kindred members strongly suggests the presence of MTC even though it may not be evident clinically. Intravenously administered calcium ion (Ca^{++}) and pentagastrin (Pg) are potent CT secretagogues which are of particular value in establishing the early diagnosis of MTC. In evaluating seven kindreds with MEN II, we detected 90 patients with MTC. Depending on the method of diagnosis, they could be divided into three categories: Group 1; patients with no clinical evidence of MTC whose undetectable basal plasma calcitonin levels became elevated following intravenous Ca^{++} or Pg, Group II; patients with no clinical evidence of MTC who had elevated basal plasma CT levels, and Group III; patients with clinically evident MTC. At the time of diagnosis of MTC, the patients in Group I were younger (20.5 ± 1.9 years) than the patients in Group II (32.5 ± 4.7 years, $p < 0.005$) and Group III (34.3 ± 2.0, $p < 0.00005$). The incidence of residual MTC, as indicated by an elevated plasma CT level following provocative testing postoperatively, was less frequent in patients diagnosed biochemically ([6/34]; Group I, 4/26 and Group II, 2/8) than in those diagnosed clinically (Group III, 15/26, $p < 0.002$). Furthermore, regional nodes were involved less often in patients diagnosed biochemically ([5/28]; Group I, 2/22 and Group II, 3/6) than in those diagnosed clinically (Group III, 15/24, $p < 0.02$). Distant metastases were only evident in Group III patients. Patients with MEN II who had the diagnosis of MTC established biochemically rather than clinically, had a more favorable pathological stage of disease at the time of thyroidectomy. This was especially true if the biochemical diagnosis had been by provocative testing.

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MULTIPLE ENDOCRINE NEOPLASIA type II (MEN II) is a disease inherited as an autosomal dominant trait and characterized by the concurrence of medullary thyroid carcinoma (MTC), pheochromocytoma(s) and parathyroid hyperplasia. Genetically, there appears to be complete penetrance but variable expressivity. The medullary thyroid carcinoma usually develops first, and is present in virtually 100% of patients affected with MEN II, whereas parathyroid hyperplasia occurs in approximately 60% of patients, and pheochromocytoma(s) in 40%.[4] The thyroid tumor cells secrete the hormone calcitonin (CT), and elevated plasma levels (>300 pg/ml) of this polypeptide, either basally or following the intravenous administration of various provocative agents,[3,5–7,9] strongly suggests the presence of MTC even though the patient's thyroid gland may be normal to palpation and radionuclide scanning. Although sensitive "provocative tests" for tumor detection are available, it remains to be demonstrated that patients diagnosed biochemically have a more favorable pathological stage of disease than do those detected by clinical means. In the present study, an attempt was made to resolve this issue.

Materials and Methods

Patient Population

Our evaluation of patients with multiple endocrine neoplasia type II began ten years ago, and initially was limited to a single large kindred. Our study has since expanded and now includes six additional kindreds, and a total of 90 patients with MEN II. Most

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of the data included in the present report concerns 60 new cases of MEN II diagnosed during the last six years.

Clinical evaluation, provocative testing, treatment and follow-up have been performed either at the Duke University Medical Center, Durham, North Carolina, the Johns Hopkins Hospital, Baltimore, Maryland, or the National Institutes of Health, Bethesda, Maryland.

Patient Evaluation and Method of Diagnosis

When patients were first seen, a history and physical examination were performed. A 24 hour urine was collected for determination of catecholamines, vanillylmandelic acid, metanephrine and normetanephrine.

During our evaluation of MEN II kindreds, the method of provocative testing for MTC has changed. Initially, we used the intravenous administration of 15 mg Ca^{++}/kg/4 hours. It was subsequently shown that the intravenous administration of Pentagastrin (Pg); (Peptavlon®, Ayerst) in a dose of 0.5 μg/kg/5 seconds produced a greater increase in plasma CT more quickly than did the four hour calcium infusion.[3,8] We have recently shown,[10] however, that the most effective provocative test and the one currently used by our group consists of the intravenous administration of calcium gluconate (2 mg Ca^{++}/kg/1 minute) followed immediately by an injection of Pentagastrin 0.5 μg/kg/5 seconds. Plasma samples were obtained before and at one, two, three, five and ten minutes after the Pg injection. Peak calcitonin levels usually occurred within three minutes.

All subjects were tested in the fasting state. Blood was immediately chilled at 4° and the plasma separated and stored frozen. Plasma calcitonin levels were determined by a radioimmunoassay method previously described in detail.[1,2,4,9]

Interpretation of Provocative Testing

Almost all normal subjects have plasma CT levels below 250 pg/ml even following Ca^{++} or Pg infusion. Patients with plasma CT values exceeding 300 pg/ml are suspect for having MTC, especially if they are members of an MEN II kindred and at risk. Whereas we formerly tested children ten years of age and older, we now initiate screening as early as five years of age with the parents' consent. This is primarily because we have recently detected MTC in three children, ages seven, seven and eight. Testing is performed annually in all kindred members at risk, and also in those patients who have undergone thyroidectomy for MTC.

Surgery

In patients with MTC, it was essential to exclude the presence of a pheochromocytoma prior to neck exploration. The medullary thyroid carcinoma was managed by total thyroidectomy and resection of lymph nodes in the central portion of the neck from the hyoid bone to the sternum and laterally to the jugular veins. The parathyroid glands were autografted if their viability were questionable or if they were enlarged. A lymph node dissection was performed when metastatic disease was apparent in the lateral neck.

Evaluation of Clinical and Pathologic Parameters

Age at the time of diagnosis. The age (mean ± standard error of the mean) of the 90 patients in Groups I (32 patients), II (8 patients) and III (50 patients) was determined and differences between groups compared statistically by Student's t-test.

Evaluation of plasma calcitonin levels in the postoperative period. Twenty-six patients in Group I, eight patients in Group II and 26 patients in Group III were evaluated postoperatively with provocative testing, and peak plasma calcitonin levels were measured. In each group, the frequency of elevated calcitonin levels was determined and the differences between groups compared statistically by the Fisher exact probability test.

Relationship of tumor size to preoperative basal calcitonin levels. Tumor volumes (in cm^3) were determined in 27 patients in Group I, seven patients in Group II and 16 patients in Group III. In patients with "C-cell hyperplasia" (CCH) the tumor volume was estimated to be <0.02 $cm.^3$ Patients with known metastases were excluded from evaluation. Tumor size was plotted as a function of the preoperative basal calcitonin level and the points evaluated by regression analysis with computation of correlation coefficients.

Evaluation of postoperative stimulated plasma calcitonin levels in patients with regional and distant metastatic disease. Regional (cervical) lymph nodes resected at thyroidectomy were evaluated for metastatic MTC in 22 patients in Group I, 6 patients in Group II and 24 patients in Group III. Peak plasma calcitonin levels following postoperative provocative testing were also determined in these patients and compared. The incidence of node positivity in each group was determined and the differences between groups compared statistically by the Fisher exact probability test. Also, the presence of distant metastases was assessed.

Results

Two hundred and eighty-nine members of seven kindreds with MEN II were evaluated and MTC was diagnosed in 90. When new families were screened, all stages of MTC would usually be found, ranging from clinically detectable disease to that evident only by provocative testing. Those patients without clinically apparent MTC whose undetectable basal CT levels be-

came elevated following provocative testing (Ca^{++}, Pg, or both) were designated Group I. Patients without clinical evidence of MTC who had elevated *basal* plasma CT levels were designated Group II. Patients with clinically evident MTC were termed Group III.

Age of Onset of MTC

The age at which MTC was diagnosed in the 90 patients with MEN II is shown in Figure 1. The age range of the 32 patients in Group I was from seven to 44 years. The mean age was 20.5 ± 1.9 years. The 8 patients in Group II ranged in age from 15 to 58 years. The mean age was 32.5 ± 4.7 years. The 50 patients in Group III ranged in age from 14 to 70 years; the mean age was 34.3 ± 2.0 years. The patients in Group I were significantly younger than the patients in Group II ($p < 0.005$), and the patients in Group III ($p < 0.00005$). There was no significant age difference between the patients in Groups II and III.

In Group I, C-cell hyperplasia (CCH), the premalignant manifestation of MTC,[11] was present in 11 (34%) of the 32 patients evaluated. Although it occurred predominantly in the younger patients, it was present in the two oldest members of this group. Ten (31%) of the 32 patients in Group I were below 15 years of age at the time of diagnosis. Conversely, no patient in Group II and only one patient in Group III was younger than 15 years of age at diagnosis.

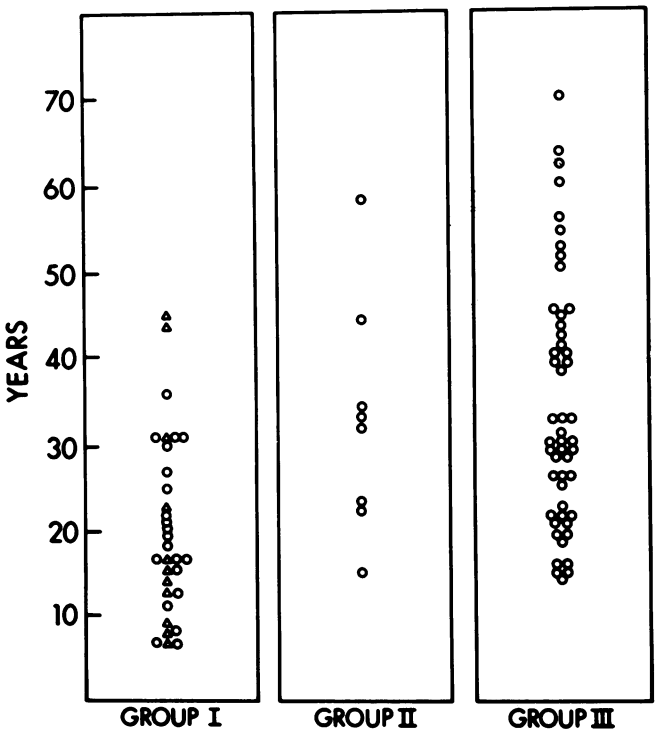

FIG. 1. Age at which MTC was diagnosed in 90 patients. The characterization of Groups I, II and III is described in the text. Each circle represents one patient. The triangles in Group I denote patients with C-cell hyperplasia.

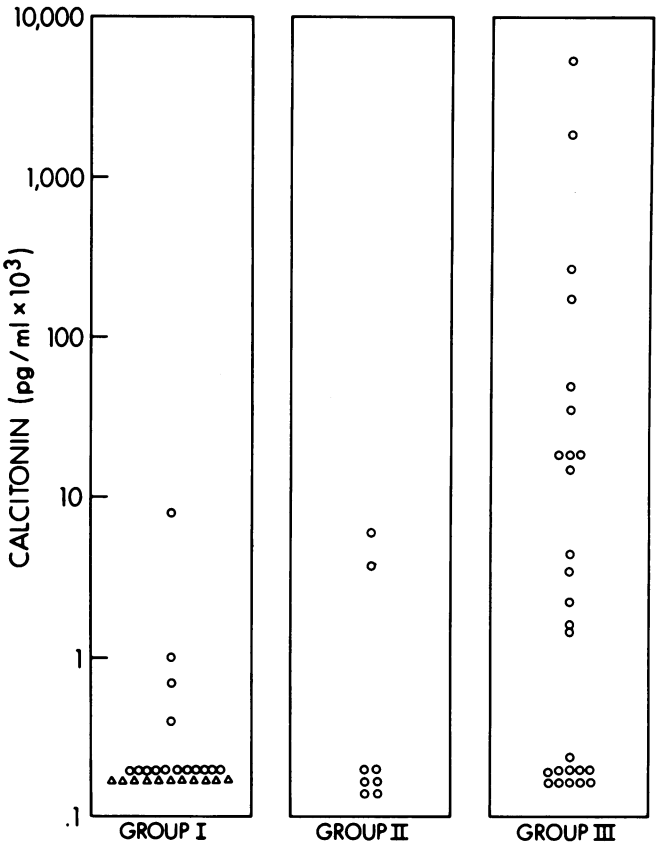

FIG. 2. Stimulated Plasma calcitonin levels in pg/ml ($\times 10^3$) following provocative testing in the postoperative period. Groups I, II and III are described in the text. Each circle represents one patient. The triangles in Group I denote patients with C-cell hyperplasia.

In Group I, 26 (81%) of 32 patients had elevated CT levels diagnostic of MTC when first tested. Five (16%) patients were negative when first tested, but had elevated CT levels one year subsequently. One (3%) 13-year-old patient with undetectable plasma CT levels for two successive years had elevated levels the third year. Seven (88%) of the eight patients in Group II had elevated basal CT levels at their initial examination. One patient (12.5%), however, had not been tested since two years previously when plasma CT levels were undetectable following provocation. All patients in Group III had clinically apparent disease at their initial examination. Elevated basal plasma levels of CT were detected in all of 46 patients evaluated.

Evaluation of Plasma Calcitonin Levels in the Postoperative Period

Probably the most sensitive indicator of curative thyroidectomy for medullary thyroid carcinoma is the level of plasma calcitonin following provocative testing postoperatively. As noted in Figure 2, four (15%) of 26 patients in Group I, two (25%) of 8 patients in Group II, and 15 (58%) of 26 patients in Group III had elevated levels of plasma calcitonin (>300 pg/ml) follow-

TABLE 1. *Stimulated Plasma Calcitonin Levels Postoperatively*

	One Week		One Year		Positive
	+	−	+	−	Conversion
Group I	1	14	1	14*	1 (5 yr)
Group II	0	4	0	4*	1 (3 yr)
Group III	9	9	9	9*	1 (5 yr)

* The incidence of elevated calcitonin levels in patients in Groups I, II and III tested at one week after thyroidectomy and also at one year subsequently.

ing postoperative provocative testing. The mean time of evaluation after surgery was 10.4 ± 3 months in Group I, 10.4 ± 6.5 months in Group II, and 11.6 ± 2.8 months in Group III. Although there was no significant difference in the times following surgery at which the different groups were tested, there was a significant difference in the incidence of elevated calcitonin levels: Group I compared to Group III ($p < 0.002$), and Group I and Group II combined compared to Group III ($p < 0.002$). There was no significant difference, however, when comparing Groups I and II ($p < 0.3$) or when comparing Groups II and III ($p < 0.09$).

A further comparison was made of 15 patients in Group I, four patients in Group II, and 18 patients in Group III who were evaluated one week postoperatively and again one year later (Table 1). Some of these patients were also evaluated subsequent to one year. Of the 15 patients in Group I, only one had elevated CT levels in the immediate postoperative period. This patient also had elevated plasma CT levels at one year. None of the remaining 14 patients in Group I had elevated plasma CT levels, either immediately postoperatively or one year following surgery. However, one patient developed a minimally elevated plasma calcitonin level (>0.40 ng/ml) following provocative testing five years postoperatively. Of the four patients in Group II, none was positive in either the immediate postoperative period or at one year. One patient, however, developed a minimally elevated plasma calcitonin level (>0.56 ng/ml) following provocative testing three years postoperatively. Of the 18 patients in Group III, nine had elevated calcitonin levels with provocation immediately after thyroidectomy. All nine of these patients had elevated plasma CT levels one year later. One of the nine patients with negative CT levels at one week and one year postoperatively developed a positive calcitonin following provocative testing five years later.

Thus, it appears that the stimulated plasma CT level in the immediate postoperative period is an indicator of whether or not surgery has been curative. Obviously, a larger number of patients will have to be evaluated over a longer time period before the reliability of this postoperative evaluation is clear.

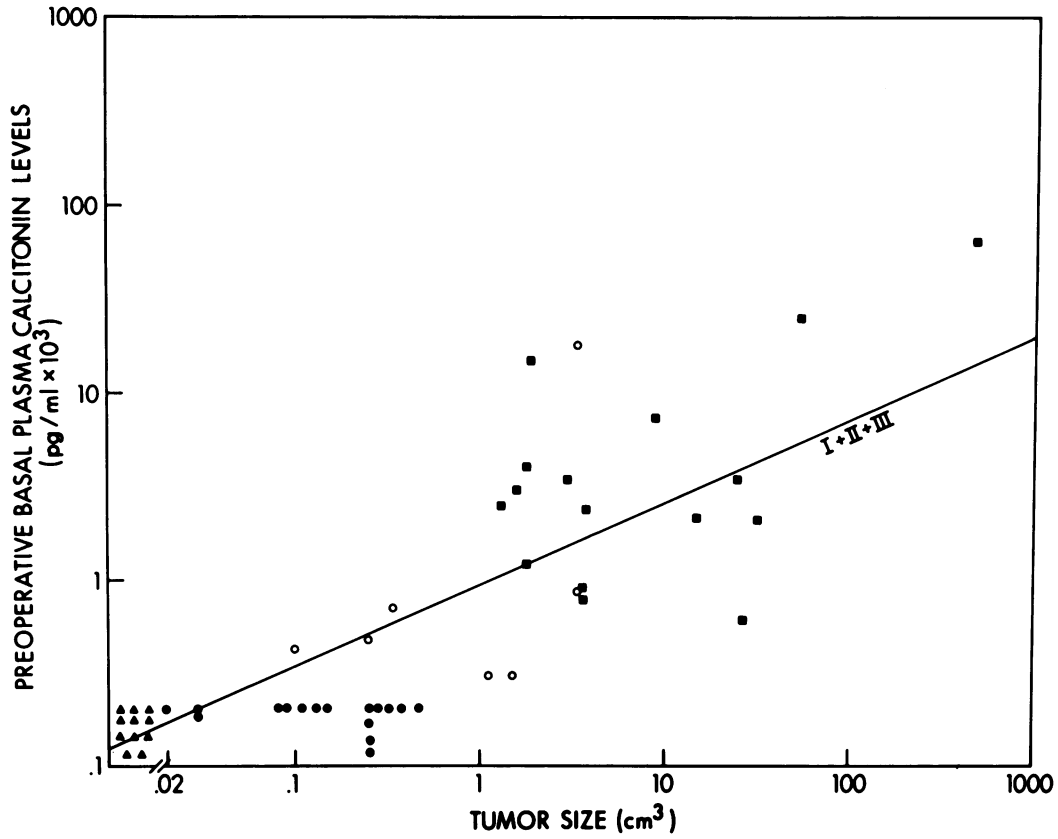

FIG. 3. Correlation of tumor size to preoperative basal calcitonin levels. The calcitonin levels are in pg/ml × 10^3. The tumor size is in cm^3. The closed circles and the closed triangles represent patients in Group I. The closed triangles denote patients with C-cell hyperplasia. The open circles represent patients in Group II and the closed squares patients in Group III.

Correlation of Tumor Size to Preoperative Basal Calcitonin Levels

The relationship between tumor size (in cm^3) and basal plasma calcitonin levels was plotted for patients in Group I, II and III (Fig. 3). A significant positive correlation was noted (correlation coefficient $r^2 = 0.64$, $p < 0.01$), thus demonstrating a direct relationship between tumor size and basal calcitonin levels. Generally patients in Group I had smaller tumors than patients in Group II and patients in Group III.

Incidence of Regional Node Positivity and Distant Metastatic Disease

As shown in Figure 4, of patients in Group I, nodes were evaluable in 22, and metastatic involvement was noted in two (9%) patients. Only one of these patients had an elevated level of plasma calcitonin (770 pg/ml) following provocation postoperatively. Of the eight patients with C-cell hyperplasia, none had evidence of nodal metastatic disease. Of patients in Group II, six had resected lymph nodes evaluated and metastatic deposits were noted in three (50%) patients. Two of these three patients had elevated plasma CT levels following provocation postoperatively, while the third patient did not.

Of patients in Group III, 24 had lymph nodes evaluated at the time of thyroidectomy, and metastatic disease was documented in 17 (71%). Of the patients with positive nodes, distant metastases were present in eight, and all but one had calcitonin levels above 10,000 pg/ml following provocation postoperatively. In six of the eight patients, distant metastatic disease was evident at the time of the initial neck exploration. There was a significant difference in the incidence of node positivity when comparing Group I to Group III ($p < 0.005$), but not when comparing Group I to Group II ($p < 0.08$) or Group II to Group III ($p < 0.34$).

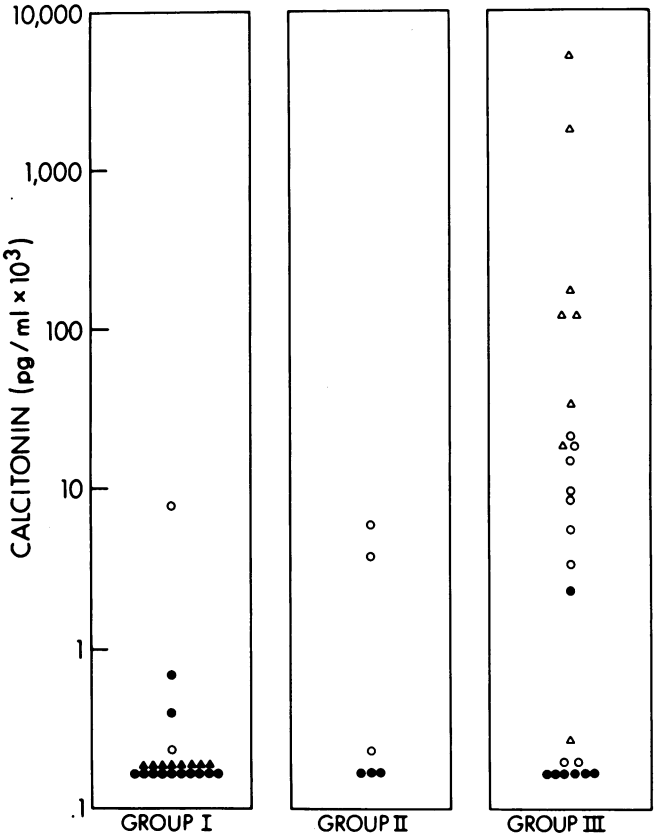

FIG. 4. Incidence of regional node positively and distant metastatic disease in patients of Groups I, II and III. Calcitonin is expressed in pg/ml $\times 10^3$ and Groups I, II and III are described in the text. The open circles represent patients with metastases to regional lymph nodes. The closed circles represent patients with histologically uninvolved nodes. The closed triangles in Group I represent patients with C-cell hyperplasia and the open triangles in Group III represent patients with distant metastatic disease.

Discussion

It is generally assumed that the early diagnosis and treatment of cancer are associated with a low incidence of tumor recurrence and prolonged survival. This is not universally so, however, for in some malignancies, metastases occur early before the primary tumor is evident clinically. It is unusual that the oncologist is able to detect malignancy preclinically; however, such is possible with the MTC in patients with MEN II. This is primarily because the marker hormone, calcitonin, is secreted by the medullary thyroid tumor cells and its concentration in plasma can be determined by radioimmunoassay. Furthermore, various agents,[3,5–7,9] especially Ca^{++} and Pg stimulate CT release from MTC cells, thus increasing plasma levels and thereby the diagnostic sensitivity of the CT assay.

We evaluate and test all MEN II kindred members on an annual or semiannual basis. If a family member is found to have a plasma calcitonin level exceeding 1000 pg/ml, either basally or following provocative testing, total thyroidectomy is advised. If the plasma CT level is less than 300 pg/ml with provocative testing, the subject is re-evaluated in one year. In those individuals whose plasma CT levels are between 300–1000 pg/ml, a catheter is placed transfemorally into the inferior thyroid vein and CT levels are again determined following provocation. Inferior thyroid vein plasma CT values exceeding 1000 pg/ml are virtually diagnostic of MTC or CCH since plasma CT levels exceeding 600 pg/ml rarely occur in unaffected subjects.[8]

Previously, we only tested children older than ten years of age. During the past year, however, we have diagnosed MTC in eight children under ten years of age; currently it is our policy to initiate provocative testing at five years with the parents' consent.

In contrast to patients in Group III, those in Group

I were younger and had smaller primary tumors. Furthermore, Group I patients rarely had metastases to regional nodes or elevated plasma CT levels following thyroidectomy whereas Group III patients commonly did.

It is of interest that C-cell hyperplasia, the premalignant counterpart of MTC, was present exclusively in Group I patients. Even though it occurred predominantly in the younger patients, it also was detected in two 40-year-old patients.

Little can be said about the effect of early diagnosis on survival as the period of follow-up has been short. Generally, the clinical progression of MTC is rapid in patients with sporadic MTC. It is especially virulent in patients with MEN IIb, the variant of MEN II characterized by MTC, pheochromocytoma(s) and mucosal neuromas. Conversely, the MTC in patients with MEN II appears to have a variable rate of progression. The tumor is usually indolent, and in our experience even though patients have metastatic disease, they usually remain asymptomatic and clinically stable for years. Uncommonly, however, the disease is extremely aggressive leading to death within a year or two of diagnosis.

The physician and surgeon should not be lulled into a sense of indifference when managing subjects from MEN II kindreds. It is imperative to initiate a program of provocative testing, especially in young children, so that MTC can be diagnosed at an early stage when treatment appears to be curative.

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Discussion

Professor Ivan D. A. Johnston (Newcastle, England): The calcitonin stimulation test presented by Dr. Wells is really a very significant advance and we can begin to apply it.

It is easy to pick up familial cases. I think it is important, however, for those of us who do not see many cases to realize that only about 5% of all our thyroid cancers will be medullary on histological examination, and it will only be in these patients that the test will be of most value.

I would like Dr. Wells to comment on the fact that sporadic cases of multiple endocrine adenopathy Type II seem to be almost as common as the familial form of the disease that he was discussing with us today. It is in these cases that the test can be of value, i.e., patients with mucosal neuromas, pheochromocytomas etc. The application of the test in these sporadic cases will help to confirm medullary cancer before clinical signs develop. It is, however, difficult to decide exactly which possible cases of the sporadic type of disease we should investigate.

There was a suggestion in the presentation that distant metastases were present in some cases where the postoperative test was negative and all the nodes were free of tumor. This suggests that distant metastases may be indolent for many years.

One of the patients in our series was identified following the resection of a pheochromocytoma, when a liver metastasis was found. The subsequent calcitonin stimulation test was positive. It has taken nine years in this particular patient for a palpable nodule to develop, and the calcitonin stimulation test, using calcium, has remained similar in its response throughout this nine-year period.

How often would Dr. Wells advise us to use this test in our routine postoperative follow up?

Dr. Melvin A. Block (Detroit, Michigan): Our experience with medullary thyroid carcinoma corresponds, for the most part, with that so precisely provided for us by Dr. Wells and his colleagues. It is worthwhile to critically assess the value of early diagnosis, although logic implies a better outlook for disease recognized early in its inception.

In our patient population we have observed a significant difference in the extent of the hereditary variety of medullary thyroid carcinoma when the primary lesions in the thyroid are not palpable (less than 3 mm diameter or at stage of C-cell hyperplasia) at operation (Slide). The diagnosis in these patients is established by an elevated serum calcitonin level. Thus, for 23 patients without a palpable thyroid nodule, all but one patient (96%) have had normal serum calcitonin levels postoperatively, even though a regional neck dissection for metastases was performed for only one of these patients. In contrast, of 16 patients with palpable primary lesions, only two (12.5%) have had normal serum calcitonin levels postoperatively, even though lateral neck dissections were performed to remove metastases for 11 patients.

In further contrast and differing from the report by Dr. Wells, for our 19 patients with sporadic medullary thyroid carcinoma detected only by a palpable and large thyroid nodule, 10 (53%) have had normal serum calcitonin levels postoperatively even through lateral neck dissections for lymph node metastases were performed for 12. It is to be recalled also that the sporadic variety of medullary thyroid carcinoma has usually been recognized at an older age than the hereditary variety.