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## Impact of Screening on Prognosis in the Multiple Endocrine Neoplasia Type 2 Syndromes: Natural History and Treatment Results in 105 Patients

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*We evaluated the effects of screening for multiple endocrine neoplasia type 2A (MEN-2A) in 12 families. Genealogical studies going back to 1730 show a common ancestry for seven Swedish families and one American family. The total number of patients included 105 individuals, 68 of whom were diagnosed by our screening program.*

In Sweden, the starting point for our studies in multiple endocrine neoplasia type 2A (MEN-2A, or the Sipple syndrome) was rather unusual, namely, the cytology of medullary carcinoma of the thyroid (MTC). In 1968 Professor Nils Söderström, a pioneer in fine needle aspiration biopsy (1), drew my attention to a then unknown and undescribed tumor cell which differed from all other types of thyroid cells we had seen. These cells had been found in aspirates of a thyroid nodule in a 32-year-old woman, who was under investigation for a suspected pheochromocytoma. This patient died suddenly in a hypertensive crisis, during angiography of her adrenal glands. Autopsy revealed bilateral pheochromocytomas, bilateral multifocal MTC, and a parathyroid adenoma. Nothing was known about her family history.

When the family was screened, we found MTC and/or pheochromocytoma in the mother, aunt, two uncles, and a cousin of our first proband or index case (Fig. 1). The pedigree of this "family I" has been published (2). Cytology obtained by fine needle aspiration biopsy was used as the initial screening method for MTC in this particular family, and the characteristic features have been described (3).

### Development and Results of Screening Techniques

Newly developed screening methods have been directed more toward MTC than toward pheochro-

*Our screening methods for medullary carcinoma of the thyroid (MTC) had an optimal sensitivity and specificity. The frequency of gene carriers detected in MEN-2A families was 55%. Screening will lead to early diagnosis and early therapy, which in turn, will significantly decrease morbidity, incidence of surgical complications, and mortality related to the tumors of this hereditary syndrome.*

mocytoma. Employing the following techniques, we found four other MEN-2 families and many new cases of MTC (2).

#### MTC cytology

The cells, as seen in air-dried smears stained with May-Grünwald-Giemsa, are often triangular with a fine red granulation. Some have cloudy, grey-blue inclusions in the cytoplasm, which have proved to be amyloid.

In alcohol-fixed aspirates stained with eosin-hematoxylin, the amyloid is light red. However, when stained with alkaline Congo red and viewed in polarized light, the amyloid appears with a faint apple-green color.

This cytological technique is an effective diagnostic method in patients with palpable MTC, both sporadic

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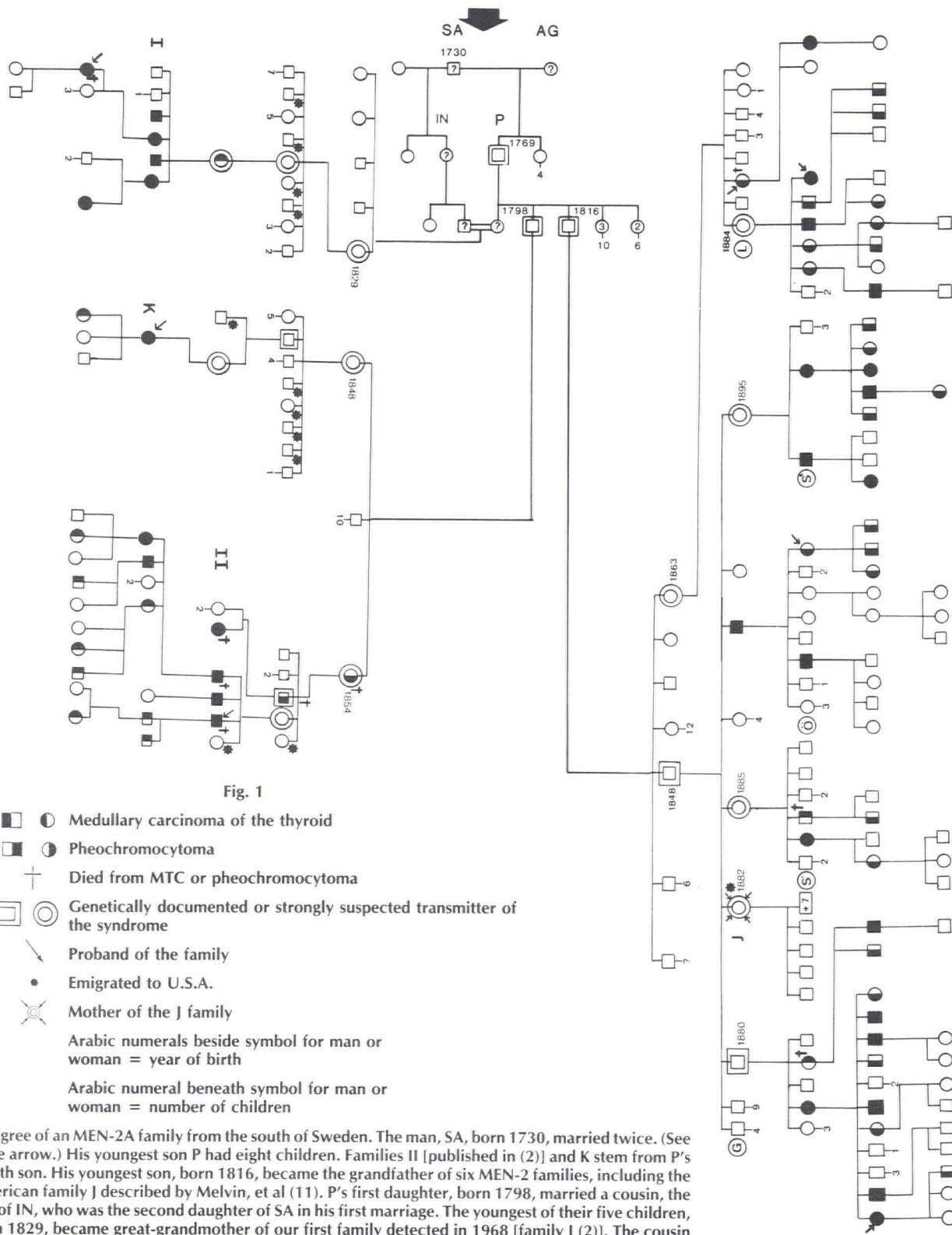


Fig. 1

- ○ Medullary carcinoma of the thyroid
- ▣ ● Pheochromocytoma
- † Died from MTC or pheochromocytoma
- ○ Genetically documented or strongly suspected transmitter of the syndrome
- ↘ Proband of the family
- Emigrated to U.S.A.
- ⊗ Mother of the J family
- Arabic numerals beside symbol for man or woman = year of birth
- Arabic numeral beneath symbol for man or woman = number of children

Pedigree of an MEN-2A family from the south of Sweden. The man, SA, born 1730, married twice. (See large arrow.) His youngest son P had eight children. Families II [published in (2)] and K stem from P's fourth son. His youngest son, born 1816, became the grandfather of six MEN-2 families, including the American family J described by Melvin, et al (11). P's first daughter, born 1798, married a cousin, the son of IN, who was the second daughter of SA in his first marriage. The youngest of their five children, born 1829, became great-grandmother of our first family detected in 1968 [family I (2)]. The cousin marriage makes it impossible to determine whether the gene transferred to family I originated from SA via IN or from AG.

and hereditary. It is simple, quick, inexpensive, with a sensitivity exceeding 90% (4) in patients with a palpable tumor. Fluorescamine, which reacts with primary amino-groups to yield intense fluorescence, can also be of value in the cytodiagnosis of MTC. Fluorescamine induces an intense fluorescence in cells from medullary and papillary thyroid carcinoma. No fluorescence is detected in cells from follicular or undifferentiated carcinoma or from benign thyroid lesions other than Hürthle cell adenomas, which do exhibit a moderate fluorescamine-induced fluorescence. These reactions can be demonstrated on fine needle aspiration biopsy smears pretreated with formaldehyde gas (5).

#### **Chemical diagnosis of MTC**

In addition, we followed the same route taken by our American colleagues and developed a sensitive radioimmunoassay for human calcitonin (6). We found that the four-hour calcium infusion test increased the diagnostic sensitivity of serum calcitonin assays as compared to basal values (7). Pentagastrin injected either subcutaneously or intravenously was equally effective, faster, and less troublesome for the patient (8).

We also tested the effectiveness of ethanol (given orally as 50 ml of whiskey), native porcine cholecystokinin-pancreozymin (CCK-PZ), and the synthetic octapeptide (C8-CCK) administered intravenously. Alcohol had the lowest diagnostic sensitivity. CCK-PZ and C8-CCK were better, but all were inferior to the four-hour calcium infusion test (8).

We used the combined stimulation test with calcium (2 mg/kg injected rapidly IV for one minute) followed immediately by pentagastrin (0.6 µg/kg IV)\* as recommended by Wells, et al (9). However, this combination did not substantially increase the diagnostic sensitivity of pentagastrin alone. Moreover, the use of two different substances in the diagnostic test doubles the risk for miscalculations of the amount to be injected.

#### **Total diagnostic sensitivity and specificity**

The sensitivity and efficacy of present diagnostic procedures for MTC are considered optimal. The disease was diagnosed in 55% of all MEN-2 family members examined (excluding the index cases), a figure which compares well with the theoretical, expected frequency for an autosomal dominant gene with high penetrance.

Since we have encountered no false positives, the diagnostic specificity is remarkably good. On the other hand, diagnostic sensitivity is so high that the tumors can be identified at an exceptionally early stage, and microscopic C-cell hyperplasia (CCH) can be detected. This contrasts with our screening methods in the late 1960s when tumors only as large as 1.5-2 cm or more in diameter could be diagnosed preoperatively by the fine needle aspiration biopsy technique. Methods for the early diagnosis of pheochromocytomas are not com-

parably efficient, and it is likely that many early cases of adrenal medullary hyperplasia and small pheochromocytomas remain undiagnosed. In our search for a safe and sensitive diagnostic method, we have evaluated the plasma catecholamine release during physical exercise. The results seem promising for the identification of early pheochromocytomas and also for the differentiation from nonpheochromocytoma patients with neurovegetative lability (10).

### **Ethical Aspects of Screening and Medical Intervention**

Our screening has been based on these hypotheses:

- The earliest stages of the MTC tumor (C-cell hyperplasia) will eventually develop into a clinically manifested cancer.
- Effective screening will lead to early diagnosis.
- Early diagnosis improves the results of surgery and makes possible a better prognosis.

After 15 years of screening, these hypotheses can be tested. The ethical aspects of screening and early intervention should be the subject of another discussion. The aim of this study is to test the validity of our hypotheses. An important part of the evaluation is to determine the clinical benefit. It is not enough to be able to delineate the MEN-2 kindred, develop sensitive diagnostic methods, and detect MTC at a very early stage unless we can decrease the adverse impact of the disease on the patient's life.

Screening programs for hereditary cancer have many drawbacks. They place a heavy burden on family members, both those who will develop the disease and those who will not. All members may have seen close relatives die, perhaps dramatically and unexpectedly, and regular testing may arouse anxiety for cancer. However, the tests may also bring a sense of security and support, and measures should be taken to minimize anxiety.

The cost-benefit analysis reveals that regular testing involves costs for both the patient and for society. Necessary genealogical studies are also difficult and time-consuming. Proof of benefit is necessary to encourage the continuation of this work.

### **Genealogical Studies and Patient Material**

In the early years of screening, development of new diagnostic methods for MTC helped us to detect many new cases in the four families examined (2). Since 1976, genealogical studies have extended the patient material considerably. Six seemingly different families have

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\*Ed. note: The dosage commonly used is 0.5 µg/kg.

been shown to be related to each other. Our families I and II were recently shown to be related to five other families which were detected during 1971-1978 (Fig. 1). These kindreds had a common ancestor born in 1730 in Sweden. This man has several hundred descendants, many of whom still remain to be traced. In addition, we have found that the J kindred in the United States described by Melvin, et al (11) and the family in Sweden described by Ljungberg, et al (12) represent two other branches of this enormous family tree.

Genealogical studies tracing the linkage between these families were very difficult and time-consuming. Many population registers were destroyed when an old wooden parish church burned down in 1850. Many of these relatives lived in this parish during the 18th and 19th centuries. We studied records of populations, wills, inventories of the deceased's goods, chattels, and other legal acts. Prime sources of information were parish registers, catechetical meeting reports, and baptismal records. Figure 1 is an abbreviated pedigree of this very large family. Omitted are branches that are either incompletely known or that have been shown to be healthy.

We consider that the male SA carried the gene since he married twice, and one child from each marriage seems to have been a carrier of the gene. However, the son of his second daughter IN married a cousin, who was the daughter of his fourth child P from the second marriage. This female cousin born in 1798 might also have been the gene carrier, and if so, either SA or his wife AG had the gene for the MEN-2A syndrome.

In the fourth generation after SA, a woman born in 1882 transferred the gene. She gave birth to four children in Sweden. The family then moved to the United States where she later had seven children. In the early 1970s MEN-2A was diagnosed in several members of this American family (J), which has been described by Melvin, et al (11).

Figure 2 shows the pedigree of the F family from the west coast of Sweden. No positive documentation has been found that this family is related to the one above. Of course, illegitimate connections cannot be excluded. There are two interesting features of this family: First, they seem to have an unusually malignant disorder. Many individuals died of MTC, and the disease seems to have an extraordinarily malignant behavior in those surviving; second, only a few (8%) have had documented pheochromocytoma, whereas the prevalence of pheochromocytoma in our entire patient population is 44%.

### Patient Material

Our present total patient group consists of 105 documented carriers of the MEN-2A gene from 12 apparently

unrelated families. Two families come from Finland, and one index case is Danish. These 105 patients have been subdivided into the following groups:

1. Twenty-nine individuals (including the probands or index cases) noticed symptoms of a thyroid tumor and sought medical advice on their own initiative. This group is called the symptomatic group.
2. Sixty-eight individuals had MTC diagnosed by the screening program. None of these had sought medical advice because of MTC or pheochromocytoma. However, 20 of them were found to have palpable thyroid tumors. This patient group is called the screening group.
3. Three individuals have had slightly raised levels of S-calcitonin at repeated pentagastrin tests. These borderline cases are believed to have C-cell hyperplasia (CCH) and will have surgery.
4. Five individuals who were genetically documented gene carriers died from pheochromocytoma. None of these had been investigated for the possible co-existence of MTC.

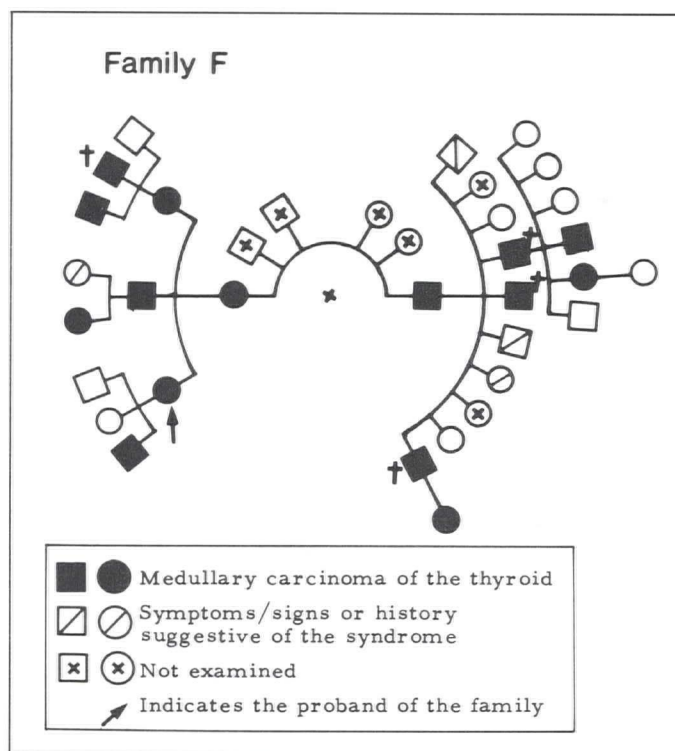


Fig. 2

Pedigree of family with MEN-2A from the west coast of Sweden.

To document the possible benefits of screening and a medical intervention program, we can compare the results of diagnosis and treatment in the screening group with the results in our symptomatic group.

Many of the patients in the symptomatic group did not have the diagnosis of MTC established before surgery because they were thought to have a benign goiter. Thus, they did not have operations designed for thyroid carcinoma, ie, total thyroidectomy and lymph node exploration. Several had reoperations when the histopathology revealed the malignant nature of the goiter. This lack of preoperative knowledge is considered to have had a negative influence on the outcome of treatment.

### Incidence of MTC at Age of Diagnosis

Figure 3 illustrates the use of a screening program with sensitive methods to compare the screening and symptomatic groups. Patients in the screening group were younger than in the symptomatic group, ie, the MTC diagnosis was established at an early stage. Most of the individuals in the screening group had nonpalpable tumors, whereas all in the symptomatic group had palpable MTC.

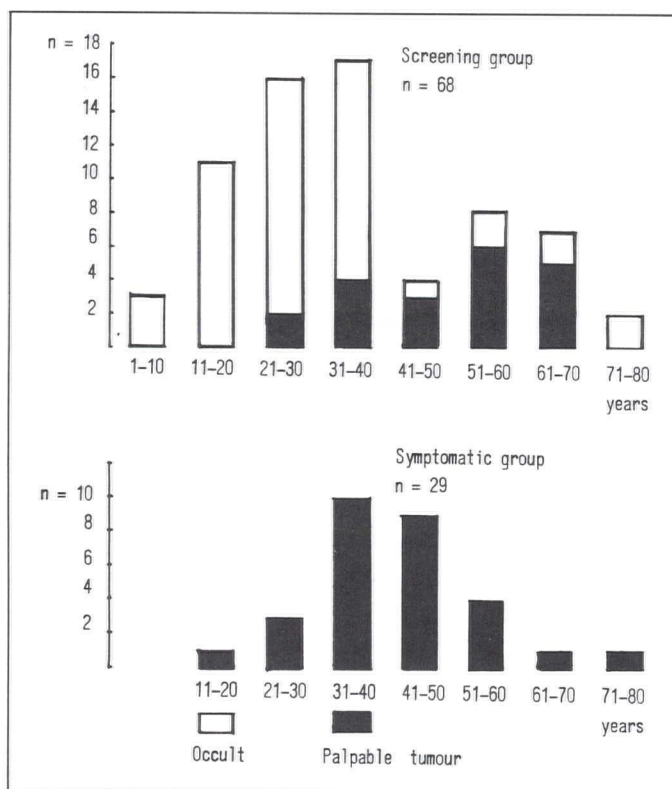


Fig. 3

Incidence of MTC in relation to age at diagnosis in the screening group and in the symptomatic group. Unfilled areas represent patients with occult, nonpalpable tumors; filled areas, patients with palpable tumors.

### Incidence of Pheochromocytoma and Age at Diagnosis

In several of the 46 patients with pheochromocytoma, the diagnosis was established only after death, at autopsy, or too late for therapy (Fig. 4). Some died during operation for pheochromocytoma or during diagnostic intervention such as angiography. Most of these hereditary pheochromocytomas became clinically apparent in the fourth decade of life, when 74% of the patients with MTC in this decade were shown to have pheochromocytoma.

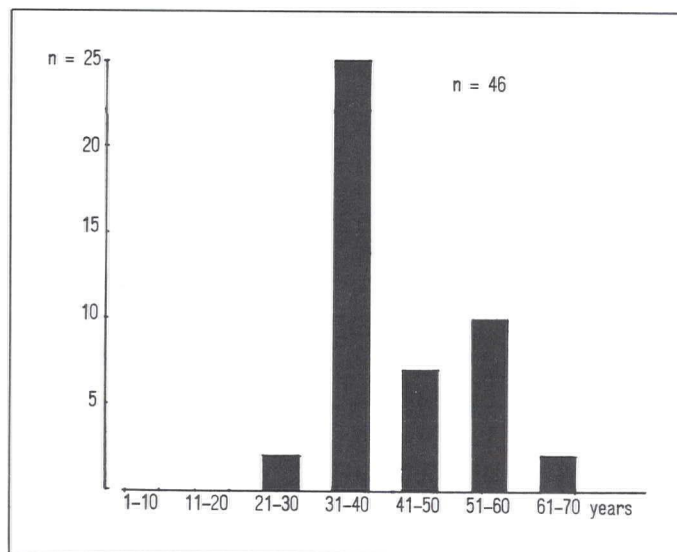


Fig. 4

Incidence of pheochromocytoma in relation to age at diagnosis.

The total frequency of pheochromocytomas in our patients was 44%. It is probable that in the screening group the number of pheochromocytomas will be higher. In the past, many MEN-2 patients died without evaluation for the possible coexistence of pheochromocytomas, even at autopsy.

### Results of Surgical Therapy of MTC

The results of therapy in the screening group were compared to those of the symptomatic group (Fig. 5, Table 1). Strict criteria for curative and noncurative treatment are necessary. The patient was considered curatively treated if no signs or symptoms of tumor disease remained, and/or S-calcitonin levels were unmeasurable or below the reference interval for healthy, nonthyroidectomized controls during pentagastrin test. Noncurative classification was defined as: 1) death from metastases of MTC, 2) documented metastases of MTC, 3) raised levels of S-calcitonin basally and/or after stimulation with pentagastrin.

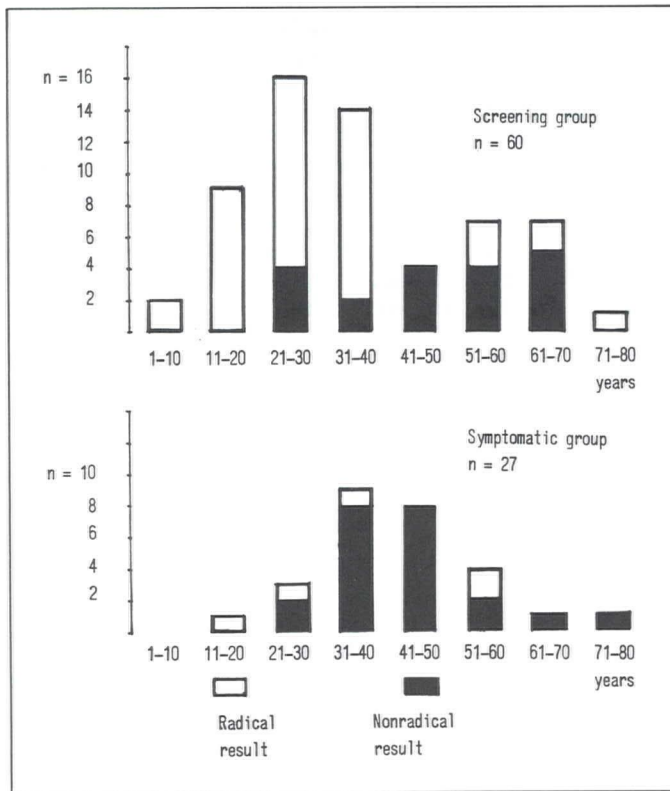


Fig. 5

Results of surgical therapy for MTC in the screening group and in the symptomatic group. Unfilled areas represent curatively treated patients; filled areas, noncuratively treated patients.

TABLE I

Curative Treatment and Mortality in MTC Patients

Patient Group	Curative Treatment	Mortality	
		MTC	MTC and Pheochromocytoma
Screening group (68)	68%	1.5%	1.5%
Symptomatic group (29)	19%	24.0%	34.0%

In the screening group, the majority of patients (68%) were curatively treated. Median observation time after surgery was more than five years. Young patients in the screening group had an especially good chance to be curatively treated, whereas in the symptomatic group, only a few (19%) were considered to be curatively treated.

### Natural History of MEN-2A

To evaluate the results of our screening efforts we must know more about the natural history of hereditary MTC

and pheochromocytoma, ie, the life expectancy in MEN-2A when no treatment is given (Table II). To illustrate one aspect of the biology of the disease, we evaluated 16 patients who died from the disease. These patients received either no treatment at all or treatment only at a very late stage of the disease, so that surgery was judged to have little influence on the prognosis. Eight individuals died from documented MTC (five men, three women). Median age at death was 55 years. Eight individuals died from pheochromocytoma (five women, three men). Median age at death was 41 years. Two women died at childbirth.

TABLE II

Age at Death of Patients with MTC and Pheochromocytoma

Age Ranges	MTC	Pheochromocytoma
31-40	1	4
41-50	1	2
51-60	3	2
61-70	2	0
71-80	1	0
<b>Total Number of Patients</b>	<b>8</b>	<b>8</b>
<b>Median Age</b>	<b>55</b>	<b>41</b>
<b>Male/Female</b>	<b>5/3</b>	<b>3/5</b>

### Mortality in Treated Patients

In the treated patients in the symptomatic group, mortality related to MTC was 24% as compared to 1.5% in the screening group (Table I); 10% of the patients in the group with symptomatic MTC died of pheochromocytoma. Thus, a total of 34% in the symptomatic group died from their hereditary tumor disease.

### Relationship Between Tumor Size, Stage of Neoplastic Disease, and Results of Treatment

Our hypotheses concerning a relationship between the size of tumor, stage of the neoplastic disease, and results of treatment have also been confirmed (Table III).

1. Twenty-seven patients had thyroid tumors less than 5 mm in size at operation. In 26, no lymph node metastases could be documented. In one 18-year-old girl, microscopic metastases were found in two cervical lymph nodes. Her primary tumors were very small and were found only after careful sectioning of the thyroid. This patient, although probably exceptional, illustrates that MTC may metastasize at an extremely early stage when the primary tumor is minimal and not readily visible even in the sectioned thyroid gland.



TABLE III  
Relationship Between Tumor Size, Stage of Neoplastic Disease,  
Results of Treatment, and Complication Rate

Number of Patients (n)	Tumor Size (mm)	Lymph Node Metastases		Results of Surgery				Complication Rate (%)
		n	(%)	Curative Treatment n	(%)	Noncurative Treatment n	(%)	
27	< 5	1	(4)	27	(100)	0	(0)	19
14	≥ 5 - <20	7	(50)	8	(57)	6	(43)	0
41	≥20	29	(71)	6	(15)	35	(85)	65

2. Fourteen patients had tumors with a diameter of greater than 5 mm but less than 20 mm. In seven, no lymph node metastases were found. Eight patients were considered curatively treated and six non-curatively treated (43%).

3. Forty-one patients had tumors larger than 20 mm. Of these, 29 had documented lymph node metastases (71%); only six (15%) were curatively treated in this group.

Tumor size has a definite relationship to the incidence of complications (Table III). Operations of large tumors carry a much higher risk of damage to the recurrent nerves and parathyroid glands, which may have to be sacrificed in order to achieve hope of cure. However, from the standpoint of the patient, these are viewed as complications of the tumor disease. Screening, leading to early diagnosis, will diminish the risk of these complications.

### Conclusions

We have verified that our hypotheses from the late 1960s are valid:

- The MEN-2 syndromes have a high penetrance, and if untreated, gene carriers have a high death rate.

- If the patient does not seek medical advice and treatment until symptoms have already appeared, the prognosis for cure is poor (19%), and mortality is high (34%).
- A clear relationship exists between size of the primary tumor, prevalence of lymph node metastases, and results of treatment.
- Screening methods are reliable and practical. They have a very high sensitivity and efficacy for MTC but less so for pheochromocytoma.
- Screening will lead to early diagnosis and early therapy which, in turn, will decrease the incidence of surgical complications and improve the prognosis for cure and life expectancy.

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