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Clinicopathological Study of Gastric Cancers and Precancerous States Detected by Fetal Sulfoglycoprotein Antigen Screening[1]

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ABSTRACT

A clinicopathological analysis is presented of gastric cancer cases detected in a mass screening trial in Finland, using the oncofetal antigen, fetal sulfoglycoprotein antigen, as a marker. The survey covered a population of 53,020 between the ages of 40 and 70, the percentage of participation being 74.8%. Of these participants, 3,508 subjects (8.8%) were found to be fetal sulfoglycoprotein antigen secretors, and among them 36 gastric cancers, one gastric carcinoid, and 10 tubular adenomas were detected. Both main histological types of gastric cancer, intestinal and diffuse, were represented. There were 15 early cancers. In addition, there were three widely spread superficial cancers. Because of early diagnosis, the prognostic view for these cases is clearly better than that found in the clinic by conventional means, curative resection being carried out in 28 cases (78%).

INTRODUCTION

During carcinogenesis, a series of events leads to biochemical changes expressed in the structure of the cell surface and in cellular secretory products (4). The process of cell transformation occurs stepwise, and the appearance of oncofetal expressions is not necessarily followed by the development of malignancy (23, 26). This may even be the most common course of events, malignant transformation being a rare exception. Our observations on the behavior of FSA[3] associated with gastric cancer (9, 11, 14, 15) give support to this suggestion. For instance, in a healthy population in the age group 40 to 70, there are a certain number of people (6.5 to 8.8%) secreting FSA into the gastric juice in amounts not distinguishable from those in clinical cases of gastric cancer (12, 13). It seems likely that the amount of FSA in gastric juice is not directly correlated to the number of malignant cells, although a part of the antigen could originate from these cells.

The idea of using FSA as a marker in screening for gastric cancer is as follows. We assume that in a stomach which will develop cancer in the near future there is a period when some of the mucosal cells begin to secrete FSA like the FSA secretors of healthy populations. At the time of the appearance of true malignant cells, the secretory rate of FSA would already be within the range of detectability by the microimmunodiffusion test. These individuals are detected as FSA positive in screening studies and consequently undergo endoscopy. Cancers can be thus detected at a very early state. Two essential practical problems, the acceptance of gastric intubation and gastroscopy by asymptomatic people, have been investigated in earlier pilot studies (12, 13). It appeared that people belonging to groups that are known to have gastric cancer as a common problem will accept measures like gastric intubation for an aspiration sample. A personal motivation is needed for gastroscopy, and a positive finding of FSA serves this purpose well. The opportunity to serve as controls for the FSA-positive group was not sufficient motivation for endoscopy.

The present mass screening for gastric cancer (about 50,000 subjects in the age group 40 to 70) was designed to answer to 2 questions: (*a*) how early are the gastric cancers detectable by FSA; (*b*) how many of the gastric cancers present in the population can be detected by FSA? The present paper aims at answering the first question. The second, closely related problem will be analyzed separately. Our epidemiological problem is that unselected populations in our country have not and cannot be submitted to gastroscopy, and the true prevalence of gastric cancer is not known with precision. Consequently, comparative and epidemiological evaluation must be based on other data available: (*a*) incidence and statistical prevalence data from the Finnish Cancer Registry; (*b*) corresponding incidence rates in Japan and results of the Japanese mass screenings (19, 24) reflecting the prevalence of gastric cancer; (*c*) clinical experience from several countries indicating that the latent period of macroscopic gastric cancer is 1 to 2 years (7) [retrospective interpretations without histological confirmation (31) possess little value in estimating the latency]; (*d*) experimental models (27) indicating that the growth rate of cancer follows certains rules and that, consequently, the prevalence and incidence are interrelated; (*e*) follow-up of the cohort screened by FSA for registration of all clinically manifested gastric cancers.

MATERIALS AND METHODS

The material consists of gastric cancer cases and a group of potentially malignant cases (tubular adenomas) revealed in an extensive mass screening study in Finland.

All the inhabitants between the ages of 40 and 70 in 46 communes in southwest Finland, 53,020 altogether, were invited between 1974 and 1977 to a screening for gastric cancer. Altogether, 39,706 people (74.8%)[4] participated. The marker used in the screening was a cancer-associated antigen, FSA. Details of this immunological screening method as well as the characteristics of FSA have been described earlier (9–15). Of the subjects who accepted the invitation, 8.8% were found to secrete FSA. All 3,508 FSA secretors were invited to clinical examination by endoscopy combined with biopsy, and 95.2%

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[3] The abbreviation used is: FSA, fetal sulfoglycoprotein antigen.

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[4] We excluded 260 people in the same age group who moved into the region after the lists were drawn up and participated on their own initiative when the percentage of participation was calculated.

Table 1

Endoscopy findings for gastric cancers detected by FSA screening

Case	Sex	Age	First gastroscopy	Reendoscopy	Interval (mos.)	Japanese class	Largest diameter (cm)	Depth of invasion	Cancer type	Location of cancer
1	F	68	Tumorous infiltrate			IIB, IIC	3	SM[a]	Int.	Antrum, curv. major
2	M	59	Gastritis			IIB	Widespread	SM	Int.	Corpus
3	F	57	Malignant—suspected ulcer			IIA, IIC	Widespread	SM	Diff.	Angulus, anterior wall
4	F	68	X-ray diagnosis, no endoscopy				Widespread	SS + E	Diff.	Whole stomach
5	M	62	Gastritis	Tumorous infiltrate	11		Widespread	SS + E + L	Int.	Cardia
6	M	65	Tumorous infiltrate			IIA, IIB	7	SM	Int.	Antrum, posterior wall
7	F	54	Ulcerative tumor			IIA	1 × 1,5	SM	Diff.	Angulus, curv. minor
(8)	M	67	See Footnote 5						Int.	See Footnote 5
9	M	50	Gastritis	Ulceration	27		3	SS + L	Int.	Corpus, curv. minor
10	F	64	Widespread tumor						Int.	Corpus
11	M	60	Malignant—suspected polyp			I, IIB	1, 5	M	Int.	Corpus, curv. major
12	M	66	Ulcerative tumor				5	PM + L	Diff.	Antrum, curv. major
13	F	66	Malignant—suspected erosion			IIC	2	SM	Diff.	Preopyloric area
14	F	68	Malignant—suspected ulcer				5	S	Diff.	Corpus, curv. major
15	M	66	Malignant—suspected ulcer				Large ulcer	PM	Int.	Corpus, curv. major
16	M	55	Ulcerative tumor				6	S +L	Int.	Corpus, curv. major
17	F	62	Malignant—suspected ulcer			III	1	SM	Int.	Angulus, curv. minor
18	F	60	Ulcerative tumor			IIC	2	SM	Int.	Corpus curv. minor
19	F	68	Erosion	Minute scar	16	IIC	0, 4	M	Int.	Pylorus
20	F	59	Tumorous infiltrate				1, 5	PM	Diff.	Antrum, curv. minor
21	M	72	Polyp	Ulceration	23	IIC	0, 1	M	Int.	Prepyloric area
22	M	70	Tumor				6	S + L	Int.	Antrum, curv. minor
23	M	51	Erosive gastritis				5	PM + L	Diff.	Gastroenteric stoma
24	F	67	Atrophic gastritis	Ulcerative infiltrate	6		6	S + L	Int.	Prepyloric area
25	M	71	X-ray diagnosis, no endoscopy				Widespread		Unclassified	Cardia
26	M	69	Polyp	Polypous tumor	7	IIA, I	1	M	Int.	Angulus, curv. minor
27	M	50	Tumorous infiltrate				5	S + E	Diff.	Corpus, curv. minor
28	F	53	Erosion			IIB	0, 1	M	Int.	Corpus, curv. minor
29	M	64	Tumor obstructing cardia						Int.	Cardia
30	M	70	Tumorous infiltrate				7	S	Int.	Corpus, fundus
31	M	61	Gastritis	Necrotic infiltrate	25		2, 5	S	Diff.	Pylorus
32	M	64	Ulcerative tumor			IIC, III	2	SM	Diff.	Angulus, curv. minor
33	M	62	Tumorous infiltrate			IIA	3	M	Int.	Corpus, curv. minor
34	F	63	Erosive gastritis	Polypous gastritis with erosion	19	IIC	0, 4	M	Int.	Angulus, posterior wall
35	M	63	Atrophic gastritis	Malignant—suspected gastritis	20	IIA	1, 5	M	Diff.	Antrum, anterior wall
36	M	63	Atrophic gastritis	Necrotic infiltrate	26	IIC	0, 5	SM	Int.	Angulus, anterior wall
37	M	52	Gastritis				Widespread	M	Carcinoid	Corpus + antrum, anterior wall

[a] SM, submucosa; Int., intestinal; curv. major, greater curvature; Diff., diffuse; SS, subserosa; E, extending to surroundings; L, lymph node metastasis; curv. minor, lesser curvature; M, mucosa; PM, muscularis propria; S, serosa.

participated. Biopsy was the routine, but brushing was used as a complementary measure in some cases. A biopsy sample was taken from all tumors, all gastric ulcers, erosions and polyps, and from other alterations, chiefly gastritides, in cases which were more advanced, or where, because of the location or special features (rigidity of wall, necroses), a malignancy could not be excluded. All these cases were regastroscoped after 2 years (some cases with suspected cancer were also studied earlier for clinical reasons).

In resected cases, the width of the spread of the carcinomas was determined both horizontally and in depth. The scheme outlined in the WHO Handbook of Registration of Stomach Cancer Patients (32) was followed. The concept of early gastric cancer was the same as defined by the Japanese Society for Gastroenterological Endoscopy (28).

Among the FSA secretors, 36 gastric cancers and one gastric carcinoid were found. We give the clinicopathological analysis of these cases,[5] as well as the prognosis up to the present. The surgical procedure was considered to be curative when carcinoma tissue was totally removed macroscopically and when microscopic examination revealed free resection lines. Prognosis was evaluated according to surgical data and clinical follow-up data thus far. The follow-up time after surgery is over 1.5 years in all but 2 cases and over 2 years in all but 5 cases. The prognosis in the present material was also compared with the prognosis for cancer cases resected in the Department of Surgery, University of Turku, between 1966 and 1972. The life table method (5) of crude survival (6) was used. When comparing the results, the primary hospital mortality was excluded. In this clinical material from Turku, there were 139 subtotal gastrectomies and 144 total gastrectomies, and 32 patients of 283 subjected to resections died within 30 days of surgery.

In addition to these cancers, 10 tubular adenoma cases which were detected in the group of FSA secretors are included, because the frequency of malignant transformation for this alteration has been reported to be as high as 69.2% (30).

RESULTS

Endoscopy Findings. Table 1 presents the material and lists endoscopy and biopsy data. Of a total of 36 malignancies, 30 had produced no symptoms. Resection was considered curative in only one symptomatic case (Case 12 with weight loss and dyspepsia). One case of cancer and the carcinoid case resembled gastritis at endoscopy, with no special local lesion. In these cases, as well as in others where a nontumorous lesion was visualized at endoscopy, a diagnosis of cancer was confirmed preoperatively by histology. There were 10 cases in which the first endoscopy finding was benign, the cancer being discovered in later examinations. In these cases, the findings at initial gastroscopy were hyperplastic polyp in one patient, one local erosion, one erosive gastritis, atrophic gastritis in 3 cases, and 3 cases of other types of gastritis (Cancer Case 26 is not included here; see next paragraph).

Tubular adenoma cases are presented in Table 2. In one case (Case A7) where the tumor was excised, a new tumor, histologically an intestinal-type cancer, appeared in another site after 7 months (Cancer Case 26).

X-ray examination was performed preoperatively in 18 cases. The endoscopy finding of cancer was found in 11 cases, whereas in 7 cases X-ray examination was negative (the 2 cases which showed no macroscopic alteration at surgery are excluded here).

Surgical Findings. Of the 31 (86%) resected cases, no apparent metastases could be visualized or palpated in 24. Local malignant lymph nodes, which were all removed *en bloc*, were found in 4 cases. In 8 cases, a widespread cancer or distant metastasis was observed. The patient was left without resection in 5 cases (2 of these were recurrences), a palliative subtotal gastrectomy was carried out in 3 cases, and another palliative operation in one case. Of 31 resections, 11 were total gastrectomies and 19 were subtotal gastrectomies; in one case (Case 11), only a local excision was made. Resection was considered curative in 28 (78%) cases.

The cancer was not palpable through the gastric wall in 15 cases. After gastrectomy, the alteration which had been biopsied could be visualized in 13 of these 15 nonpalpable cases. One case of widespread superficial invasive adenocarcinoma (Case 2) and the widespread carcinoid case showed no observable macroscopic changes at surgery. Both these cases had been classified as gastritis at endoscopy. In 2 cases, the tumor was more widespread than the surgeon (and endoscopist) had estimated, and the resection was enlarged to total gastrectomy after histological analysis of the primary resection lines (Cases 2 and 3).

Pathological Findings. The mean age of the patients with intestinal-type carcinomas was 63.5 years (range, 50 to 72), and the mean age of diffuse-type carcinomas was 59.6 years (range, 51 to 68). The proportion of intestinal to diffuse was 23/12 (one could not be classified). In 6 cases, both structures occurred simultaneously. These cases were classified according to the dominant structure. The location of the carcinomas was evenly distributed between the corpus and the antrum. In the corpus (and cardia), the carcinomas were predominantly of

Table 2

Tubular adenoma cases detected by FSA screening

In a total of 10 patients, the mean age was 62.9 years.

Case	Sex	Age	Location of tumor	Size of tumor
A1	F	66	Corpus, lesser curvature	2 cm
A2	M	66	Angulus, greater curvature	5 mm
A3	M	61	Antrum, anterior wall	1 cm
A4	M	53	Prepyloric area, lesser curvature	5 mm
A5	M	69	Angulus, lesser curvature	5 mm
A6	F	56	Corpus, lesser curvature	Multiple foci
A7	M	69	Angulus, lesser curvature	6 mm
A8	M	51	Angulus, lesser curvature	4 mm
A9	M	68	Antrum, anterior wall	5 mm
A10	F	70	Angulus, posterior wall	1 cm

Table 3

Size of gastric cancers resected after diagnosis by FSA screening

Largest horizontal diameter (cm)	No. of cases	No. of early cases
0–3	18	15
3–6	6	0
6–	7[a]	0

[a] These cases included 3 widely spread superficial cancers.

[5] Excluded from the clinical analysis is one subject (Case 8) screened with FSA, who apparently had been diagnosed with gastric cancer at laparatomy 8 months earlier.

Table 4
Extent of cancerous invasion (intestinal or diffuse type): gastric cancers resected after diagnosis by FSA screening

Depth of invasion	Total No. of cases	Intestinal	Diffuse	Carcinoid
Limited to				
Mucosa	9	7	1	1
Submucosa	10[a]	6[a]	4[a]	
Muscularis propria	4	1	3	
Subserosa	2	2	0	
Extending to serosa and surroundings	6	4	2	
Early carcinomas	15	11	4	
All cases	31	20	10	1
Metastasis in lymph nodes	7	5	2	

[a] Of 3 widely spread superficial carcinomas, 2 were of the intestinal and one of the diffuse type.

the intestinal type (13/4), distribution being about equal in the angular area and antrum (4/3 and 6/5). Table 3 shows the size of cancers, and Table 4 shows the extent of cancerous invasion for both types in all resected cases. The Japanese classification (28) is indicated for early cancers in Table 1.

The carcinoid tumor appeared to be widespread in the mucosa, showing no invasion into deeper layers. The lesions were multiple independent foci rather than mucosal extensions or metastases from a single source.

The adenomas, 10 altogether, were evenly distributed between corpus and antrum, most of them being situated in the angular region, at the lesser curvature. The largest adenoma was 2 cm in diameter. All adenomas were classified as tubular, and there was no papillary case in the material. One of the adenomas was found histologically to be an integral part of a hyperplastic polyp, with large intestinal metaplasia and cellular atypia.

Prognostic Survey. Resectability in our material was 86%; in the material of Inberg *et al.* (21), it was 45.1%. Resection was considered curative in 78% (Inberg *et al.*: 23.6%). There were signs of tumor spread in one case; all other cancer patients on whom a radical resection was carried out seem to have been treated curatively in the light of the data thus far. Two of the patients who underwent radical total resection (Cases 2 and 23) died of postoperative complications, and one case (Case 12) died of another disease (vascular stroke) 12 months after the operation, at which time there were no signs of recurrence or metastasis.

Crude survival by means of the life table method was 94% for the FSA-screened material (curative resections); in the general Turku group, the figure for curative resections was 37%.

DISCUSSION

The gastric cancer cases in our material, screened from unselected population because of positive reaction to the oncofetal antigen FSA, represent a wide selection of gastric cancers. Both the main histological types, intestinal and diffuse, are represented, and approximately in the same proportions as among gastric cancers in general (17, 20, 22, 25). The location of the FSA-positive cancers in the stomach did not show any special features. The age and sex distribution (within the 40- to 70-year age group that was studied) compared well with the general picture for gastric cancers in Finland.

A feature peculiar to this material is the high proportion of early cancers. In nearly one-half of the cases, the tumor did not extend beyond the submucosa. With regard to the purpose of population screening, *i.e.*, improvement of the prognosis for gastric cancer, this observation is of importance. It is also important to note the great number of tubular adenomas, because this alteration is found to be potentially precancerous. More adenocarcinomas than diffuse carcinomas were observed among early cancers. Whether this is caused by a slower growth rate for the adenocarcinomas remains to be clarified later, when all the epidemiological and statistical data for this population screening are available.

In our material, there were 3 microfocal carcinomas, several cases of which have been described previously by Nagayo (29).

From the clinical point of view, an interesting feature is that extension of gastric cancer is indeed difficult to visualize in some instances and that, in order to achieve a curative resection, histology of both resection lines must be a routine measure.

The question concerning the importance of early detection in general is outside the scope of this study. According to the Japanese mass screening material with 10-year survival data, prognosis is directly related to the depth of involvement of the gastric wall (24). The follow-up period of the resected cases already allows calculation of crude survival by means of the life table method. This prognostic indicator was distinctly better for the FSA-screened material (curative resections) compared with the general material in the same clinic (21).[6] Whether this means an improved prognosis cannot be judged by use of this method alone. In any case, tumor spread after radical resection has thus far been confronted in only one case in the group of FSA-screened cancers.

In our study, time must still elapse in order to obtain the final epidemiological data. Are the 36 (37)[5] cancers and 10 adenomas a yield of the FSA screening or merely of the endoscopy? If endoscopy done randomly were responsible for our result, a simple calculation would tell us that there were about 400 gastric cancers in our screened cohort. We know the annual incidence rate, which is about 20 for this cohort (1–3). This would mean a latency of about 20 years for macroscopic gastric cancer. Despite some theoretical calculations (8), the yield of the Japanese mass screening (19, 24), roughly corresponding to their 1-year incidence rate (16), with a false-

[6] The general Turku group included the age group over 70 years. The error caused by the small number of patients over 70 years old resected curatively must be small considering the large difference.

negative rate of 9.9% (18), is strongly against such a long latency. It seems likely that the FSA screening detected a majority of the macroscopic cancers existing at the actual moment. Performing 3,500 gastroscopies is a very realistic task, considering that in this way perhaps about 36,000 clinical examinations could be omitted.

REFERENCES

1. Cancer Incidence in Finland 1974. Cancer Society of Finland, Publication 24, Helsinki, 1978.
2. Cancer Incidence in Finland 1975. Cancer Society of Finland, Publication 25, Helsinki, 1978.
3. Cancer Incidence in Finland 1976. Cancer Society of Finland, Publication 27, Helsinki, 1979.
4. Culliton, B. J. Cancer virus theories: focus of research debate. Science (Wash. D.C.), *177:* 44–47, 1972.
5. Cutler, S. J., and Ederer, F. Maximum utilization of the life table method in analyzing survival. J. Chronic Dis., *8:* 699–712, 1958.
6. Ederer, F., Axtell, L. M., and Cutler, S. J. The relative survival rate; a statistical methodology. Natl. Cancer Inst. Monogr., *6:* 101–121, 1961.
7. Fogh, B. Forekomsten af stumme maligne ventrikeltumorer. Ugeskr. Laeg., *44:* 2455–2457, 1974.
8. Fujita, S. Biology of early gastric carcinoma. Pathol. Res. Pract., *163:* 297–309, 1978.
9. Häkkinen, I. An immunochemical method for detecting carcinomatous secretion from human gastric juice. Scand. J. Gastroenterol., *1:* 28–32, 1966.
10. Häkkinen, I. Immunological relationship of the carcinoembryonic antigen and the fetal sulfoglycoprotein antigen. Immunochemistry, *9:* 1115–1119, 1972.
11. Häkkinen, I. FSA—Foetal sulphoglycoprotein antigen associated with gastric cancer. Transplant. Rev., *20:* 61–76, 1974.
12. Häkkinen, I. A population screening for fetal sulfoglycoprotein antigen in gastric juice. Cancer Res., *34:* 3069–3072, 1974.
13. Häkkinen, I. The FSA reaction in early detection of gastric cancer. *In:* H. Boström, T. Larsson, and N. Ljungstedt (eds.), Health Control in Detection of Cancer (Skandia International Symposia), pp. 105–117. Stockholm: Almqvist & Wiksell International, 1976.
14. Häkkinen, I., Järvi, O., and Grönroos, J. Sulphoglycoprotein antigens in the human alimentary canal and gastric cancer. Int. J. Cancer, *3:* 572–581, 1968.
15. Häkkinen, I., and Viikari, S. Occurrence of fetal sulphoglycoprotein antigen in the gastric juice of patients with gastric diseases. Ann. Surg., *169:* 277–281, 1969.
16. Hanai, A., and Fujimoto, I. Cancer registry statistics in Japan. *In:* T. Hirayama (ed.), Epidemiology of Stomach Cancer: Key Questions and Answers, pp. 21–33. Tokyo: WHO Collaborating Center for Evaluation of Methods of Diagnosis and Treatment of Stomach Cancer, c/o National Cancer Center, 1977.
17. Heilmann, K., Burkhardt, H. U., and Kayser, K. Der intestinale und diffuse Typ des Magenkarzinoms. Untersuchungen zur Verteilung und Morphologie. Zentralbl. Allg. Pathol. Pathol. Anat., *122:* 293, 1978.
18. Hisamichi, S., Sugawara, M., Fuchigami, A., Aikawa, K., Chuma, Y., Takeuchi, Y., Takahashi, K., Yoshikawa, K., Fijita, R., Iinuma, T., Yamada, T., and Ichikawa, H. False negative rate of stomach cancer in gastric mass survey. Gan. No. Rinsho, *24:* 189–194, 1978.
19. Ichikawa, H. Early detection of gastric cancer. *In:* H. Boström, T. Larsson, and N. Ljungstedt (eds.), Health Control in Detection of Cancer (Skandia International Symposia), pp. 276–291. Stockholm: Almqvist & Wiksell International, 1976.
20. Inberg, M. V., Laurén, P., Vuori, J., and Viikari, S. J. Prognosis in intestinal type and diffuse gastric carcinoma with special reference to the effect of the stromal reaction. Acta Chir. Scand., *139:* 272–278, 1973.
21. Inberg, M. V., Heinonen, R., Rantakokko, V., and Viikari, S. J. Surgical treatment of gastric carcinoma. A regional study of 2,590 patients over a 27-year period. Arch. Surg., *110:* 703–707, 1975.
22. Järvi, O., Nevalainen, T., Ekfors, T., and Kulatunga, A. The classification and histogenesis of gastric cancer. *In:* Proceedings of the Eleventh International Cancer Congress, Florence, 1974, Excerpta Medica International Congress Series, No. 354, vol. 6, pp. 228–234, Amsterdam: Excerpta Medica, 1975.
23. Joint National Cancer Institute of Canada/American Cancer Society Investigation. A collaborative study of a test for carcino-embryonic antigen (CEA) in the sera of patients with carcinoma of the colon and rectum. Can. Med. Assoc. J., *107:* 25–33, 1972.
24. Kawai, K. Screening for gastric cancer in Japan. Clin. Gastroenterol., *7:* 605–622, 1978.
25. Laurén, P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histoclinical classification. Acta Pathol. Microbiol. Scand., *64:* 31–49, 1965.
26. Lehmann, F. G. Prognostic significance of alpha-1-fetoprotein in liver cirrhosis: five year prospective study. *In:* W. H. Fishman and S. Sell (eds.), Oncodevelopmental Gene Expression, pp. 407–415. New York: Academic Press, Inc., 1976.
27. Maskens, A. P. Mathematical models of carcinogenesis and tumor growth in an experimental rat colon adenocarcinoma. *In:* M. Lipkin and R. A. Good (eds.), Gastrointestinal Tract Cancer, Sloan-Kettering Institute Cancer Series, pp. 361–384. New York: Plenum Publishing Corp., 1978.
28. Murakami, T. Pathomorphological diagnosis. Definition and gross classification of early gastric cancer. Gann Monogr., *11:* 53–55, 1971.
29. Nagayo, T. Microscopical cancer of the stomach—a study on histogenesis of gastric carcinoma. Int. J. Cancer, *16:* 52–60, 1975.
30. Nagayo, T. Precursors of human gastric cancer: their frequencies and histological characteristics. *In:* E. Farber, T. Kawachi, T. Nagayo, H. Sugano, T. Sugimura, and J. H. Weisburger (eds.), Pathophysiology of Carcinogenesis in Digestive Organs, pp. 151–161. Tokyo: University of Tokyo Press, 1977.
31. Okabe, H. Growth of early gastric cancer. Clinical study of growth and invasion patterns of early gastric cancer: its position in the natural history of gastric cancer. Gann Monogr., *11:* 67–79, 1971.
32. WHO Handbook of Registration of Stomach Cancer Patients. Tokyo: WHO International Reference Center to Evaluate Methods of Diagnosis and Treatment of Stomach Cancer, 1973.