Secondary Malignant Tumors of the Pericardium

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Though most patients with secondary neoplastic involvement of the heart or pericardium seem to manifest no symptoms or signs of such involvement, a sizable proportion do have actual impairment of cardiac function. Refinements in thoracic, and specifically cardiac, surgery, in roentgen therapy, and in the use of isotopic and chemotherapeutic agents have made definite palliation available for metastatic neoplasms of the pericardium. Thus the diagnosis of such functional involvement assumes an increasing importance. The study to be reported is a retrospective one wherein records of patients with extensive lesions at necropsy were studied in an attempt to correlate clinical and pathologic manifestations of secondary pericardial tumors significant enough to interfere with cardiac function.

Background Data

A detailed review of the literature on this subject has been presented elsewhere and will not be repeated here.

As recently as 1934, Heninger reported that in only five cases of secondary tumors of the heart or pericardium had the diagnosis been made during life. However, several necropsy studies in cases of malignant disease have shown incidences of 2.3 to 13.1 per cent for pericardial involvement. Necropsies in cases of leukemia, carcinoma of the lung, and carcinoma of the breast have revealed pericardial involvement in 11.1, 10.4, and 20.9 per cent, respectively.

Usually, pericardial metastatic tumors are found at necropsy only when there is extensive metastatic involvement elsewhere in the body, but occasionally pericardial involvement is related to the initial symptoms of malignancy, or it represents the sole metastatic lesion found at necropsy.

Manner of Interference with Cardiac Function

The ways in which malignant lesions of the pericardium theoretically could interfere with normal cardiac function are as follows: (1) cardiac tamponade due to pericardial effusion; (2) mechanical constriction of the heart by tumor tissue; (3) interference with the inflow or outflow tracts of the heart by encroachment on the great vessels as they pass through the pericardial sac; (4) interference with coronary circulation by (a) compression from without, (b) neoplastic embolism within the coronary arteries, or (c) direct invasion of the coronary vessels; and (5) encroachment on the nerve supply of the myocardium.

Clinical Manifestations

The clinical manifestations of secondary malignant lesions in the pericardium have not been well differentiated from those in the heart as a whole or even from the systemic effects of widespread malignant disease. Yater subdivided cases of cardiac tumors into two groups: in one, symptoms did not specifically suggest a cardiac tumor; in the other, symptoms did suggest it. He noted that a large majority of cases were in the former group. Clinical types suggesting tumor of the heart included accumulations of hemorrhagic pericardial fluid and changes in the cardiac silhouette in the thoracic roentgenogram. He also stated, "If in a person who is known to harbor a malignant neoplasm cardiac symptoms develop which cannot be otherwise explained, it is reasonable to assume that metastatic invasion of the heart has occurred." Variations of this statement are widely made.
although most authors have attempted to be more specific in defining the clinical manifestations.

**Electrocardiographic Manifestations**

The electrocardiographic aberrations associated with pericardial malignant tumors have not been well established or differentiated from those of myocardial metastasis in any large series. Barnes, Beaver, and Snell stated that most of the electrocardiographic changes seen in tumors of the heart were due directly to neoplastic invasion of the ventricles. Lamberta, Nareff, and Schwab noted that the electrocardiographic changes of pericarditis were often minimal in pericardial malignant tumors. In 1923, Oppenheimer and Mann described a valuable electrocardiographic sign in pericardial effusion, that is, "a decided lowering of the voltage of the main deflection in all three [standard] leads." McGregor and Baskind stated that electrical alternans was frequently associated with pericardial effusion and that simultaneous alternation of atrial and ventricular complexes was uniquely associated with pericardial effusion.

**Cytologic Examination of Pericardial Fluid**

Cytologic examination of pericardial fluid is probably the most direct and satisfactory method of establishing the diagnosis of a malignant pericardial effusion.

**Methods**

From January 1, 1942, through December 31, 1958, 13,314 necropsies in which the heart was examined were performed in the Section of Pathologic Anatomy of the Mayo Clinic. From this series were selected all cases in which the diagnosis of secondary malignant disease of the heart, pericardium, or epicardium was established. Necropsy protocols and clinical abstracts were reviewed on all these patients. For the purpose of this presentation, "pericardium" refers to the fibrous pericardial sac that is comprised of both visceral (epicardium) and parietal pericardium and includes the subepicardial tissues between the epicardium and myocardium. The term "malignant tumors" includes carcinoma, sarcoma, lymphoma, leukemia, and histiocytosis X. "Metastatic lesions" of the pericardium refer to secondary involvement by malignant tissue irrespective of the route or manner of spread to the pericardium.

**Figure 1**

Functional significance of pericardial metastasis related to the primary malignant lesion.

From this preliminary study, cases in which there was actual neoplastic involvement of the pericardium were separated into two groups: (1) the group in which the pathologic examination and the clinical course did not suggest impairment of normal cardiac function by the pericardial malignant lesion and (2) the group in which such a malignant lesion probably did impair cardiac function. Next, histologic sections of the heart, pericardium, epicardium, liver, and spleen, photographs of gross specimens, and the preserved organs of the cases in the group of impaired cardiac function were reviewed in detail. Clinical records were reviewed as were the available electrocardiograms.

**Over-all Results**

As a result of this study, 189 patients (1.42 per cent of the 13,314 necropsies) were selected as meeting the stated criteria. Of these, 134 patients (70.9 per cent) comprised the group with pathologically proved malignant lesions of the pericardium that caused no apparent impairment of cardiac function, and 55 patients (29 per cent) were considered to have had significant impairment of cardiac function during life as a direct result of the pericardial metastasis.

The sites of the primary malignant lesions in the series are presented in table 1. As noted in this table, carcinomas of the lung and breast together comprise almost half (46.0 per cent) of the primary tumors causing pericardial metastasis. They differed, however, in the frequency in which they caused functional
cardiac impairment, as shown in figure 1. Metastasis to the pericardium from carcinoma of the lung impaired cardiac function in 37 per cent of the 52 patients so affected whereas those from carcinoma of the breast caused impairment in only 17 per cent of the 35 patients so affected. Patients with lymphoma or leukemia comprised 28 per cent of the entire group of cases of pericardial metastasis and were significant in 35 per cent of the 52 cases of this type of malignancy. Although eight patients in the series had malignant melanoma, none of these had significant cardiac embarrassment.

Impairment of Cardiac Function by Metastatic Lesions in the Pericardium

The remainder of this discussion pertains only to the group of 55 patients whose pericardial malignant lesions impaired cardiac function during life and we shall refer to this impairment as "significant pericardial disease."

Age and Sex Incidence

In this group there were 28 men and 27 women. The mean age was 43.7 years. The younger patients had lymphoma or leukemia for the most part, whereas the older ones had carcinoma (fig. 2).

Importance of Pericardial Metastasis in Causing Death

After we had reviewed and correlated clinical and necropsy material on each patient, we considered pericardial involvement or its immediate effects as the primary cause of death in 20 patients (36 per cent) of the 55 patients with significant pericardial disease. In 27 additional patients (49 per cent), pericardial metastasis was considered a contribu-

Table 1

<table>
<thead>
<tr>
<th>Primary malignancy</th>
<th>Impairment of cardiac function during life</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not significant Percent</td>
<td>Significant Percent</td>
</tr>
<tr>
<td></td>
<td>Patients</td>
<td>Per cent</td>
</tr>
<tr>
<td>1. Carcinoma of lung</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>14</td>
<td>10.4</td>
</tr>
<tr>
<td>Left</td>
<td>15</td>
<td>11.2</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
<td>21.6</td>
</tr>
<tr>
<td>2. Lymphoma</td>
<td>9</td>
<td>6.7</td>
</tr>
<tr>
<td>3. Carcinoma of breast</td>
<td>8</td>
<td>6.0</td>
</tr>
<tr>
<td>4. Sarcoma</td>
<td>3.3</td>
<td>3.3</td>
</tr>
<tr>
<td>5. Renal carcinoma</td>
<td>7</td>
<td>5.2</td>
</tr>
<tr>
<td>6. Pancreatic carcinoma</td>
<td>4</td>
<td>3.0</td>
</tr>
<tr>
<td>7. Thymoma</td>
<td>2</td>
<td>1.5</td>
</tr>
<tr>
<td>8. Gastric carcinoma</td>
<td>2</td>
<td>1.5</td>
</tr>
<tr>
<td>9. Rectal carcinoma</td>
<td>2</td>
<td>1.5</td>
</tr>
<tr>
<td>10. Esophageal carcinoma</td>
<td>2</td>
<td>1.5</td>
</tr>
<tr>
<td>11. Carcinoma of uterine fundus</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>12. Miscellaneous types and sites</td>
<td>6</td>
<td>4.5</td>
</tr>
<tr>
<td>Grand total</td>
<td>134</td>
<td>100.0</td>
</tr>
</tbody>
</table>

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tory cause of death and in only eight (15 per cent) were the pericardial lesions considered unrelated to death although they interfered with cardiac function.

**Pericardial Fluid at Necropsy**

The quantity of pericardial fluid or lack of it at necropsy was reported in 52 of the 55 patients. In eight of these there was no fluid because pericardial adhesions had obliterated the sac. In one patient a pleuropericardial window had been established surgically and consequently no free fluid was found at necropsy. Of the remaining 43 patients, five were less than 14 years of age. In 28 of the 38 patients who were more than 13 years of age at time of death, the pericardial sac contained more than 250 ml. of fluid. These 28 patients together with two 5-year-old patients who had 200 and 100 ml. of pericardial fluid removed at necropsy and the patient with the pleuropericardial window who had had 600 ml. of pericardial fluid removed preoperatively were assumed to have had sufficient pericardial fluid so that cardiac action may have been impaired by tamponade. The quantity of pericardial fluid in the adult group ranged from 300 ml. (six patients) to 2,000 ml. (three patients) with a mean of 746 ml. The fluid was clear or serous in 10, serosanguineous in seven, frankly hemorrhagic in 12, and fibrinous in two of the patients.

Forty-five (82 per cent) of the hearts showed evidence of focal or generalized fibrinous pericarditis on gross or microscopic examination.

**Pleural Fluid at Necropsy**

The quantity and quality of pleural fluid at necropsy were reported in 52 of the 55 patients and fluid was present in 48 (92 per cent). The pleural effusion was bilateral in 38 persons, limited to the right side in eight, and to the left side in two. This high incidence of pleural effusion is not unexpected from a group in which 46 per cent of the patients had carcinoma of the lung or breast and in which 26 persons (47 per cent) had grossly visible metastatic lesions in the pleura. The quality of the pleural fluid, however, did seem unusual in that the effusion was reported as frankly bloody in only five of the 86 pleural cavities.

**Ascites at Necropsy**

Ascites was noted at necropsy in 22 cases, was stated to be absent in 22, and was not specifically reported in 11 cases, although one of these patients had a paracentetic scar. The quantity of fluid tended to be rather small: 500 ml. or less was present in 15 patients, and 800 ml. or more in seven patients. The patient with the largest quantity of fluid (3,000 ml.) had chylos ascites.

**Metastasis to Other Sites**

All but one patient, who had leukemia, in the series had metastatic lesions in thoracic structures other than the heart. The frequency with which various thoracic sites were involved with metastatic lesions is presented in table 2.

Forty-three of 47 patients with malignant lesions other than leukemia* or a terminal leukemic phase of lymphoma had metastatic lesions in sites outside the thorax. Of the four who did not, three had primary intrathoracic tumors and one had carcinoma of the cervix. The sites of metastatic lesions outside the thorax are listed in table 2. The brain was examined in 39 patients. Thus, metastatic lesions were present in the cerebrum and dura.

*Excluded to avoid confusion with involvement of liver and spleen by leukemic cells.
in 15 per cent and 10 per cent respectively of those examined.

**Chronic Passive Congestion of Liver and Spleen**

Chronic passive congestion of the liver was arbitrarily graded from 0 to 4 (absent to most severe) on the basis of sinusoidal congestion and central atrophy or necrosis. It was graded 0 in 13 patients, 1 in 17, 2 in 10, 3 in 12, and 4 in three.

Weights of spleens used as an index of chronic passive congestion showed poor correlation with the quantity of pericardial fluid present. Weights of spleens averaged 170 Gm. in patients considered to have significant pericardial effusion and if one 540-Gm. spleen was omitted, the average spleen weight would be 153 Gm., a figure that is within normal limits.

**Mechanisms of Cardiac Embarrassment**

From both gross and microscopic study and from the descriptions of findings at the time of necropsy, the primary mechanisms whereby metastasis to the pericardium interfered with normal cardiac function were formulated. The commonest mechanism was pericardial effusion, which was found in 14 patients. Next in frequency was a combination of pericardial effusion and myocardial invasion by neoplastic tissue, which occurred in 11 patients. Cardiac constriction caused by encasement by neoplastic tissue was responsible for impaired function in eight patients. Encroachment on great vessels combined with myocardial invasion or myocardial invasion alone interfered with cardiac function in four patients each. Myocardial invasion and pericardial constrictive effects were responsible in three patients, as were pericardial effusion and encroachment on great vessels. Eight patients suffered from other mechanisms or combinations of mechanisms. One patient also was found to have incidental coronary sclerosis reducing a segment of a major coronary artery to less than 50 per cent of normal size. The quantity of pericardial fluid could not be determined in another patient as permission for necropsy was limited to the abdominal incision. Examples of the primary mechanisms found in this study are shown in figures 3 to 7.

**Clinical Manifestations**

A diagnosis of pericardial or cardiac malignant tumor was established or suspected clinically for 16 of the 55 patients although 34 were treated for either recognized congestive heart failure or mediastinal malignancy. When the patients were first seen at the clinic, the presenting symptoms, although often masked by or possibly due to other manifestations of malignancy, could have been related to the effects of metastasis to the pericardium or to anatomically related structures in 35 patients (64 per cent). Of these 35 patients, 29 had dyspnea as one of their presenting symptoms, 10 had cough, nine, anterior thoracic pain, and three, peripheral edema.

The signs and symptoms that may have

### Table 2

**Sites of Other Gross Metastatic Lesions in 55 Patients with Impairment of Cardiac Function due to Pericardial Metastasis**

<table>
<thead>
<tr>
<th>Site</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infrathoracic sites (55 patients) (leukemia excluded)</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>35</td>
</tr>
<tr>
<td>Nodes</td>
<td>28</td>
</tr>
<tr>
<td>Pleura and diaphragm</td>
<td>26</td>
</tr>
<tr>
<td>Other mediastinal structures</td>
<td>12</td>
</tr>
<tr>
<td>Ribs</td>
<td>8</td>
</tr>
<tr>
<td>Thymus</td>
<td>4</td>
</tr>
<tr>
<td>Thoracic vertebrae</td>
<td>2</td>
</tr>
<tr>
<td>Sternum</td>
<td>2</td>
</tr>
<tr>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Extrapulmonary sites (47 patients)</td>
<td></td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>24</td>
</tr>
<tr>
<td>Adrenal glands</td>
<td>18*</td>
</tr>
<tr>
<td>Liver</td>
<td>15</td>
</tr>
<tr>
<td>Bone</td>
<td>12</td>
</tr>
<tr>
<td>Kidneys</td>
<td>10</td>
</tr>
<tr>
<td>Pancreas</td>
<td>7</td>
</tr>
<tr>
<td>Brain</td>
<td>6†</td>
</tr>
<tr>
<td>Dura</td>
<td>4†</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>4</td>
</tr>
<tr>
<td>Ovaries</td>
<td>4</td>
</tr>
<tr>
<td>Spleen</td>
<td>3</td>
</tr>
<tr>
<td>Omentum, skin, stomach, ureter, and bowel</td>
<td>2 each</td>
</tr>
<tr>
<td>Muscle, orbit, and thyroid gland</td>
<td>1 each</td>
</tr>
<tr>
<td>None</td>
<td>4</td>
</tr>
</tbody>
</table>

* Bilateral lesions in 12; limited to left adrenal gland in three and to the right in three patients.
† Brain and spinal cord examined in 39 patients only.
Table 3

Clinical Manifestations of 55 Patients with “Significant” Pericardial Metastatic Tumors Which May Have Been Related to This Lesion or Its Effects

<table>
<thead>
<tr>
<th>Clinical manifestation</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>50</td>
</tr>
<tr>
<td>Cough</td>
<td>36</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>29</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>28</td>
</tr>
<tr>
<td>Thoracic pain</td>
<td>26</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>21</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>19</td>
</tr>
<tr>
<td>Venous distention</td>
<td>18</td>
</tr>
<tr>
<td>Edema (leg)</td>
<td>17</td>
</tr>
<tr>
<td>Cardiac enlargement</td>
<td>16</td>
</tr>
<tr>
<td>Pulmonary rales</td>
<td>11</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>10</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>9</td>
</tr>
<tr>
<td>Systolic murmur</td>
<td>5</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>4</td>
</tr>
<tr>
<td>Paradoxic pulse</td>
<td>3</td>
</tr>
<tr>
<td>Ascites</td>
<td>3</td>
</tr>
<tr>
<td>Syncope and diastolic gallop</td>
<td>2 each</td>
</tr>
<tr>
<td>Distant heart sounds, hiccup, paroxysmal nocturnal dyspnea, pulsat alternans, palpitation, friction rub, and paroxysmal supraventricular tachycardia</td>
<td>1 each</td>
</tr>
</tbody>
</table>

been related to a malignant tumor of the pericardium or anatomically related structures in order of frequency of their clinical recognition are listed in table 3. The frequency of dyspnea, cough, thoracic pain, and orthopnea is rather striking although certainly it is not surprising in a group of patients with terminal malignant lesions. Conspicuous by its infrequency was the recording of a friction rub in only one patient. This is particularly striking when contrasted with the high incidence (82 per cent) of fibrinous pericarditis found at necropsy. Also striking is the absence of the clinical recording of Ewart’s sign in any patient.

Fifty-three patients had thoracic roentgenograms. Of these, only four were reported as entirely negative. Cardiac enlargement, mediastinal widening, hilar adenopathy, or hilar mass was noted in the roentgenograms of 28 (53 per cent) of the 53 patients. Eighteen of these had pericardial effusion. Roentgenoscopic examination was performed at the clinic on two patients, and in the one patient with pericardial effusion, fluid was readily demonstrable. Neither angioangiography nor the pneumopericardial procedure was performed on any patient.

Electrocardiographic Manifestations

The electrocardiographic findings on the 27 patients for whom at least the three standard leads were available for study are correlated with the major pathologic condition and the assumed mechanism of cardiac embarrassment in table 4. Isolated inversion of T waves in lead III or unipolar lead aVF is not included under ‘‘T-wave abnormalities,’’ and ‘‘sinus tachycardia’’ refers only to rates in excess of 100 beats per minute. Tracings on 24 patients were obtained within 1 month of death; one tracing was made 3 1/2 months, one, 5 months, and one, 7 months before death. Four patients had arrhythmias documented by the electrocardiogram. Two had atrial fibrillation, one, atrial flutter, and one, simultaneous alternation of the P waves and QRS complexes. Numerous premature contractions were noted.
in three electrocardiograms. Right axis deviation was present in five, and left axis deviation in three.

Electrocardiograms before and after a pleuropericardial window was established surgically are compared in figure 8.

Cytologic Examination of Pericardial Fluid

Pericardicentesis was attempted on four patients but was unsuccessful on one. Cytologic examination of the pericardial fluid gave negative results on the one specimen on which it was done.

Treatment

Twenty-two patients were treated with a congestive failure regimen. Seven of these also received roentgen therapy to the mediastinum and two of them underwent pericardicentesis. Another nine received roentgen therapy to the mediastinum alone and one other underwent pericardicentesis alone. One patient had roentgen therapy and a pleuropericardial window was established after pericardicentesis. Thus, 34 (62 per cent) received some form of treatment directed toward either the impaired cardiac function or the mediastinal malignant lesion, even though the specific diagnosis was made or suspected in only 16 patients.

Discussion

The reason for the lack of detailed clinical findings and for the apparent paucity of diagnostic technics applied to these patients is understandable. As was noted, widespread malignant disease was usually present and with the primary diagnosis having been established previously, most of the clinician's efforts were directed toward psychologic support and simple palliative measures in the last weeks of life. Disturbing, occasionally painful, diagnostic procedures are often unrewarding and only add to the patient's distress and to the financial burden. Consequently, the at-

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Total</th>
<th>Sinus tachycardia</th>
<th>Low QRS voltage</th>
<th>T-wave abnormality</th>
<th>ST-segment depression*</th>
<th>Premature contractions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericardial effusion only</td>
<td>8</td>
<td>5</td>
<td>6†</td>
<td>7</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pericardial effusion and myocardial invasion</td>
<td>6</td>
<td>3</td>
<td>6</td>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Constrictive pericarditis</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Encaement of great vessels and myocardial invasion</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial invasion only</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Encaement of great vessels and pericardial effusion</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Invasion of left atrium and pulmonary veins with coronary tumor or coronary sclerosis</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Pericardial effusion and myocardium adherent to chest wall</td>
<td>1</td>
<td>1</td>
<td>1†</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Constrictive pericarditis and myocardial invasion</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>15</td>
<td>22</td>
<td>25</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

*In standard leads.
†One patient with a normal electrocardiogram had last tracing 3½ months before death.
‡Voltage improved after pleuropericardial window.
tending physician is often justified in limiting his approach to the immediate problem. However, with the advent of new palliative and therapeutic technics, the diagnosis of malignant involvement of the heart or anatomically related structures becomes more important in the management of widespread malignant lesions.

The high incidence of pericardial invasion secondary to carcinoma of the lung and breast in our series agrees with the findings of other authors. Obvious explanations for this are (1) the relative frequency of carcinoma of the lung and breast among malignant lesions in general and (2) the proximity of the primary sites of these carcinomas to the pericardium. Although carcinoma of the left lung has been stated to involve the pericardium frequently, we found no unilateral predominance of primary carcinoma from either lung or breast.

That malignant tumor in the pericardium was adjudged important as a cause of death in 86 per cent of this selected group with impairment of cardiac function should furnish added incentive for detecting its presence. The most frequent mechanism whereby a secondary pericardial malignant lesion caused significant cardiac embarrassment was pericardial effusion. One cannot be certain, however, that the large quantities of fluid frequently found actually caused tamponade during life, for the pericardial sac can adapt itself progressively to large quantities of

Figure 4

Patient with chronic myelogenous leukemia. a. Electrocardiogram obtained 3 days before death. b. The heart.
fluid without transmitting correspondingly elevated pressures to the venae cavae, pulmonary veins, and atria. Thus, one can be certain that tamponade was actually present only from the signs, symptoms, and hydrostatic measurements during life. In addition, we cannot assume that once begun the development of pericardial fluid is an incessantly progressive phenomenon in pericardial malignancy. There are three reports of incomplete but apparently spontaneous absorption of pericardial fluid in patients with malignant lesions of the heart.\textsuperscript{25-27} The finding of a frankly hemorrhagic effusion in only 12 of the 31 patients with a significant quantity of pericardial fluid and of a hemorrhagic effusion in only five of 86 pleural cavities with effusion indicates that a majority of secondary malignant lesions of these serous membranes gives rise to nonbloody effusions.

That usually the malignant process is already widespread when the pericardium is involved is apparent from table 4 and has been observed by other authors. Worthy of note is the large number of patients with adrenal metastasis. However, Willis\textsuperscript{25} found that carcinoma of the lung and breast were the most common malignant lesions metastasizing to the adrenal glands, and hence no direct relationship between adrenal and pericardial metastasis can be inferred.

The mechanisms of cardiac impairment by secondary pericardial malignant lesions have not been classified previously, but all have been referred to by one or more authors. Although coronary veins were involved by malignant lesions in two cases, we could not definitely establish that malignant invasion or tumor embolization was present in sizable branches of the coronary arteries. In addi-
tion, involvement of cardiac nervous tissue could not be found in any of our patients. In eight of the 12 cases in which cardiac constriction from pericardial malignant lesions was believed to have impaired cardiac function, the primary lesion was either lymphoma or leukemia; in two, carcinoma of the breast; in one, pulmonary carcinoma, and in one a fibrosarcoma was the primary lesion. Carcinoma of the breast\textsuperscript{19} and carcinoma of the lung\textsuperscript{10,29,30} have caused this syndrome, but to our knowledge, a metastatic sarcoma has not been implicated previously. Encroachment on the great vessels by a mass of neoplastic tissue contiguous with that involving the pericardium probably interfered directly with either cardiac inflow or outflow. Anatomic reflection of the pericardium onto the adventitia of the great vessels undoubtedly plays a role in permitting this mechanism to occur. The degree of functional encroachment or even its differentiation from encasement of the heart could not be established from the preserved specimens.

Reasons for infrequent clinical recognition of malignant involvement of the pericardium have been given, but even when signs and symptoms are selected as possibly being related to metastatic involvement of the pericardium or anatomically related structures, the most frequently occurring are the most nonspecific. Relatively specific diagnostic findings (for example, venous distention, cardiac enlargement, paradoxical pulse, distant heart sounds, pulsus alternans and friction rub) were much less common in the list of recognized signs and symptoms. Symptoms of thoracic pain followed no definite pattern and undoubtedly were related to involvement of thoracic structures other than the pericardium in many patients.

The electrocardiographic abnormalities were suggestive of cardiac or pericardial involvement in some patients. Although sinus tachycardia might seem usual in terminal malignancy, Lefkovits\textsuperscript{31} emphasized its importance as a sign of cardiac involvement. Whereas T-wave changes are probably not unusual in a group of patients with terminal malignancy, the high incidence of low voltage tracings has considerable diagnostic value. Although these voltage changes were associated with cardiac compression mechanisms (pericardial effusion or constrictive effects) in nearly all cases, similar findings were frequent in the group as a whole. A feature that may be of some

\textit{Figure 6}

\textit{Early myocardial invasion by metastatic bronchogenic carcinoma of the pericardium (hematoxylin and eosin; ×18).}
diagnostic aid in separating this group from patients with nonspecific pericarditis is the infrequency of ST-segment elevation in the standard leads among the patients with malignancy, since segment elevations are rather frequent in the electrocardiograms of patients with nonspecific pericarditis. One of our patients presented a subtle simultaneous alternation of the P waves and QRS complexes, which apparently appears only in pericardial effusion.

The thoracic roentgenogram was somewhat disappointing as a specific diagnostic aid, as it was of value in only about half of the patients. Undoubtedly, the presence of pleural effusion and other thoracic metastatic lesions or primary lesions contributed to obscure the pericardial lesion. More frequent use of roentgenoscopy, angiocardiology, and pneumopericardiography probably would have suggested the diagnosis in more cases.

The small number of patients undergoing pericardieentesis is the result of several factors: (1) low index of suspicion of pericardial effusion; (2) development of pericardial effusion late in the course of a terminal illness, and (3) hesitancy of the attending physicians to recommend further diagnostic procedures in a patient with terminal widespread malignant disease. The decision to perform pericardieentesis must be individualized, but our study suggests that this procedure might frequently lead to considerable palliation. A patient whose case is reported in the literature obtained marked, but temporary, relief after each of six pericardieenteses. One of our patients on whom the procedure unequivocally established the diagnosis of pericardial effusion subsequently had a pleuropericardial window established surgically with survival for 5 months thereafter.

Cytologic examination for malignant cells in the pericardial fluid is undoubtedly the most direct method by which one can establish the diagnosis of pericardial malignant lesion. Should the diagnosis be strongly suspected, but the pericardial fluid negative for tumor cells, repeated examinations are indicated, since several authors have cited cases in which negative cytologic findings were posi-

Figure 7

Invasion of coronary veins by metastatic bronchogenic carcinoma in two patients (hematoxylin and eosin: a, magnification reduced from ×12, b, magnification reduced from ×11).
tive after repeated pericardcenteses.

It is interesting that more than twice as many patients (34) were treated for either congestive failure or mediastinal malignant lesions as were suspected clinically of having cardiac metastasis (16). Thus, although some patients received therapy, newer developments in surgery, roentgen therapy, and chemotherapy would render such treatment inadequate by current standards.

Summary

Among 13,314 necropsies following death from neoplastic and nonneoplastic diseases performed at the Mayo Clinic from 1942 through 1958, 189 cases of secondary malignant lesions of the pericardium were demonstrated, an incidence of 1.42 per cent. Carcinoma of the lung and breast, the lymphomas, and leukemia constituted the large majority of the primary malignant lesions that caused the pericardial metastasis. Fifty-five of the 189 patients were adjudged to have had some impairment of cardiac function as a consequence of the pericardial metastasis and the following conclusions concern this group.

1. In 47 patients (86 per cent), the lesions were either the immediate or a contributory cause of death.

2. The most common mechanism whereby metastatic lesions in the pericardium interfered with cardiac function was by the development of pericardial effusion. Next in frequency was effusion combined with myocardial invasion and then cardiac constriction by tumor. Combinations of these processes with malignant encroachment on the great vessels and with invasion of coronary veins were the other mechanisms noted. Involvement of coronary arteries and the cardiac nerve supply was not noted.

3. Pericardial fluid was significant in causing tamponade in 31 cases. The fluid was frankly hemorrhagic in a small minority of

Figure 8

Electrocardiograms obtained before and after a surgical pleuropericardial window was established on December 21, 1957, for pericardial effusion due to metastatic involvement by a mediastinal sarcoma.
these cases although fibrinous pericarditis was present in 45 (82 per cent) of the group. Pleural effusion was present in 48 (92 per cent) of 52 cases and was usually bilateral. Ascites was present in 22 (50 per cent) of 44 cases; the quantity was usually rather small.

4. Only one patient had metastasis to the pericardium without metastasis to other thoracic structures; exclusive of patients with leukemia, 43 (92 per cent) of 47 patients had extrathoracic metastatic lesions.

5. Dyspnea, cough, pleural effusion, hepatomegaly, and thoracic pain were the most commonly recorded signs and symptoms that might be related to the pericardial lesions. However, more specific signs and symptoms directing attention to pericardial or cardiac involvement were not usually recorded.

6. The diagnosis of pericardial metastatic disease was suspected or established in only 16 (29 per cent) of the 55 patients, although 34 (62 per cent) either received treatment for congestive heart failure or were given roentgen therapy to mediastinal structures.

7. Of the 27 patients whose electrocardiograms were available, 25 had T-wave abnormalities, 22 had low QRS voltage, and 15 showed sinus tachycardia.

8. Thoracic roentgenograms, made on 53 patients, supplied clues to the diagnosis of pericardial malignancy in 28.

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Death Hath No Terrors
I thank GOD I have not those strait ligaments, or narrow obligations to the World,
as to jote on life, or be convulst and tremble at the name of death. Not that I am
insensible of the dread and horror thereof; or by raking into the bowels of the
decayed, continual sight of Anatomies, Skeletons, or Cadaverous relics, like Vespilloes,
or Grave-makers, I am become stupid, or have forgot the apprehension of Mortality; but
that, marshalling all the horrors, and contemplating the extremities thereof, I find not
any thing therein able to daunt the courage of a man, much less a well-resolved Chris-
tian; and therefore am not angry at the error of our first Parents, or unwilling to
bear a part of this common fate, and like the best of them to dye, that is, to cease to
breathe, to take a farewell of the elements, to be a kind of nothing for a moment, to be
within one instant of a Spirit.—Sir Thomas Browne. Religio Medici. Edited by W. A.
Secondary Malignant Tumors of the Pericardium

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