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FROZEN SECTION *in* SURGICAL PATHOLOGY: AN ATLAS

Volume II

Joseph Kovi

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Frozen Section In Surgical Pathology: An Atlas

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FOREWORD

Frozen section has assumed an indispensible role in the surgical management of the patient. Reserved entirely for the pathologist, the interpretation of the frozen section imposes a major responsibility on the pathologist: Is it malignant or benign? What type of malignancy is it? Is it completely removed? Are the lymph nodes negative or positive? These are some of the questions that a frozen section must answer.

For the proper interpretation of any biopsy, and most certainly the frozen section, during the examination of which there is no time to consult books, the pathologist must know the natural history of the suspected disease and the lesions that simulate it. However, information relative to interpretation of frozen sections is meager and it is dispersed. Dr. Kovi has effectively and successfully filled this gap. In this Atlas the discussion of equipment, technique, its nuances, and problems is followed by clinical and pathological presentations. Over 300 photomicrographs taken from actual frozen sections provide an extensive illustration of the subject and the reproductions are extremely good.

Dr. Kovi has not only produced a beautiful Atlas, he has done a great deal more. Supplementing his rich experience gained through many years of careful observation and meticulous collection with clinical and pathological discussion of the suspected lesion and its differential diagnosis, Dr. Kovi has, in fact, produced a richly illustrated textbook of surgical pathology.

The Atlas will be a most valuable guide to the newcomer to pathology and add immeasurably to the armamentarium of the practicing pathologist, providing them both with a much needed illustrative text for the interpretation of frozen sections. I congratulate Dr. Kovi on his highly successful accomplishment.

F. K. Mostofi, M.D.

INTRODUCTION

This illustrative Atlas is intended to be a ready reference guide for the pathologist and the surgeon in the interpretation of frozen section appearances. Frozen section technique is a procedure of great value to the surgeon. Biopsy diagnosis by frozen section significantly contributes to patient care, and often means one operation less. This leads to reduced bed occupancy and measurable cost-containment. In most hospitals in this country to date frozen sections are cut on a cryostat. In the past decade, cryostat became the standard equipment of virtually every surgical pathology laboratory. It is without question that frozen section diagnosis is vital in patient care because the decision to remove a breast, to resect a lung, to amputate a leg, or terminate the operative procedure depends upon the interpretation of frozen sections. With adequately trained personnel a frozen section report can be communicated to the surgeon within minutes.

The criteria of frozen section diagnosis are similar to those applied to paraffin sections, except that the interpretation must be made within seconds or minutes, and because the tissue has not been fixed, the morphologic appearance is somewhat different from the paraffin-embedded sections. Numerous atlases and textbooks of microscopic pathology have been published based on photomicrographs made from permanent paraffin sections. As far as it is known, no Atlas of biopsy diagnosis by frozen section has yet been published in the U.S. The only publication of relevance in the English literature is the monograph of Shivas and Fraser, *Frozen Section in Surgical Diagnosis,* published by Churchill Livingstone, Edinburgh, in 1971.

Most of the material for this Atlas has been obtained from the busy frozen section service of the Department of Pathology, Howard University Hospital, Washington, D.C. With the annual 8000 to 10,000 surgical accessions, about 500 to 800 frozen sections are prepared yearly. All photomicrographs have been taken by the author with the available Leitz automatic microphoto equipment. Each representative photomicrograph has a short description stressing the salient features of pathology and noting the important differential diagnostic possibilities.

The two volumes contain approximately 300 photomicrographs of actual frozen sections, a number of illustrative diagrams and charts, as well as tables for concise presentation of relevant data.

THE AUTHOR

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Dr. Kovi received his M.D. degree from the College of Medicine University of Budapest, Hungary in 1953. After having completed his residency in pathology at Roswell Park Memorial Institute, Buffalo, N.Y., he became a Diplomate of the American Board of Pathology in 1967. Dr. Kovi has been on the faculty of Howard University College of Medicine since 1970. In 1979 he spent his sabbatical leave as a Visiting Professor in Virology at the Department of Molecular Carcinogenesis and Virology, M. D. Anderson Hospital and Tumor Institute, Houston, Texas.

Dr. Kovi was a founder member of the College of Pathologists of Great Britain. He is presently a fellow of the Royal College of Pathologists, College of American Pathologists, American Society of Clinical Pathologists, and a member of the International Academy of Pathology and the Electron Microscopy Society of America.

Dr. Kovi has published more than 70 research papers and has been the principal investigator or co-investigator of research grants from the National Cancer Institute.

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J.K.

Volume II

Chapter 1

GASTROINTESTINAL TRACT

PART A: ESOPHAGUS

I. SQUAMOUS CELL CARCINOMA

A 60-year-old black man was admitted to the hospital complaining of difficulty in ingesting solid foods and even liquids. The patient lost more than 30 lbs in the last 6 months. He admitted to having been a heavy smoker and drinker in his life. X-Ray examination of the esophagus revealed an irregular, ragged mucosal lining with annular constriction of the lumen. A biopsy taken with the fiberoptic esophagoscope demonstrated invasive squamous cell carcinoma. A transthoracic resection of the distal two thirds of the esophagus was performed, and the upper line of resection submitted for frozen section examination. Microscopically, most of the mucosal lining was covered by mature squamous epithelium. In one area the surface appeared ulcerated. Underneath, large sheets and nests of de-differentiated squamous epithelial cells infiltrated the mucosa and the submucosa. The neoplastic cells were extensively keratinized. The nuclei were pleomorphic, hyperchromatic, and numerous mitotic figures were noted (Figures 1 and 2).

Frozen section diagnosis: ***Invasive well differentiated squamous cell carcinoma***

General features of the disease:
INCIDENCE: Incidence varies widely throughout the world; it is extremely high in certain parts of South Africa, in China, Japan, in the Dutch West Indies, in Russia, in Scotland, and in Puerto Rico.[176,177] In the U.S., the disease is more common in blacks than in whites.[178]
AGE: 50 to 70 years.
SEX: Male to female ratio = 3:1.[176]
SITE: Upper portion 16%, middle portion 52%, and lower portion 32%.[179]
RADIOLOGIC FINDINGS: Annular constriction of the lumen.[180]
CLINICAL FINDINGS: Progressive dysphagia, a sensation of substernal fullness, weight loss, and weakness.

DIFFERENTIAL DIAGNOSIS:

Microscopic

The histological diagnosis of squamous cell carcinoma of the esophagus is generally not difficult. Occasionally, the neoplastic cells are poorly differentiated, and the separation of the individual cells within the infiltrating cords leads to the formation of *pseudoglandular* structures. In the lumina of these gland-like formations pyknotic, degenerating tumor cells are seen, instead of *mucin* which would have been expected in true glandular carcinoma.[179] Squamous cell carcinoma of the esophagus often extends subepithelially beyond the main mass of the tumor, either in continuity with the main lesion or through the lymphatics. When radical resection of the esophagus is attempted, it is important to submit tissue from the proximal resection line for frozen section study to assure the adequacy of the operation.[179,181]

PART B: STOMACH

The distribution of gastric lesions in three frozen section series is shown in Table 1. "Ulcer and nonspecific inflammation", were the single most common lesions in all three series. Carcinoma was second, and the category "other tumors" was third in frequency.

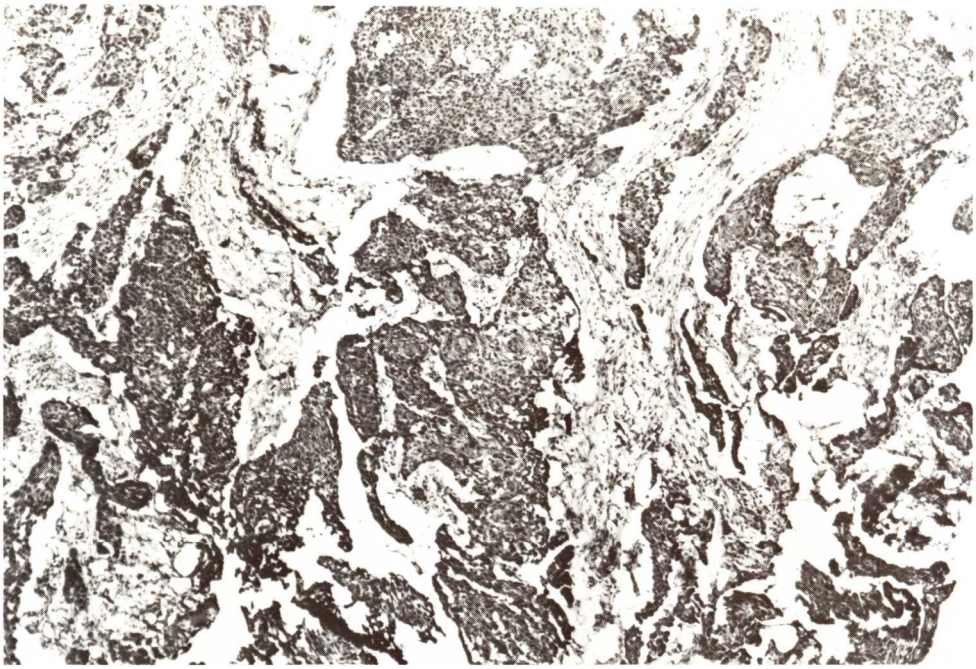

FIGURE 1. Esophagus. Invasive well differentiated squamous cell carcinoma. The mucosa is destroyed. Large anastomosing sheets of neoplastic epithelial cells infiltrate the submucosa. (H & E stain; magnification × 25.)

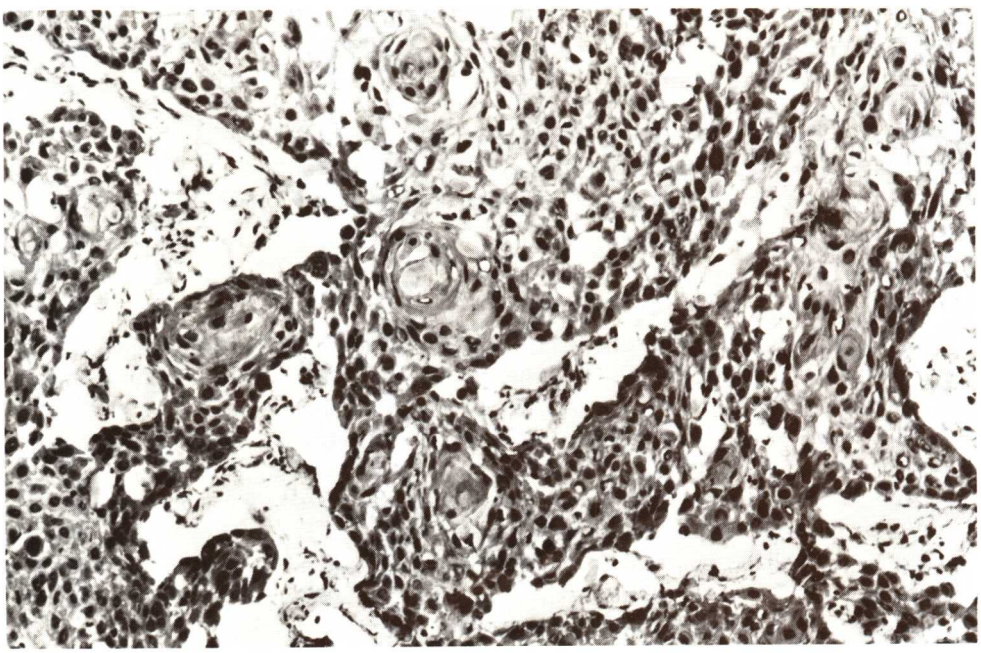

FIGURE 2. Esophagus. Invasive well differentiated squamous cell carcinoma. Note keratin pearl formation. (H & E stain; magnification × 100.)

In 1930, carcinoma of the stomach was the leading cause of cancer death in the U.S. For entirely unknown reasons, the incidence of carcinoma of the stomach has been declining during the last decades.[182,183] In the U.S. the age-adjusted mortality rate for cancer of the stomach fell from 29/100,000 population in 1930 to 7/100,000 population in 1966. A similar decrease in mortality figures was reported from the Netherlands, Norway, and the U.K. On the other hand, carcinoma of the stomach became more prevalent in Japan, Chile, Iceland, Finland, and in the Scandinavian countries.[184]

The age-adjusted gastric cancer death rate per 100,000 population for 1976—1977 was 9.2 for males and 4.4 for females in this country. The comparable figures reported from Japan were 70.2 for males and 34.9 for females.[29]

I. SIGNET RING CELL CARCINOMA

A 62-year-old black man was admitted to the hospital complaining of dull pain in the gastric area which was relieved by food intake. He had lost 30 lbs in the last few months. The patient was noted to have indigestion, loss of appetite, and heartburn for more than a year. The day before admission he vomited twice, and the vomited material had a coffee-ground appearance. Radiologically, the stomach was markedly diminished in size. It was rigid without visible peristalsis. Barium passed rapidly from the esophagus into the duodenum. A biopsy taken through the flexible fiberoptic gastroscope demonstrated carcinoma. At laparatomy, no perigastric lymphadenopathy was found, a distal subtotal resection of the stomach was performed, and a portion of the proximal line of resection was submitted for frozen section study. Microscopically, the mucosa, submucosa, the muscular layer, and the subserosal area were diffusely infiltrated by small neoplastic cells. The individual cells were round or polygonal and many contained intracellular vacuoles which appeared to compress the nuclei to the cytoplasmic membrane. These cells were characteristic so-called "signet ring" cells (Figures 3 and 4).

Frozen section diagnosis: ***Signet ring cell carcinoma***

General features of the disease:
INCIDENCE: The disease is more common among blacks than among whites in this country.[183,185]
AGE: 50 to 70 years of age.
SEX: Male-to-female ratio = 2:1.
SITE: Proximal part of the stomach and the greater curvature.
RADIOLOGIC FINDINGS: Marked diminution in the size of the stomach with the disappearance of peristalsis. Rapid flow of contrast material from the esophagus into the duodenum (in diffuse type of carcinoma). The fungating type manifests as an intraluminal filling defect.[180]
CLINICAL FINDINGS: Weight loss, indigestion, postprandial fullness, anorexia, heartburn, and eructation[184,186]

DIFFERENTIAL DIAGNOSIS:

Clinical

Carcinoma of the stomach should be distinguished from the following conditions: *benign gastric neoplasms, leiomyosarcoma or lymphoma of the stomach, syphilis or tuberculosis involving the organ, bezoar, congenital hypertrophic stenosis in adults and functional prepyloric abnormalities.*[183]

Gross Anatomical

Uniform thickening of the stomach wall resembling diffuse carcinoma has been reported in various diseases such as *syphilis, sarcoidosis, and eosinophilic gastritis.*[179]

Table 1
DISTRIBUTION OF GASTRIC LESIONS IN PUBLISHED FROZEN SECTION SERIES

Type of lesion	Ackerman and Ramirez,[3] St. Louis, 1959 (58 cases)	Nakazawa et al.,[11] New York, 1968 (80 cases)	Dehner and Rosai,[18] Minnesota, 1977 (12 cases)
Carcinoma	27.6	28.8	41.7
Other tumors	13.8	15.0	16.6
Ulcer and nonspecific inflammation	51.7	38.7	41.7
Other lesions	6.9	17.5	0.0
Total	100.0%	100.0%	100.0%

Microscopic

Diffuse carcinoma, so-called "linitis plastica" should be differentiated from two conditions affecting the stomach: chronic nonspecific gastritis and malignant lymphoma.

Chronic non-specific gastritis: (1) Whereas diffuse carcinoma is characterized by a single cell population, the cell composition in chronic nonspecific gastritis is *mixed.* Lymphocytes, plasma cells, histiocytes, eosinophils, and neutrophils are present in the infiltrate. (2) *Nuclear atypia,* increased chromatin content, and pleomorphism are common in diffuse carcinoma but absent in gastritis. (3) The so-called *signet ring cell type* of diffuse carcinoma exhibits intracytoplasmic vacuoles in the tumor cells. Signet ring cells are not found in chronic non-specific gastritis. (4) *Mitotic activity* is significant in the cell population of linitis plastica. Only sparse, and always normal mitotic figures are noted in chronic non-specific gastritis. (5) *Blood vessel proliferation* is not an important feature of diffuse carcinoma; it may be prominent in chronic non-specific gastritis.

Malignant lymphoma: (1) Both diffuse carcinoma and malignant lymphoma of the stomach, except the rare Hodgkin's disease, are characterized by a single cell population. The diffuse infiltrate in carcinoma is often associated with substantial *desmoplasia* (fibrous tissue production.)[15,179,187] Desmoplasia is absent in gastric lymphoma. (2) In the vicinity of infiltrating carcinoma the *mucosal glands* usually show *atypical changes.* The mucosal glands retain their normal appearance in gastric lymphoma. (3) Nuclear atypia is more pronounced in diffuse carcinoma than in malignant lymphoma.

II. LEIOMYOMA

In the course of removing the chronically inflammed gallbladder of this 40 year old white female, a round, rubbery nodule, measuring 2 by 2 cm was felt in the prepyloric portion of the gastric wall. The mass was excised with an ample margin of the surrounding normal tissue and submitted for frozen section study. The tumor appeared to be within the gastric wall, and the overlying mucosa was entirely intact. On cut surface, the well circumscribed nodule was gray-white and had a lobulated appearance. Microscopically, the tumor was composed of bundles of smooth muscle cells which were arranged commonly in a whorled pattern. Occasionally, prominent nuclear palisading could be observed. No mitotic activity was noted (Figure 5).

Frozen section diagnosis: ***Leiomyoma***

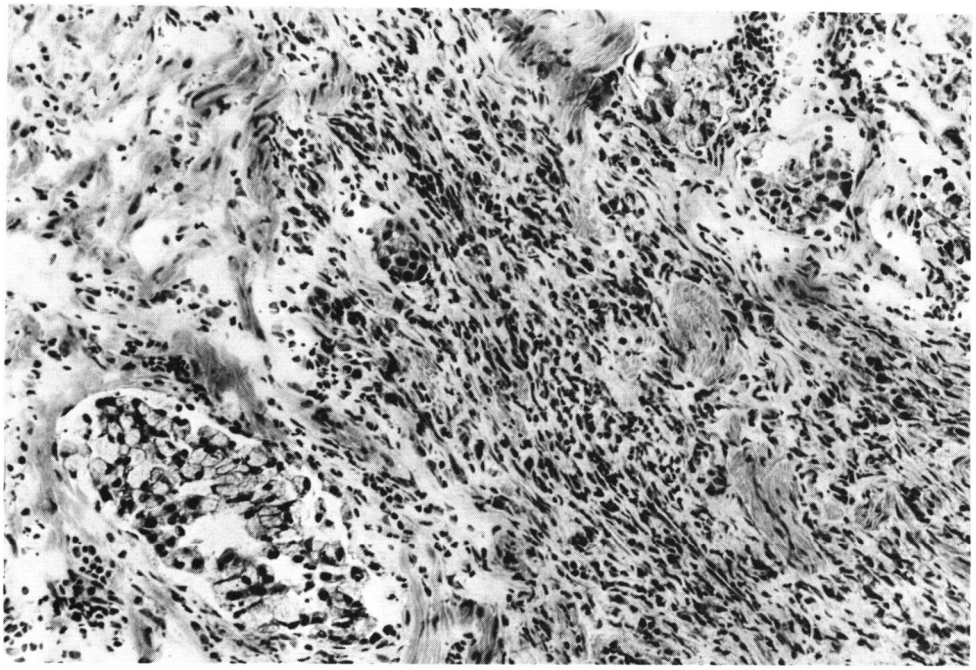

FIGURE 3. Stomach. Signet ring cell carcinoma. The submucosal area is infiltrated by nests of epithelial cells. These have a characteristic signet ring appearance. The nuclei are compressed to the plasma membrane by the accumulation of mucinous substance within the cytoplasm. (H & E stain; magnification × 100.)

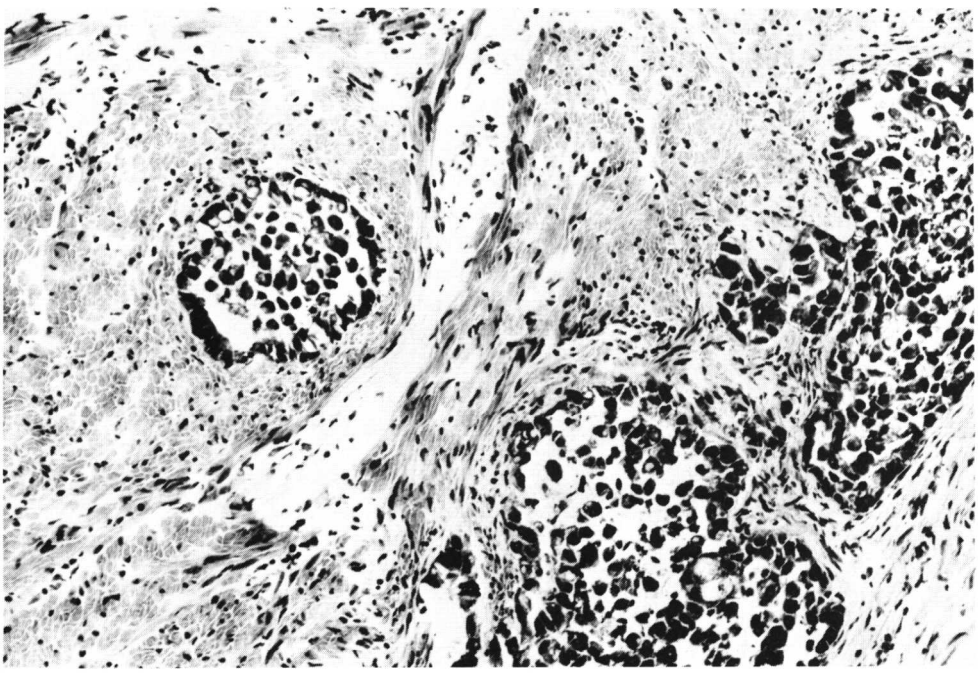

FIGURE 4. Stomach. Signet ring cell carcinoma. The neoplasia invaded the muscular coat of the stomach. Note destruction of muscle bundles by invading tumor cells. (H & E stain; magnification × 100.)

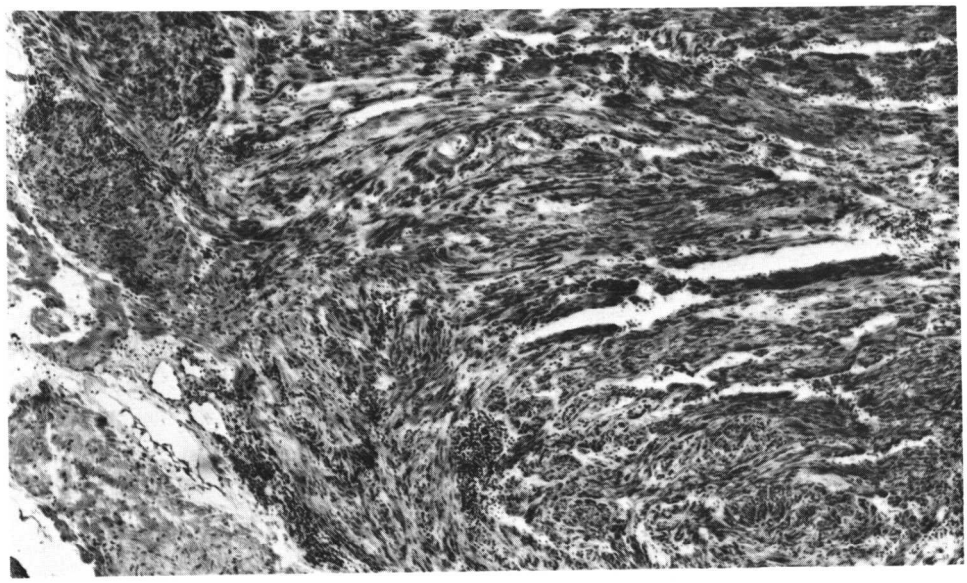

FIGURE 5. Stomach. Leiomyoma. The tumor is composed of bundles of well differentiated smooth muscle cells. High magnification did not reveal any mitotic activity in the tumor cells. (H & E stain; magnification × 25.)

General features of the disease:
INCIDENCE: 2% of tumors of the stomach.[179]
AGE: 9 to 94 years.
SEX: Equal distribution between the sexes.
SITE: Fundus (54%).[188]
RADIOLOGIC FINDINGS: Smooth, rounded, mobile filling defect with regular margins.
CLINICAL FINDINGS: Virtually all leiomyomas are asymptomatic and are discovered in the course of an unrelated operation.

III. LEIOMYOSARCOMA

A 65-year-old woman was seen by her family physician because of severe epigastric pain of 2 months duration. She has been vomiting frequently and the vomitus had a coffee-ground appearance. She lost about 10 lbs in the last two months. A huge, firm mass was palpated in the left upper quadrant of the abdomen. The patient was referred to the hospital. X-Ray revealed a large intramural filling defect protruding into the lumen of the stomach from the fundus. The overlying mucosa was smooth and regular except in an area in the center of the lesion where it appeared ulcerated. In the course of surgery, a biopsy was taken and submitted for frozen section study. Microscopically, the tumor was highly cellular. The neoplastic cells were ovoid or spindle-shaped. Large numbers of mitotic figures were encountered (Figures 6 and 7).

Frozen section diagnosis: ***Leiomyosarcoma***

General features of the disease:
INCIDENCE: Leiomyosarcoma accounts for 1.7% of tumors of the stomach.[179]
AGE: Average age 56 years.
SEX: Equal distribution between the sexes.
SITE: 72% occurs in the fundus and body of the stomach.[188]
RADIOLOGIC FINDINGS: Polypoid, submucosal mass, occasionally with an ulcer in the center. The surface is generally smooth and regular.[180]
CLINICAL FINDINGS: GI bleeding, hypochromic anemia, epigastric pain, nausea and vomiting, and occasionally palpable mass in the left upper quadrant.

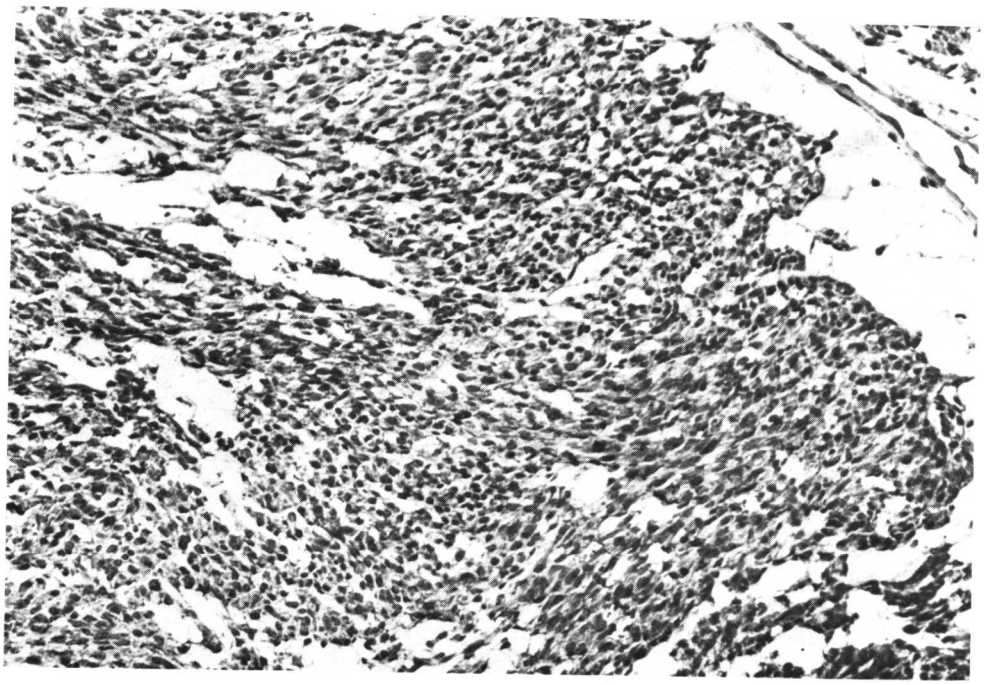

FIGURE 6. Stomach. Leiomyosarcoma. Highly cellular neoplasm. The neoplastic cells are elongated and possess spindle shaped nuclei. The nuclei are slightly pleomorphic and quite hyperchromatic. (H & E stain; magnification × 100.)

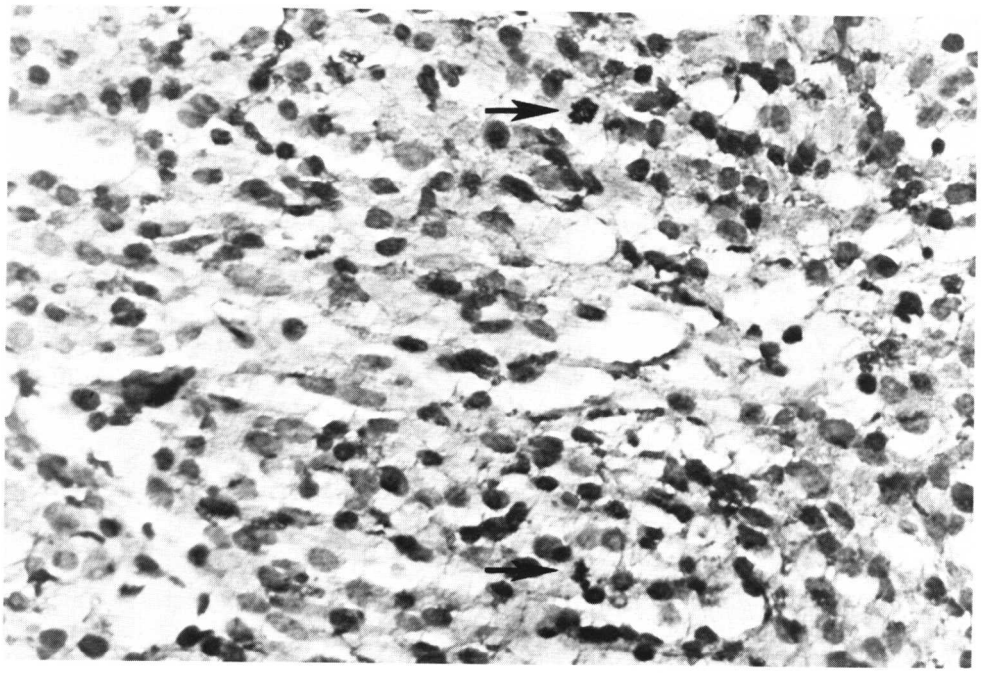

FIGURE 7. Stomach. Leiomyosarcoma. High magnification. Mitotic figures (arrows). (H & E stain; magnification × 400.)