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.

Thus, we have followed the policy of omitting lateral cervical lymph node dissections if the patient with hereditary medullary thyroid carcinoma, operated only on the basis of an elevated serum calcitonin level, is not found to have a palpable thyroid lesion at operation and a mid-jugular lymph node is negative for metastasis. In such patients, only slight elevations of serum calcitonin have usually been present preoperatively, even with the use of provocative agents. Each side of the neck is individualized in these considerations. This policy is supported by postoperative tests with provocative agents which are now so sensitive that collections of a few cells of medullary thyroid carcinoma, evident only microscopically, can be detected. The great importance of this is that earlier detection not only can permit a greater chance for "cure" but also a reduced extent of operation.

Only time will determine the overall lifesaving value of early detection of medullary thyroid carcinoma, although current information indicates this. Thus, we have observed elevations of serum calcitonin in a number of our patients recently reported, without clinical evidence of metastatic carcinoma, these patients living asymptomatically for many years after eradication of the disease from the neck. Also, we do not yet know if this group of patients has a susceptibility for another neoplasm, once the medullary thyroid carcinoma is controlled.

I would like to ask the authors several questions. First, are they willing to omit a lateral cervical lymph node dissection for certain patients, such as those without a palpable primary lesion in the lobe of the thyroid under consideration? A total thyroidectomy is considered necessary for all patients with the hereditary variety of thyroid carcinoma.

Second, is there an age level for kindred of families involved by hereditary medullary thyroid carcinoma at which point a negative test makes further determinations of serum calcitonin unnecessary?

Third, have the authors established the diagnosis of medullary thyroid carcinoma for a patient only on the basis of an elevated serum calcitonin after provocation with both pentagastrin and calcium where the test with pentagastrin alone was normal?

DR. ROBERT C. HICKEY (Houston, Texas): It's been less than two decades since Hazard and his colleagues carved out from the thyroid carcinoma milieu medullary, or solid, carcinoma of the thyroid, and for a decade we have had a tool, immunoreactive serum calcitonin, as a biological marker. It's one of high specificity and sensitivity.

In testing since 1974, and looking at Dr. Wells' second slide, we have used pentagastrin exactly as he has outlined it in his Test No. 3. We have found pentagastrin more powerful, more reliable and less time-consuming than the calcium infusions, and comparing thirteen patients where both tests were used (the calcium and the pentagastrin) the calcium was found less reliable. We have not used a combination of the two.

At the M. D. Anderson, we have now something over 140 patients with medullary carcinoma of the thyroid, and we have carved out one subset of 32 patients to study sequentially, pre- and posttherapy, whether the therapy might be by surgery, radiation therapy, chemotherapy or hepatic artery embolization. In this group there were 16 patients in the familial group; the others were sporadic. In the familial group the family history was very critical, as were the calcitonin levels, in the making of the diagnosis. Of the 16 patients in the familial subset, the average age was one decade less than the sporadic, and all of these, interestingly enough, had bilateral, multifocal disease; only one half had such in the sporadic group, and in terms of extrathyroidal disease, they were less advanced in the familial group.

Now, attempting to clearly correlate the extent of disease and the therapeutic procedures by the calcitonin levels, there are some cloudy areas. There is no question that calcitonin is an excellent tool in screening and in diagnosis, and I believe that, carefully interpreted, it aids in following the clinical course of the patients.

We would suggest that when the disease is confined to the thyroid, the calcitonins will be relatively low initially and be reduced postoperatively. With regional nodal spread, a low level may be reached posttherapy—surgically—and it will rise subsequently. There is no firm correlation, as far as we can determine, between the number of cancerous regional nodes that are removed and the preoperative and the postoperative calcitonin levels. This may be related to the biological aggressiveness of the disease.

As Dr. Block has said, we have 20 patients with elevated calcitonin levels and no clinical evidence of disease. It may be that micrometastatic, quiescent disease is the cause of such elevations.

Gross metastases, particularly to the extracervical region—to bone and to viscera, and especially to the liver—are associated with conspicuous elevated levels, and at the time of impending death from metastases, the calcitonin levels are conspicuously elevated.

DR. SAMUEL A. WELLS, JR. (Closing discussion): Regarding Dr. Johnson's question of the frequency of occurrence of sporadic MEN II, we are not sure that we have a well documented case of this. The variant syndrome, MEN IIB (medullary thyroid carcinoma, mucosal neuromas and pheochromocytomas) is almost always sporadic, however, familial occurrence has been reported. MEN IIB is the most virulent form of medullary carcinoma. The disease progresses rapidly, metastasizes early and causes death at a relatively young age.

We only have one patient with a positive clinical diagnosis and yet normal calcitonin levels. In the process of metastasizing, the tumor apparently selects for a cell which does not produce calcitonin. This is extremely unusual in medullary thyroid carcinoma; however, it has been reported in oat cell carcinoma. The primary oat cell tumor contains the enzyme histaminase; however, this substance is infrequently detected in metastatic tumor cells.

Regarding the indolence of the disease, this is a characteristic of the MTC in patients with MEN II. We have patients who have been diagnosed at 70 years of age. They have primary disease, have never undergone surgery, and are essentially asymptomatic except for a neck mass. Also, we have several patients with metastatic disease who have demonstrated no clinical progression and no change in basal calcitonin levels for years.

Probably the most important factor in evaluating patients for treatment with chemotherapy is not the calcitonin level when they are initially observed, but rather how rapidly this level increases over a given period of time. Patients who demonstrate a rapidly increasing calcitonin level over a few months obviously have a more aggressive disease than those who maintain stable calcitonin levels without increases.

In regard to Dr. Block's comment, we have usually done a total thyroidectomy with a central neck dissection taking the nodes medial to the jugular veins and from the hyoid bone to the sternal notch. Patients with MEN II always have bilateral medullary thyroid carcinoma unless part of the thyroid has previously been resected. We have not seen a single exception to this.

We do not know at what age provocative testing should be terminated in MEN II kindred members at risk. As I have shown in this presentation, two of the patients with C-cell hyperplasia diagnosed by provocative testing were 44 and 45 years of age. Currently we are recommending that patients be evaluated until the age of 45, but perhaps this is too conservative an approach.

In answer to your question regarding the combined use of calcium plus pentagastrin, this slide demonstrates that compared to either pentagastrin alone or calcium alone, the combined infusion of these two substances was generally superior. As can be noted, there were three patients who would not have been diagnosed if either calcium alone or pentagastrin alone had been used as provocative agents. With both of these agents administered in combination, however, calcitonin levels diagnostic of MTC were elicited. Furthermore, occasional patients will have elevated levels of calcitonin following pentagastrin alone but not calcium, and vice versa. We are therefore currently using only the intravenous administration of calcium gluconate *and* pentagastrin.

Regarding Dr. Hickey's remarks, I would again like to stress that this disease can be very indolent, and patients can maintain evidence of nonprogressive metastatic medullary thyroid carcinoma for exceedingly long periods of time.