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FROZEN SECTION *in* SURGICAL PATHOLOGY: AN ATLAS

Volume I

Joseph Kovi

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Frozen Section In Surgical Pathology: An Atlas

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Author

Joseph Kovi, M.D., F.R.C.Path., F.C.A.P.
Professor
Department of Pathology
Howard University College of Medicine
Washington, D.C.

With Special Assistance From

Hung Dinh Duong, M.D.
Department of Pathology
Howard University College of Medicine
Washington, D.C.

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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

Joseph Kovi, M.D., F.R.C. Path., F.C.A.P., is Professor, Departments of Pathology and Oncology, Howard University College of Medicine, Washington, D.C.

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.

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Chapter 1

INTRODUCTION

I. FROZEN SECTION DIAGNOSIS

The earliest use of the frozen section technique is attributed to Welch of Johns Hopkins Hospital, who in 1891 performed the first frozen section on a benign breast tumor removed by Halstead. In 1895, Cullen described a rapid method of making permanent specimens from frozen sections by the use of formalin. In 1905, Wilson of the Mayo Clinic published his method of staining frozen sections with methylene blue for rapid intraoperative tissue diagnosis.[1] Today, in the two Mayo Clinic-affiliated hospitals, approximately 45,000 surgical pathology reports are generated annually. The material for all required microscopic sections is subjected to frozen section examination.[2]

In 1959, Ackerman and Ramirez[3] in a review of 1269 consecutive frozen section diagnoses, specified the indications for and limitation of frozen section diagnosis. It was Shivas and Fraser[4] who in 1971 published the first major illustrated monograph of frozen section diagnosis, entitled "Frozen Section in Surgical Diagnosis", from Edinburgh, Scotland. One year later, Hermanek and Bünte[5] from Erlangen, West Germany, reported on their experiences with the method in a book *Die intraoperative Schnellschnittuntersuchung. Methoden und Konsequenzen,* or *Intraoperative Frozen Section Examination. Methods and Results.*

As Shivas and Fraser[4] noted, "the prime role of frozen section in surgical diagnosis is to spare the patient at most an operation, at least a period of distress and anxiety — often the most unpleasant feature of the entire illness — while a laboratory report is awaited. For the surgeon, anaesthetist and operating theatre staff, similarly, a diagnosis on frozen section often means one operation fewer." Frozen section method is a reliable diagnostic procedure in trained hands. Spread of the tumor in the interval between the biopsy and the definitive surgery, e.g., mastectomy is avoided.[6]

A. Indications for Frozen Section Examination

- The need for the surgeon as Ackerman and Ramirez[3] summed up, "to make a therapeutic decision."
- To determine whether the lesion is benign or malignant.
- To make sure that the *margins* of the excision are free of tumor.
- In the case when no immediate diagnosis can be made from the biopsied specimen, to make sure that the removed tissue is representative, viable, and thereby a definitive diagnosis can be achieved by examination of the paraffin sections later.
- Identification of the tissue, e.g., parathyroid glands, vagus nerve, presence or absence of ganglion cells in Hirschsprung's disease, etc.

B. Reliability of the Frozen Section Diagnosis

Application of the frozen section method for rapid tissue diagnosis during the course of surgical operations has become an essential part of the daily routine in hospitals throughout the U.S.[1]

The overall accuracy of frozen section diagnosis in published frozen section series is

Table 1
OVERALL ACCURACY OF DIAGNOSIS IN PUBLISHED FROZEN SECTION SERIES

Author, date, and location	Total no. of cases	False positive cases	%	False negative cases	%	Accuracy (%)
Winship and Rosvoll[7] Washington, D.C., 1959	1,810	3	0.2	18	1.0	98.8
Ackerman and Ramirez[3] St. Louis, 1959	1,269	4	0.3	22	1.7	98
Khoo[8] Singapore, 1965	443	3	0.7	10	2.3	97
Funkhouser et al.[9] Dayton, 1966	1,176	2	0.2	20	1.7	98.1
Elsner[10] St. Louis, 1968	2,240	5	0.2	13	0.6	99.2
Nakazawa et al.[11] New York, 1968	3,000	8	0.3	35	1.2	98.5
Funkhouser et al.[12] Dayton, 1970	3,986	8	0.2	61	1.5	98.3
Bredahl and Simonsen[13] Copenhagen, 1970	1,964	12	0.6	17	0.9	98.5
Hermanek and Bünte[5] Erlangen, 1972	2,000	3	0.2	48	2.4	97.4
Saltzstein and Nahum[14] San Diego, 1973	2,665	4	0.2	43	1.6	98.2
Holaday and Assor[15] Columbus, 1974	10,000	15	0.2	88	0.9	98.9
Lessells and Simpson[16] Aberdeen, 1976	3,556	6	0.2	13	0.4	99.4
Iri[17] Tokyo, 1977	760	5	0.7	22	2.9	96.4
Dehner and Rosai[18] Minnesota, 1977	778	0	0.0	11	1.4	98.6
Dalal et al.[19] Chandigarh, 1979	1,051	15	1.4	13	1.2	97.4
Total	36,698	93	0.3	434	1.2	98.5

A *false negative* diagnosis of cancer is *not* an incorrigible mistake. A *false positive* diagnosis, on the other hand, is a *most serious error* and may result in unjustifiable surgery, an unnecessary mastectomy, or an unwarranted resection of a portion of the pancreas, etc. As noted, among 36,698 biopsies diagnosed on frozen section, only 93 false positive diagnoses were made. Sparkman[1] pointed out that diagnostic errors occur also when the diagnosis is rendered from paraffin sections.

The relative frequency of *deferred diagnoses* of surgical biopsies in published frozen section series is documented in Table 2. In this composite series of a total of 26,493 biopsies the diagnosis was deferred only in 315 cases, that is, in 1.2% of the patients. When the pathologist defers the diagnosis the surgeon must wait 12 to 24 hr until the paraffin sections are available and a definitive diagnosis can be rendered. There has been no report on any harmful effect to the patient because of this brief waiting period.

The frozen section method must be considered as a highly reliable diagnostic procedure until the pathologist follows the principles foreset by Ackerman[20] in 1953; only three possible frozen section diagnoses can be rendered, (1) positive for cancer, (2) negative for cancer, and (3) deferred.

Table 2
RELATIVE FREQUENCY OF DEFERRED DIAGNOSES IN PUBLISHED FROZEN SECTION SERIES

Author, date, and location	Total no. of cases	Deferred diagnosis	
		No.	%
Khoo[8] Singapore, 1965	443	11	2.5
Elsner[10] St. Louis, 1968	2,240	38	1.7
Nakazawa et al.[11] New York, 1968	3,000	37	1.2
Hermanek and Bünte[5] Erlangen, 1972	2,000	66	3.3
Saltzstein and Nahum[14] San Diego, 1973	2,665	46	1.7
Holaday and Assor[15] Columbus, 1974	10,000	50	0.5
Lessells and Simpson[16] Aberdeen, 1976	3,556	7	0.2
Iri[17] Tokyo, 1977	760	7	0.9
Dehner and Rosai[18] Minnesota, 1977	778	32	4.1
Dalal et al.[19] Chandigarh, 1979	1,051	21	2.0
Total	26,493	315	1.2

C. Limitations of the Frozen Section Method

Since the first utilization of the frozen section procedure by Welch at Johns Hopkins in 1891, it has been conceded that one of the major limitations of the use of the frozen section method in surgical pathology is the imperfections of the technique.[9] Many prominent pathologists in the period 1920 to 1940, such as Ewing, Warthin, Breuer, and Simpson were quite skeptical about the procedure.[12] The introduction of the cryostat in surgical pathology by Ibanez et al.,[21] Chang et al.,[22] and Russell et al.,[23] in 1960 to 1961 contributed immensely to the gradual acceptance of the technique. As Funkhouser et al.[12] noted, the quality of cryostat frozen section is in most instances equal to or only slightly different from the quality of the paraffin sections.

Implantation of tumor at the time of the biopsy is a distinct possibility, especially in the thyroid gland and in the lung. Ackerman and Ramirez[3] pointed out that when the tumor is excised with an ample margin of normal tissue the risk can be completely avoided.

The technique is not suitable for the study of bone, teeth, and fat tissue.[24]

II. SOURCES OF ERROR

A. The Role of the Surgeon

1. *Sampling error.* The surgeon may submit to the pathologist tissue which does not contain the lesion. Foraker (as quoted by Sparkman[1]) noted that pathologists have not yet learned to make tumor diagnoses from tissue taken *near* the lesion.

2. *Insufficient clinical information.* The pathologist must be informed of all the relevant clinical data, such as sex, age of the patient, precise location of the lesion, the symptoms and signs, pertinent X-ray findings, history of trauma, and irradiation or previous surgery.
3. *"Unreasonable demands for haste, for frozen sections on unsuitable tissues, or for categorical diagnoses when the pathologist is uncertain"* to quote Sparkman.[1] False positive frozen section reports are quite likely if the surgeon insists that a definite diagnosis be made from the frozen section when the pathologist wants to defer the diagnosis. As Cammarata et al.[25] noted, most surgical pathology laboratories today can process tissues by rapid procedures within 24 hr to obtain paraffin sections if necessary.
4. A *positive* frozen section diagnosis of cancer authorizes the surgeon to proceed with definitive surgery. A *negative* frozen section diagnosis *does not rule out the possibility* that cancer will be found in the paraffin sections. The frozen section method is a diagnostic procedure limited technically by time. Usually, only one or perhaps two microscopic sections can be examined in the available short time period. These sections may not be representative of the lesion. The excised material is studied in much greater detail when the pathologist receives the paraffin sections. It is imperative that the surgeon *refrain from giving the patient definite assurance* that he or she has no cancer until the paraffin sections have been studied.[25,26]

B. Shortcomings of the Pathologist

Sparkman[1] submitted questionnaires to 50 prominent surgeons and pathologists throughout the U.S. containing specific questions concerning the reliability of frozen sections in the diagnosis of breast lesions. On the basis of information gained from this study, the pathologist was found to be responsible for failures of the frozen section method in the following instances:

1. *Inadequate experience with the method.* Ackerman and Ramirez[3] emphasized that, "the responsibility of frozen section diagnosis should be that of a senior pathologist and such a man should be rich in experience, conservative in attitude, and, most important, he must have judgement."
2. *Reluctance to examine the submitted specimen and select the proper portion for freezing* or delegating this responsibility to an inexperienced person. Winship and Rosvoll[7] emphasized that the most important step in frozen section diagnosis is the *"thorough inspection of the specimen and selection of the most suspicious area for examination."* This implies that the individual who will render the frozen section diagnosis is the individual who is responsible for sampling the gross specimen. Sampling errors account for more than one half of the false negative diagnoses.[14]
3. *Unwillingness to say "I don't know"* and to defer the diagnosis. It is wiser to admit ignorance than to give a false positive diagnosis which may result in unjustifiable, mutilating surgery.
4. *Misinterpretation of the microscopic section.* The quality of cryostat frozen section is comparable to that of the paraffin sections. Certain differences, however, exist.

The artefactual shrinkage of cells and intercellular matrix which is a consequence of formalin fixation and paraffin embedding, is absent in the frozen section. In comparison to paraffin sections in frozen sections, (1) the cells are always larger, (2) the cell borders are not distinct, (3) there are not artificial clefts between epithelium and stroma, and (4) the lumina of the glands are narrow.[5]

Because of the shrinkage factor, misinterpretation of frozen sections is possible if the pathologist is not quite familiar with the technique.

To illustrate this point briefly, a few examples can be given:

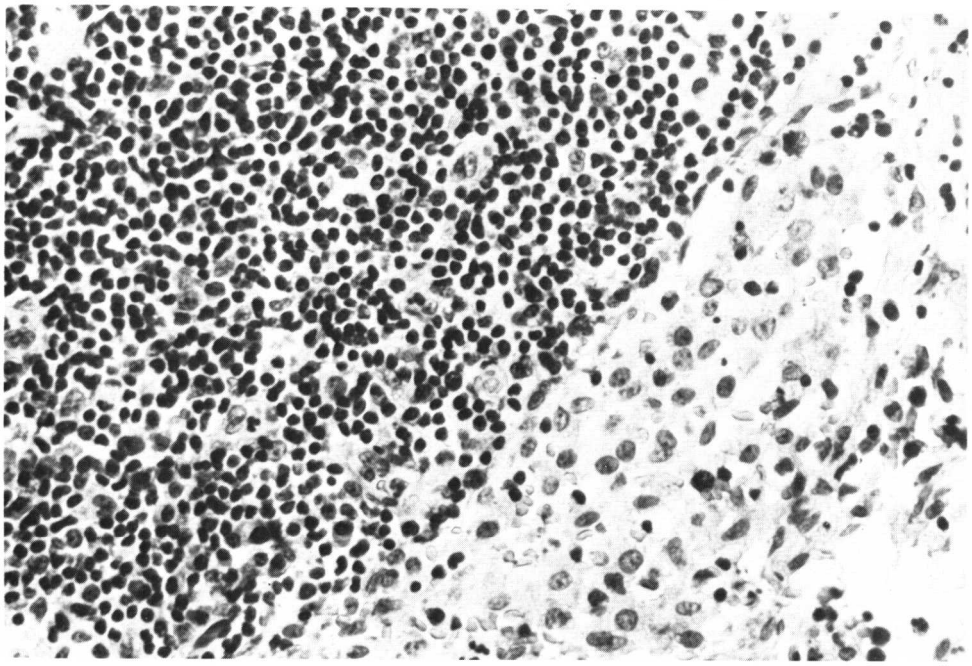

FIGURE 1. Lymph node. Sinus histiocytosis. (H & E stain; magnification × 200.)

1. *Sinus histiocytosis* in lymph nodes can mimic metastatic carcinoma in frozen sections. The histiocytes in the sinusoids may be atypical appearing, and may have large, prominent nuclei (Figures 1 to 3). For differential diagnosis see the chapter on lymph node.*
2. *Plasma cells* in lymph nodes may form clusters and can simulate groups of metastatic carcinoma cells (Figure 4).
3. It is a real possibility to confuse *tuberculous lymphadenitis* with carcinoma. The *epitheloid cells,* which are called epitheloid because in clusters these resemble squamous epithelium, can be mistaken for nests of metastatic carcinoma (Figures 5 to 9).
4. Localized *proliferation of mesothelial cells* at the surface of the peritoneum has been falsely diagnosed as a metastatic carcinomatous deposit (Figures 10 and 11).

It is felt that to summarize the information contained in this chapter it is best to quote Azzopardi's[27] simple dicta on how to approach a frozen section:

"1. Never report on a frozen section when you are mentally or physically preoccupied with something else. Never report without examining the gross specimen.
2. If the microscopic pathology does not fit the macroscopic description or the clinical history, you may be missing something vital.
3. Underdiagnosis on frozen section is not too serious. Overdiagnosis of infiltrating carcinoma is a mutilating error. If in doubt await paraffin sections.
4. If the macroscopic appearance is benign, beware of diagnosing carcinoma. Think again. The microscopic interpretation is probably wrong."

* See page 81.

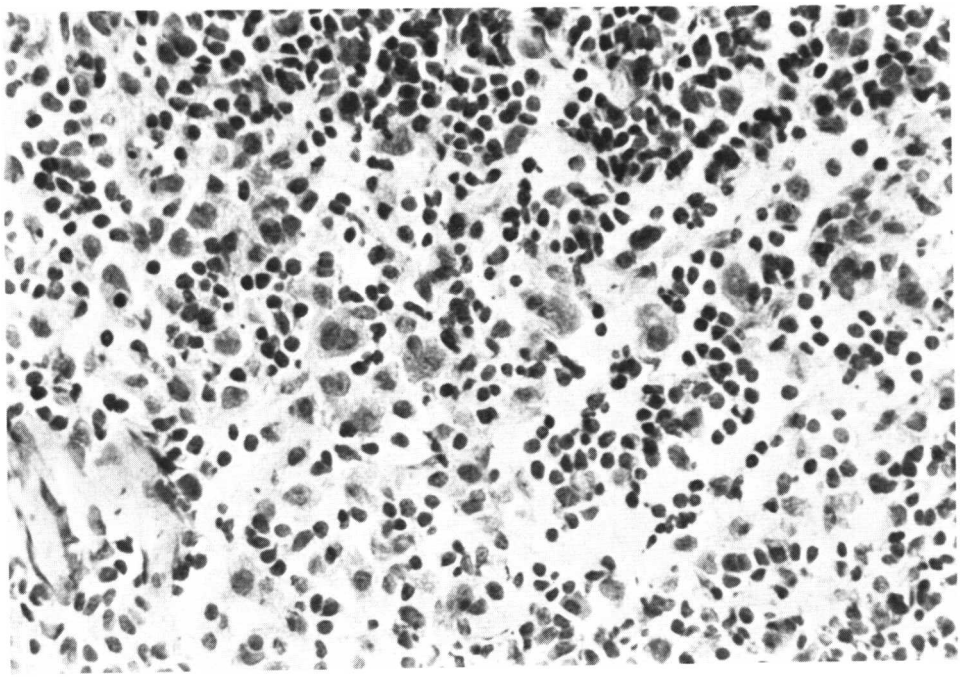

FIGURE 2. Lymph node. The sinus is filled with histiocytes possessing large, atypical nuclei. (H & E stain; magnification × 200.)

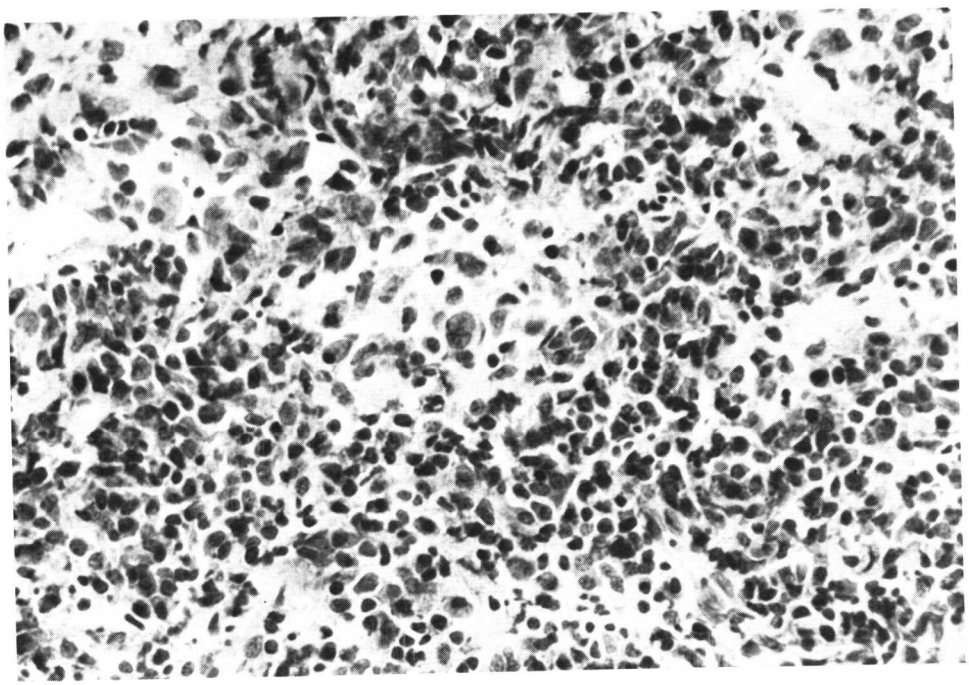

FIGURE 3. Lymph node. Binucleated histiocyte in the center and many plasma cells are present. (H & E stain; magnification × 200.)

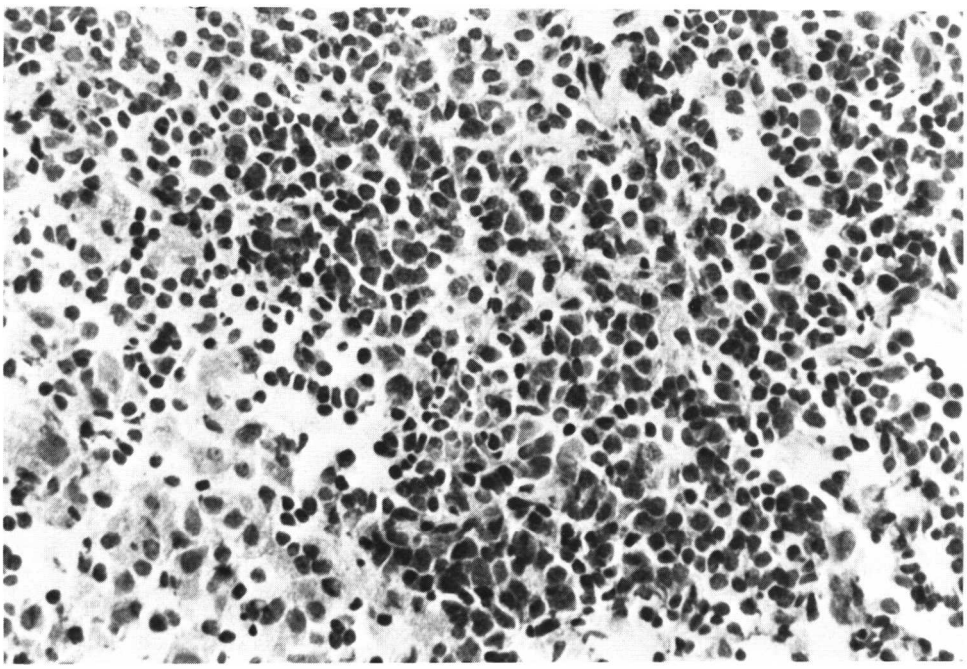

FIGURE 4. Lymph node. There are clusters of plasma cells resembling nests of metastatic carcinoma cells. (H & E stain; magnification × 200.)

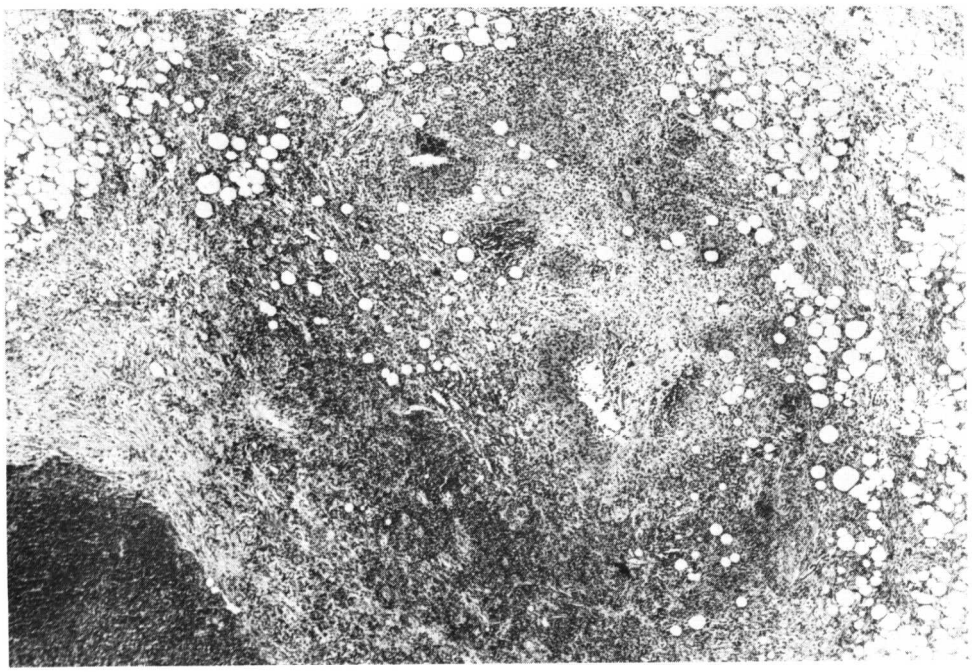

FIGURE 5. Lymph node. The normal lymphoreticular architecture has been effaced and replaced by a cellular infiltrate which also extends into the perinodal fat tissue. (H & E stain; magnification × 25.)