Metastases of Undetermined Source

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The patient with proven cancer in a lymph node or other accessible site, arising from an unknown primary, presents a diagnostic challenge and a therapeutic problem. Early determination of the occult source improves prognosis and helps the physician to proceed with the most effective therapy. Since reasonable hope for good palliation or even long-term control exists in some patients, an aggressive approach is warranted. However, in over half the patients, the primary lesion will never be found—this even includes patients who are closely followed and those eventually autopsied. The patient who presents late in the course of disease is a diagnostic problem since the neoplasm is so widely disseminated that the primary site may be unclear, or he may succumb during the evaluation. A final group of patients refuse complete diagnostic work-up.

The most common clinical situation in which this problem arises is the patient with a metastatic lymph node in the neck and no apparent primary source. A number of papers have been published on the perplexing problem of metastatic cancer in cervical lymph nodes. In over half of these patients, the primary tumor was found either by repeated examination or at autopsy. A similar problem involves other lymph node areas and sites where distant metastases occur, such as bone, lung, liver, kidney, soft tissues or skin. Malignant effusions without obvious primary source are also occasionally encountered. The purpose of this report is to review the clinical situations in which metastases of undetermined primary source occur, to indicate in each the site where the occult primary most commonly arises, to present effective methods of diagnosis and to suggest appropriate therapy.

Material
Records from the tumor registry at Charity Hospital of Louisiana in New Orleans.

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Orleans were reviewed to identify patients who had presented with a metastatic tumor of unknown origin. This registry includes records of over 45,000 cases of malignant disease diagnosed since 1948. Only for the past ten years has the registry specifically identified the records of patients presenting with occult primary lesions. These include patients in whom the primary was found months or years after the original diagnosis of cancer was made. The usual policy of many registries when finding an occult primary, is to revise the record so that it is coded as a known primary; this material is then lost for subsequent study and review. Of 45,728 cases of cancer recorded from 1948 through 1975, there were 56 cases of unknown primaries at the time of diagnosis in whom the primary site was later found. During that same time period, there were an additional 1,512 cancer cases in whom the primary site was never identified. In the former group, it is of interest that of the 56 patients, the primary site was identified at autopsy in 43 cases; there were 21 different sites involved. Of these sites (Table 1), the pancreas was most frequently the source of the primary tumor. Of the pancreatic cancers, none of the primary sites were identified prior to autopsy, and the longest survivor was eight months with a mean survival of 1.9 months per patient. Patients with head and neck tumors had the longest survival with a mean of three years per patient followed by ovarian carcinoma, with an average survival of two years and nine months.

**General Diagnostic Evaluation**

The reviewed material emphasizes the importance of a thorough search for the primary cancer. This should start with a careful history and physical examination, including pelvic, rectal, and proctoscopic examination, as well as a thorough ear, nose and throat evaluation. The standard laboratory work-up, including investigation of stool and urine for gross or occult blood, and a liver profile should be performed. Additionally, cytologic examination of abnormal exudates or body fluids may be helpful. Routine chest X-rays should be supplemented with intravenous pyelograms, gastrointestinal series, and barium enemas. Appropriate radionuclear scans of the liver, thyroid, kidney, brain and bone, when indicated, should be included. Total body scans with 67 Gallium citrate may be useful in establishing a pattern of metastatic disease (breasts, thyroid, lung and prostate) or in identifying occult lesions in the abdomen and mediastinum.

Other diagnostic aids may be divided into invasive and non-invasive. The invasive techniques means include: selective arteriography, endoscopic retrograde cholangiopancreatography, (ERCP), fiberoptic bronchoscopy, gastroscopy and colonoscopy, high speed trephine biopsy, and open-lung biopsy. Non-invasive diagnostic methods presently include xerography, ultrasonography, and computerized axial tomography.

Ultrasound is most useful in the evaluation of occult neoplasia in the retroperitoneum and pelvis but does not penetrate bone or gas. Probably the best method to evaluate the retroperitoneum for occult malignancy is computerized axial tomography. A technically adequate computerized tomogram is unparalleled in demonstrating vertebral and pelvic masses and by determining extension to osseous or other surrounding structures can be useful in the discovery and staging of lesions.

These newer procedures are now beginning to aid us in the particular problem of occult malignancies, and undoubtedly will be of even greater benefit with increasing experience and technical refinements.
activites in certain human cancer tissues. However, approximately five percent of all well-differentiated breast carcinomas, including metastatic lesions, have a low or normal activity pattern for G-6-PD and LDH. This correlates well with tumor metabolism and the presence of elevated estrogen binding protein (EBP) values in breast cancer. EBP are capable of transporting estrogens into the nucleus of the cell and stimulating cellular replication. In contrast, poorly differentiated malignancies usually contain increased activities for these enzymes (Table 2). Approximately 25 percent of all renal cell carcinomas, 15 percent of melanomas, 10 percent of colorectal cancers, 20 percent of bronchogenic carcinomas, and most sarcomas have low G-6-PD and/or LDH activities. Most poorly differentiated or anaplastic carcinomas contain ele-
vated amounts of G-6-PD and LDH (Table 2).

Arylsulfatase is a hydrolytic enzyme associated with both microsome and lysosome organelles in cells. Elevated arylsulfatase activities are present in varying percentages of all sarcomas and adenocarcinomas. Approximately 40 percent of all breast carcinomas have low arylsulfatase activities.2, 3 This is usually associated with low glycolytic enzyme activities, (e.g., LDH, G-6-PD), and elevated EBP values.2, 3 Patients who have a pattern of low G-6-PD, LDH, and arylsulfatase activities are usually associated with tumors of estrogen dependent organs, such as breast, endometrial, and renal. Metastatic anaplastic gastrointestinal malignancies, such as large bowel and gastric, and bronchogenic carcinomas usually have elevated arylsulfatase, G-6-PD, and LDH activities.4 Most melanomas that lack tyrosinase activities have very high arylsulfatase activities.

Alkaline phosphatase is also a hydrolytic enzyme associated with cellular lysosomes whose activities can be elevated in human malignancies. Malignancies with characteristic elevated alkaline phosphatase activities are bronchogenic and ovarian carcinomas and lymphomas.5 Poorly differentiated breast cancer can also demonstrate elevated alkaline phosphatase activities. No attempts have been made to determine if it is a specific isoenzyme of the alkaline phosphatase that is elevated.

Dihydrofolate reductase (DHFR) is an enzyme involved in the methylation of uracil during the synthesis of thymidine and DNA.6 Most germinal-cell derived carcinomas (ovarian and testicular), some well-differentiated large bowel carcinomas, and estrogen dependent breast carcinomas contain low DHFR activities. Sarcomas, especially osteogenic sarcoma, also have low DHFR activities. In contrast, most bronchogenic carcinomas, poorly differentiated large bowel cancers, anaplastic pancreas carcinomas have elevated DHFR activities. Poorly differentiated or anaplastic breast carcinomas, especially those that are hormone independent, have elevated DHFR activities.6

As any cancer becomes more anaplastic and undifferentiated, there are more cells, less cellular volume, and more cells per unit of tissue. However, tumor tissue DNA concentration has not correlated well with the organ from which the tumor arose.

Table 2 attempts to describe the enzyme patterns, certain glycolytic, hydrolytic, and reductase enzyme patterns seen in metastatic, poorly differentiated lesions from common malignancies. Unfortunately, not enough types of sarcomas have been evaluated in order to describe patterns. These studies are being continued in an attempt to better elucidate the patterns in malignant disease.

Metastasis to Lymph Nodes

Cervical Lymph Nodes

Most lymph node metastases from an unknown primary are found in the neck. A summary of material from the literature on this subject is presented in Table 3. It indicates that the primary tumor will eventually be determined in 32 percent of the cases and that the source will be from the head and neck areas in about 60 percent, and below the clavicle in the remaining 40 percent. The most common sites for occult primary tumors in the head and neck are the nasopharynx, thyroid, tonsil, base of the tongue, or hypopharynx; whereas the frequent sites of primary tumors located below the clavicle are the lung, gastrointestinal tract, pancreas, prostate and breast (Fig. 1).
Specific studies particularly indicated for metastatic lesions in the neck should include direct laryngoscopy and nasopharyngoscopy. When the lesion is located high in the neck, blind biopsies of the tonsil and the nasopharynx on the affected side should be taken from those patients in whom no obvious source can be found. For metastases in the lower portion of the neck, bronchoesophagoscopy, gastroscopy, or cystoscopy may be indicated. Thyroid scan should be performed even if there is no palpable mass in the gland, particularly if the histology of the node is suspicious. If there is reason to suspect medullary carcinoma of the thyroid, a serum calcitonin may be helpful.

**Axillary Lymph Nodes**
Metastases to the axilla when the primary tumor is not obviously apparent are usually from the breast. Occasionally, they may come from the lung or from melanoma of the arm or trunk. Histologic study of the metastases is helpful in most cases. Mammography or xeroradiography should be performed in the female; if negative, resection of the upper outer quadrant of the ipsilateral breast should be considered.

**Inguinal Lymph Nodes**
Metastases to this area, when the primary is not apparent, in the female, are usually due to cancer of one of the pelvic organs such as the cervix, uterus, or ovary. Barclay reported that in a series of patients with ovarian tumors found on pelvic examination, histologic diagnosis of carcinoma could be made in 45 percent by cul-de-sac puncture and routine inguinal node biopsy on the affected side. In ovarian
carcinoma, a cystadenocarcinoma antigen may be helpful. In the male, the prostate should be examined, and in both sexes the anus and rectum should be carefully investigated. Transrectal prostate biopsy should be considered when the serum acid phosphatase is elevated even if the rectal examination is normal. Ordinarily, the serum acid phosphatase is elevated if extracapsular carcinoma of the prostate is present. Again, melanoma and lymphoma must be kept in mind when metastatic inguinal nodes are present.

Special diagnostic studies in the female include dilation and curettage of the uterus, conization of the cervix and cul-de-sac punctures. Ultrasonography of the pelvis has been demonstrated to be 82 percent effective in localizing pelvic tumors in the female. Proctoscopy and barium enema should be routine. Where in the past open polypectomy had been performed for inaccessible colon lesions, presently it is reported by Overholt in 6,214 cases that fiberoptic colonoscopy allows biopsy and snaring of right-sided colon lesions with 100 percent accuracy and only a 0.32 percent incidence of perforation and 1.7 percent incidence of bleeding.

Metastasis to Other Sites

Lung

The lung is frequently involved with blood-borne metastases without an obvious source. Diagnosis of pulmonary metastases is easier than determination of the source, and the solitary lesion can present a more difficult diagnostic problem than multiple pulmonary lesions. In the first instance, the solitary pulmonary nodule ("coin lesion") raises the problem of differentiating primary or metastatic cancer, granulomas, mycotic infection, benign tumor, or other lesions. Diagnosing the pulmonary lesion can be done by utilizing one or more commonly used methods. These include brush biopsy under fluoroscopic control with fiberoptic bronchoscopy, high speed trephine lung biopsy, and open lung biopsy. The least conservative of the three methods, open lung biopsy, is the most direct. The yield of positive diagnoses ranges from 65 to 95 percent in several reported series. Overall complication rates have been low, but mortality rates have been reported as high as 2.2 percent.

Brush biopsy and transbronchial lung biopsy have continued to give excellent results since Ikeda’s first description in 1968 of the fiberoptic bronchoscope. Positive diagnoses have been obtained from 79 to 89 percent of reported series. In a report of over 24,000 accumulated procedures studied by Credle, the complication and mortality rate was 0.08 percent and 0.01 percent respectively with most complications being caused by oversedation or hemorrhage. High speed trephine lung biopsy is a third method that has produced quite satisfactory results. In separate studies of selected patients with diffuse lung disease, Boylen and Neff were able to give a positive yield of 89 percent and 85 percent respectively. However, the incidence of pneumothorax requiring chest tube placement has been as high as 65 percent and in Boylen’s study one patient died of massive hemothysis.

Bone

As indicated previously, the skeletal system is, after the lungs, the most common site for blood-borne metastases. Metastases are usually found in bones with the largest quantity of red marrow, such as pelvis, ribs, and axial skeleton. Most metastases are osteolytic, especially those arising from stratified squamous or transitional
epithelium, while osteoblastic metastases most often come from prostate or breast. Tofe\textsuperscript{29} reviewed 1,355 diphosphosphate bone scans and found that carcinoma of the breast, lung, and prostate accounted for 58 percent of all patients with positive scans. In several comparative series\textsuperscript{30,31} the\textsuperscript{99m} Tc-labelled bone agent, Osteoscan (\textsuperscript{99m} Tc-Sn • EHDP) has shown a much higher level of skeletal detection of bone metastases. Tofe\textsuperscript{29} was also able to demonstrate in his study a 67 percent incidence of skeletal involvement with breast carcinoma using the \textsuperscript{99m} TC-SN • EHDP bone agent. This figure closely approximates an incidence of 73 percent of bone involvement with breast carcinoma as reported in an autopsy study by Abrams.\textsuperscript{31}

Liver
This large intra-abdominal organ is one of the more frequent areas of metastatic deposits. Experimentally, by increasing the circulating blood volume and by the use of dextran, both the size and the incidence of hepatic metastases in the animal can be increased.\textsuperscript{33} It has also been shown\textsuperscript{14} that incidence of metastases in the liver of experimental animals may be augmented by increasing the number of circulating tumor cells and by direct hepatic trauma or damage; on the other hand, heparin and fibrinolysin when used to hinder thrombus formation, decrease the incidence of metastases. It is not presently possible to define the precise meaning and relative importance of the various factors influencing formation of hepatic metastases. Although most primary tumors are from areas drained by the portal vein, some are carried to the liver by the hepatic artery.

Liver metastases may present as
masses found either on physical examination or abdominal exploration, or the search may be set off by abdominal pain. Heupel\textsuperscript{15} reported six patients who were operated upon for an acute abdominal condition and were found to have metastatic carcinoma of the liver. The primary sites were the colon, pancreas, ileum and liver.

The most important method for differentiating liver tumors is histologic and cytologic study of biopsy material.\textsuperscript{36} Liver scanning with \textsuperscript{99m}Tc colloid should always be performed and, in some cases, selective ateriography, with the resultant “tumor blush” and/or radionuclide scans may be helpful to determine tumor neovascularity. The presence of alphafetoproteins should be searched for when there is a suspicion of primary hepatic tumor.

Of the commonly used laboratory tests, the serum alkaline phosphatase, BSP, SGOT, and direct fraction of bilirubin are reported to be abnormal most frequently in malignant liver involvement.\textsuperscript{37}

Because hepatic metastasis is initially extracellular, levels of enzyme alkaline phosphatase, found in the ground substance lining the sinusoids and in the bile canaliculi of the liver, are elevated early. Fractionation of serum alkaline phosphatase further eliminates the risk of confusing elevated intestinal, bone, or liver alkaline phosphatase. One of the intracellular enzymes detected earliest is the serum following liver metastases is lactic dehydrogenase (LDH). It is a “soluble enzyme” easily lysed from the cell; additionally, fractionation of serum LDH separates hepatic LDH from the LDH of the other organs. When facilities for fractionating alkaline phosphatase and LDH are available, they are the two most helpful function tests for determining the presence of liver metastases.\textsuperscript{38}

**Pancreas**

The pancreas is rarely a site of metastatic tumor deposits. Because of its location and rich lymphatic and venous drainage, primary pancreatic tumors are too often diagnosed late and are therefore inoperable. In our series of 56 unknown primaries, 11 of these involved the pancreas, five of the 11 (45 percent) presented with either abdominal pain or anorexia and weight loss, and three (27 percent) had tumors at metastatic sites that required exploration for diagnosis. Most significantly, none of the 11 were diagnosed until autopsy.

Whereas arteriography and pancreatic scanning have been the main methods of investigating the pancreas, only within the last five years have more sophisticated and accurate methods become available. Bookskin et al.\textsuperscript{38} were able to make a correct diagnosis of pancreatic carcinoma in 36 out of 41 patients (88 percent) of clinically proven cases by using pancreatic angiography. Major angiographic features that proved to be the most reliable signs of carcinoma were irregular encasement, pathologic vessels, and occlusion of large arteries. The most recent advancement in invasive means of diagnosis has been endoscopic retrograde cholangiopancreatography (ERCP) using the fiberoptic duodenoscope. Stadelmann\textsuperscript{39} reviewed over 1,000 examinations and was able to diagnose carcinoma in 54 patients. He was able to successfully visualize the pancreatic duct 78 percent of the time. Although a long stenotic pancreatic duct with or without complete occlusion of the duct was most suggestive of a tumorous process, clear distinction between carcinoma and chronic pancreatitis is not possible with ERCP. In a comparative study of the four major means of evaluating the pancreas, Wood\textsuperscript{40} quoted a 75 to 80 percent accuracy.
with ERCP and felt that ERCP gave the highest rate of definitive diagnosis. In spite of this, ultrasonography has become the first line of investigation in many institutions. It is the most pleasant for the patient and free of any complications. Wood also showed it to be more reliable than pancreatic scan or arteriography. The fact that it requires no special preparation and acts independently of organ function (in contrast to pancreatic scan with its low yield \(46\)), contributes to its usefulness. When dealing with lesions greater than three cm. in diameter a straightforward distinction between pancreatitis and carcinoma can usually be made.\(^{41}\)

**Computerized Axial Tomography**

C.A.T. may also be helpful in patients with pancreatic lesions, especially in differentiating obstructive and non-obstructive jaundice. Thin-walled needle biopsy under ultrasound guidance has been used successfully in the biopsy of liver and renal tumors.\(^{42}\) Its use in diagnosing pancreatic lesions remains a promising field of investigation.

**Umbilicus**

A firm nodule in the umbilicus may lead to the diagnosis of an occult intra-abdominal neoplasm—"SMJS".

**Malignant Effusions**

Patients occasionally present with a pleural effusion or ascites containing malignant cells and the primary lesion is not apparent. In this type of patient,
the prognosis is very poor; 65 percent are dead within three months and 89 percent within 24 months. Nevertheless, the physician is faced with the responsibility of establishing the correct diagnosis in order to plan future treatment. About 20 to 40 percent of non-traumatic pleural effusions are not adequately explained after examination of the patient and the pleural fluid, and after routine laboratory tests. However, 50 percent of so-called idiopathic non-traumatic effusions are due to malignancy.

In a comparison of results obtained by a pathologist and a cytologist studying malignant cells in pleural and ascitic fluid, Berge and Hellsten concluded that tumor cells were more often found in ascitic fluid, probably because this group contains cells of papillary ovarian cancer which shed easily recognized cells. The best diagnostic results were obtained in the group of well-differentiated tumors; 85 percent of 174 of these cases were either positive or suspected. Grunze reported 87 percent correct positive diagnoses of 200 cases of malignant tumors in pleural and ascitic fluid. If one suspects the effusion to be due to metastasis and no cells are found in the sediment, pleural biopsy combined with pleural fluid cytology may be performed. Salyer in a study of 271 patients undergoing this procedure utilizing an Abram's pleural punch biopsy needle was able to establish a correct diagnosis in 90 percent of cases. A malignant tumor involving the pleura was present in 95 cases and the lung and breast were the most common primary sites. In 17 patients (18 percent), a primary site could not be identified. The fact that pleural effusion with carcinoma cells is more likely to arise from the breast or lung has also been established by others. In effusions due to lymphomas those with positive cells most likely come from patients with Hodgkin's disease.

Morgan has called our attention to the fact that the finding of elevated LDH activity in a pleural effusion with a nearly normal serum LDH activity may help point the way to pulmonary metastatic lesions.

Treatment

Because of the many areas in which metastatic tumors with an occult primary may be present and the varying types of tumors involved, treatment must be highly individualized. The most important consideration is to determine the primary tumor. Studies to aid in this search have been suggested. The degree of vigor with which therapy is applied depends on the age and condition of the patient, as well as on the type of primary tumor.

In those lesions with a node metastasis located high in the neck, we believe that radical neck dissection with post-operative irradiation is the treatment of choice. It is preferable that the primary be located and excised in continuity. When practical, needle biopsy of a cervical lymph node is preferred to open biopsy if excision of the needle tract can be carried out at the definitive operation to follow. Since 50 percent of node metastases in the lower part of the neck stem from a primary in an organ below the clavicle, we believe that only irradiation should be used, at least until the primary tumor can be found.

Most centers favor pulmonary resection for metastases to the lung. The best results have been obtained when the primary lesion was controlled. Pulmonary metastases were limited to one lung and were detected more than a year following control of the primary. Five and 10 year survival rates of 47 percent and 25 percent respectively have been obtained on resectable tumors. The patient's age and
number of resected unilateral pulmonary lesions had no effect on survival.

The majority of human metastatic tumors grow at a relatively constant rate or doubling time, and this concept has been applied to pulmonary lesions in determining advisability of resection. Joseph has urged that all patients with metastatic pulmonary lesions which have a tumor doubling time greater than 40 days be considered for surgical removal even though the lesions are multiple and bilateral.

In our experience, the patients benefiting most from resection for solitary metastases of the lung are those with carcinoma of the kidney, uterus, or colon. Occasionally, the patient with slow growing melanoma, or soft tissue or bony sarcoma, may also benefit from resection or removal. Those with pulmonary lesions from the breast, stomach, or bone seldom have solitary metastases. Systemic chemotherapy or irradiation shall be considered if resection is felt to be contraindicated. If the criteria for resection are favorable, appropriate maintenance chemotherapy is advised.

When a metastatic tumor is discovered in bone without a known primary, it is our opinion that one should consider treatment by irradiation first. Endocrine therapy or chemotherapy may also be used, depending upon responsiveness of the tumor to the agents available. Palliative amputation may be considered for peripheral lesions.

Resection should be considered in those patients with solitary liver metastases, especially if the lesion is peripheral and particularly if it is a functioning neoplasm such as a carcinoid. In the latter instance, partial resection may be helpful in relieving symptoms. If the patient's condition does not warrant surgery, consideration should be given to continuous hepatic artery infusion with 5-fluorouracil, methotrexate, or systemic chemotherapy.

In patients with a solitary soft tissue metastasis, excision is preferable, especially if the lesion is apt to ulcerate and is amenable to resection. Irradiation, steroids, hormones, and chemotherapy are other modalities which may be utilized. If the lesion is in the extremities or other area suitable for regional chemotherapy, perfusion or intra-arterial infusion can be considered.

References

1. Warburg, O.: The Metabolism of Tumors. New York: Richard R. Smith, Inc., 1931.
2. Savlov, E.D., et al.: Correlations between certain biochemical properties of breast cancer and response to therapy: A preliminary report. Cancer 33: 303-309, 1974.
3. Morgan, L.R., Jr.; Posey, L.E., and Trench, L.: Preliminary results on the use of arylsulfatase and estrogen binding proteins in predicting response to hormone manipulation. Clin. Res. 23: 173, 1975.
4. Morgan, L.R., Jr., et al.: Arylsulfatase B in colorectal cancer. Cancer 36: 2337-2345, 1975.
5. Macaluso, J.N., Jr., and Morgan, L.R., Jr.: Serum and tissue alkaline phosphatase activities in patients with lung cancer. Abstraced in Proc. Amer. Assoc. Cancer Res., Southwest Section, 1976.
6. Kremetz, E.T., Jr., et al.: Effects of DTIC on mouse B16 melanoma, lysosomes and melatonin enzymes. Abstracted in Proc. Amer. Assoc. Cancer Res., Southwest Section, 1973.
7. Jesse, H.H.; Perez, C.A., and Fletcher, G.H.: Cervical lymph node metastasis: Unknown primary cancer. Cancer 31: 854-859, 1973.
8. MacComb, W.S.: Diagnosis and treatment of metastatic cervical cancerous nodes from an unknown primary site. Amer. J. Surg. 124: 441-449, 1972.
9. Jesse, R.H., and Neff, L.E.: Metastatic carcinoma in cervical nodes with an unknown primary lesion. Amer. J. Surg. 112: 547-553, 1966.
10. Comess, M.S.; Beahrs, O.H., and Dockerty, M.B.: Cervical metastasis from occult
carcinoma. Surg., Gynec., Obstet. 104: 607-617, 1957.
11. Smith, P.E.; Krementz, E.T., and Chapman, W.: Metastatic cancer without a detectable primary site. Amer. J. Surg. 113: 633-637, 1967.
12. France, C.J., and Lucas, R.: Management and prognosis of metastatic neoplasms of the neck with an unknown primary. Amer. J. Surg. 106: 835-839, 1963.
13. Marchetta, F.C.; Murphy, W.T., and Kovacic, J.J.: Carcinoma of the neck. Amer. J. Surg. 106: 974-979, 1963.
14. Robinson, D.W.: Management of metastases in lymph nodes when the primary tumor cannot be found. Plast. & Reconstr. Surg. 23: 27-35, 1959.
15. Acquarrello, M.J.; Matsunaga, R.S., and Cruze, K.: Metastatic carcinoma of the neck of unknown primary origin. Laryngoscope 71: 962-974, 1961.
16. Barclay, David (personal communication).
17. Cochrane, W.J., and Thomas, M.A.: Ultrasound diagnosis of gynecologic pelvic masses. Radiology 110: 649-654, 1974.
18. Overholt, Bergein F.: Progress in gastroenterology: Colonoscopy. A Review. Gastroenterology 68: 1308-1320, 1975.
19. Klassen, K.P.; Anlyan, A.J., and Curtis, G.M.: Biopsy of diffuse pulmonary lesions. Arch. Surg. 59: 694-704, 1949.
20. Aaron, B.L.; Bellinger, S.B.; Shepard, B.M., and Doohen, D.J.: Open lung biopsy: a strong-stand. Chest 59: 18-22, 1971.
21. Trummer, M.J.; Doohen, D.J., and Timmes, J.J.: Open lung biopsy. Surgery 53: 443-448, 1963.
22. Ikeda, S.; Yanai, N., and Ishikawa, S.: Flexible bronchofiberscope. Keio J. Med. 17: 1-16, 1968.
23. Levin, D.C.; Wicks, A.B., and Ellis, J.H., Jr.: Transbronchial lung biopsy via the fiberoptic bronchoscope. Amer. Rev. Resp. Dis. 110: 4-12, 1974.
24. Richardson, R.H.; Zavala, D.C.; Mukerje, P.K., and Bedell, G.N.: The use of fiberoptic bronchoscopy and brush biopsy in the diagnosis of suspected pulmonary malignancy. Amer. Rev. Resp. Dis. 63: 63-66, 1974.
25. Zavala, D.C., et al.: Use of the bronchofiberscope for bronchial brush biopsy. Chest 63: 889-892, 1973.
26. Credle, W.F., Jr.; Smiddy, J.F., and Elliott, R.C.: Complications of fiberoptic bronchoscopy. Amer. Rev. Resp. Dis. 109: 67-72, 1974.
27. Boylen, C.T.; Johnson, R.; Richters, V., and Balchum, O.J.; High speed trephine lung biopsy: methods and results. Chest 63: 59-62, 1973.
28. Neff, Thomas A.: Percutaneous trephine biopsy of the lung. Chest 61: 18-23, 1972.
29. Tofe, A.J.; Francis, M.D., and Harvey, W.J.: Correlation of neoplasms with incidence and localization of skeletal metastases. An analysis of 1,355 diprophosphate bone scans. J. Nuclear Med. 16: 986-989, 1975.
30. Silberstein, E.B.; et al.: Imaging of bone metastases with ⁹⁹ᵐTc-Sn-EHDP (diphosphonate), ¹¹¹In, and skeletal radigraphy. Radiology 107: 551-553, 1973.
31. Wellman, H.N.; et al.: Optimization of a new kit prepared skeletal-imaging agent, ⁹⁹ᵐTc-Sn-EHDP, compared with ¹¹¹In. In: Radio Pharmaceuticals and Labelled Compounds, Vol. 1. AEA, 1973.
32. Abrams, H.L.; Spiro, R., and Goldstein, N.: Metastases in carcinoma: Analysis of 1,000 autopsied cases. Cancer 3: 74-85, 1950.
33. Fisher, B.; and Fisher, E.R.: Experimental studies of factors influencing hepatic metastases in canine. Rheologic alterations. Cancer Res. 26: 183-192, 1966.
34. Fisher, B.; and Fisher, E.R.: Host factors influencing the development of metastases. Surg. Clin. N. Amer. 42: 335-351, 1962.
35. Humpe, H.W.: Liver metastases simulating acute surgical abdomen. Arch. Surg. 92: 273-276, 1966.
36. Menghini, G.: One-second needle biopsy of the liver. Gastroenterology 35: 190-199, 1958.
37. Schaffer, J.; and Schiff, L.: Liver function tests in metastatic tumor of the liver: Study of 100 cases. Gastroenterology 49: 360-363, 1965.
38. Bookstein, J.J.; Reuter, S.R., and Martel, W.: Angiographic evaluation of pancreatic carcinoma. Radiology 93: 757-764, 1969.
39. Stadelmann, O., et al.: Endoscopic retrograde choanalopancreatography in the diagnosis of pancreatic cancer. Endoscopy 6: 84-93, 1974.
40. Wood, R.A.B., et al.: Comparative value of four methods of investigating the pancreas. Surgery 80: 518-522, 1976.
41. Doust, B.: The use of ultrasound in the diagnosis of gastroenterological disease. Gastroenterology 70: 602-610, 1976.
42. Holm, H.H.; Rasmussen, S.N., and Kristensen, J.K.: Ultrasonically guided percutaneous puncture technique. J. Clin. Ultrasonic 1: 27-31, 1973.
43. Rome, D.: Discussion. In: Grunze, H. (ed.). The comparative diagnostic accuracy, efficiency and specificity of cytologic technics used in the diagnosis of malignant neoplasm in serous effusions of the pleural and pericardial cavities. Acta. Cytol. 8: 150-163, 1964.
44. Parker, R.H.: Idiopathic pleural effusions. Med. Sci. 15: 53-56, 1964.
45. Berge, T.; and Hellsten, S.: Cytological diagnosis of cancer cells in pleural and ascitic fluid. Acta. Cytol. 10: 138-140, 1966.
46. Salzer, W.R.; Egleston, J.C., and Erozan, Y.S.: Efficacy of pleural needle biopsy and pleural fluid cytopathology in the diagnosis of malignant neoplasms involving the pleura. Chest 67: 536-539, 1975.
47. Melamed, M.R.: The cytological presentation of malignant lymphomas and related disease in effusions. Cancer 16: 413-431, 1963.
48. Johnson, R.M., and Lindskog, G.E.: 100 cases of tumor metastatic to lung and mediastinum. JAMA 202: 112-116, 1967.