Clinicopathologic Findings in 52 Patients Studied by Technetium-99m Stannous Pyrophosphate Myocardial Scintigraphy

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SUMMARY Scintigraphic, clinical and pathological findings were correlated in 52 patients studied by technetium-99m stannous pyrophosphate (99mTc-PYP) myocardial scintigraphy before death or surgical resection of myocardium. Fifty-nine clinical events were studied with scintigraphy in the 52 patients; 41 of the 59 were associated with one or more abnormal 99mTc-PYP studies and 18 with normal 99mTc-PYP scintigrams. Myocardial scintigrams were positive in 29 of 31 cases with clinicopathological evidence of a corresponding discrete, grossly obvious acute myocardial infarct, including 16 of 16 transmural myocardial infarcts and 13 of 15 subendocardial infarcts. In 16 of 18 cases, negative myocardial scintigrams correlated with the absence of acute myocardial infarction determined by clinicopathological evidence. In two cases small subendocardial infarcts (<3 g) were not detected by 99mTc-PYP myocardial scintigraphy. Of the 12 additional instances of positive 99mTc-PYP myocardial scintigrams, five were associated with clinical unstable angina pectoris and seven were in the category of persistently positive scintigrams, since the scans were obtained 2.5 months or longer after proven or suspected acute myocardial infarcts. In all 12 instances, the positive 99mTc-PYP scintigrams were associated with evidence of multifocal irreversible myocardial damage consisting of myocytolysis, coagulation necrosis and/or fibrosis, and the histological age of the lesions was compatible with acute injury corresponding to the time of scintigraphy. The findings indicate that a positive 99mTc-PYP myocardial scintigram is a sensitive indicator of significant myocardial injury which may occur as confluent coagulation necrosis corresponding to clinical acute myocardial infarction, or as multifocal coagulation necrosis or myocytolysis associated with unstable angina pectoris or recurrent ischemic heart disease, especially after previous infarctions.

MYOCARDIAL SCINTIGRAPHY with technetium-99m stannous pyrophosphate (99mTc-PYP) is a sensitive and accurate test to detect myocardial necrosis. Evidence of this includes: 1) several reported series with a high incidence of abnormal 99mTc-PYP myocardial scintigrams in patients with historical, electrocardiographic and/or serum enzymatic evidence of acute myocardial infarction, including subendocardial and transmural infarcts; 2) experimental studies showing that selective 99mTc-PYP concentration after coronary occlusion is limited to myocardium with advanced necrosis or severe damage; and 3) studies in patients and experimental animals documenting the presence of myocardial necrosis associated with abnormal 99mTc-PYP scintigrams in conditions besides coronary heart disease, including cardioversion-induced injury and metastatic cardiac tumor.

Nevertheless, other observations have raised some uncertainties about 99mTc-PYP myocardial scintigraphy for detecting myocardial necrosis. These include: 1) documentation of low-grade positive 99mTc-PYP myocardial scintigrams in approximately one-third of patients with the clinical syndrome of unstable angina pectoris without diagnostic electrocardiographic or serum enzyme changes of acute myocardial infarction; 2) some reports of a relatively low incidence of abnormal 99mTc-PYP myocardial scintigrams in patients with clinical and laboratory evidence of acute myocardial infarcts, particularly subendocardial infarcts; 3) controversy regarding the significance of poorly localized or diffusely abnormal scintigrams and difficulty in distinguishing low-grade positive from artificial radionuclide blood pool scintigrams; and 4) occurrence of persistently positive 99mTc-PYP myocardial scintigrams in some patients weeks to months after acute myocardial infarction without definite clinical evidence of new infarction.

Questions regarding 99mTc-PYP myocardial scintigraphy might be resolved by detailed correlation of clinical and 99mTc-PYP scintigraphic findings with pathological findings in patients. Some information of this type has been reported previously. In this study we tried to get a broader perspective through detailed analysis of clinicopathological correlates of 99mTc-PYP myocardial scintigraphy in a large series of patients.

Patients and Methods
Fifty-two patients were studied over a 3.5-year period (June 1974 to December 1977) who had under-
gone $^{99m}$Tc-PYP myocardial scintigraphy before autopsy or surgical resection of myocardium. In all patients we evaluated the possibility of acute myocardial infarction. Forty-six had coronary heart disease confirmed by coronary angiography or at necropsy. Thirteen of these 46 patients had coronary heart disease in addition to other types of cardiovascular disease, including calcific aortic valve disease (five patients), infective endocarditis of aortic valve (one patient), mitral valve stenosis and insufficiency (one patient), floppy mitral valve (one patient), luetic aortitis (one patient), metastatic carcinoma of heart (two patients), atrial septal defect (one patient), and severe systemic hypertension (one patient). Three of these patients with valvular heart disease, including the one with infective endocarditis, had undergone valve replacement before $^{99m}$Tc-PYP myocardial scintigraphy. Six patients had other types of heart disease without significant coronary atherosclerosis, including massive pulmonary embolus (one patient), idiopathic congestive cardiomyopathy (two patients), mitral stenosis (two patients), and transposition of the great vessels surgically corrected by a Mustard procedure (one patient). The clinical, scintigraphic and pathologic findings in these patients were reviewed independently by three investigators.

More than 100 $^{99m}$Tc-PYP myocardial scintigrams in the 52 patients were studied. The scintigrams were obtained in at least three projections (anterior, left lateral and left anterior oblique) according to a standard technique using a Searle Pho-Gamma III scintillation camera with high resolution collimator.\(^1\) An investigator reviewed the scintigrams without knowing the clinical or pathological findings. The scintigrams were graded from 0-4+ activity according to the following criteria: 0 — no activity; 1+ — minimal activity felt usually to be related to non-myocardial uptake in blood pool or chest wall; 2+ — definite myocardial activity with uptake less than bone; 3+ — myocardial activity equal to bone, and 4+ — myocardial activity greater than bone activity.

Only myocardial scintigrams of grades 2-4+ were reported as positive with definitely abnormal myocardial uptake.\(^1\) Localization of abnormal uptake (2-4+) was also evaluated.

We reviewed the history and laboratory data to determine the clinical diagnosis associated with the $^{99m}$Tc-PYP myocardial scintigraphic study. ECGs were interpreted as consistent with but not diagnostic of acute myocardial infarction if changes were limited to ST-segment and T-wave abnormalities. We evaluated acute myocardial infarction by enzymatic techniques with standard laboratory tests, including determination of total serum creatine kinase (CK) and glutamic oxaloacetic transaminase (SGOT). Patients evaluated in the last year of this investigation were also studied using a radioimmunoassay to measure the CK-B isoenzyme.\(^4\) Serum enzyme changes were considered positive for acute myocardial infarction if a single study showed values equal to or greater than twice normal, or if serial determinations showed typical evolutionary changes with peak values at or above upper limits of normal.

The heart was examined at necropsy in 46 patients, myocardial tissue removed at operation was evaluated in four patients and both were performed in two patients. Standard gross and histological methods were used for documentation of coronary artery lesions, and age and location of discrete, grossly obvious myocardial infarcts and multifocal myocardial lesions.\(^5\) Lesions showing coagulation necrosis without evidence of healing were judged to be less than 5 days old and were subclassified chronologically according to the extent and character of the neutrophilic infiltrate.\(^6\) The age of healing lesions with coagulation necrosis was estimated as 1 week-2 months, depending upon the relative proportions of granulation tissue,
TABLE 3. Evidence of Prior or Subsequent Myocardial Infarcts (MI) in Relation to 59 Clinical Events Studied by 99mTc-PYP Myocardial Scintigraphy in 52 Patients

<table>
<thead>
<tr>
<th>Interval between 99mTc-PYP scan and death or operation</th>
<th>Prior MI &lt;5 weeks</th>
<th>Prior MI &gt;5 weeks</th>
<th>Subsequent MI &lt;5 weeks</th>
<th>Subsequent MI &gt;5 weeks</th>
<th>Prior and subsequent MI &lt;5 weeks</th>
<th>Prior and subsequent MI &gt;5 weeks</th>
<th>No prior or subsequent MI &lt;5 weeks</th>
<th>No prior or subsequent MI &gt;5 weeks</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myocardial infarct (AMI) (N = 31)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Abnormal scan</td>
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<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Normal scan</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Unstable angina pectoris (UAP) (N = 10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal scan</td>
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<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Normal scan</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Ischemic heart disease without AMI or UAP (N = 12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal scan</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
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<td>7</td>
</tr>
<tr>
<td>Normal scan</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Other heart disease (N = 6)</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>Normal scan</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>6</td>
</tr>
<tr>
<td>Totals</td>
<td>21</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>14</td>
<td>11</td>
<td>59</td>
</tr>
</tbody>
</table>

Fibrous tissue and unresorbed necrotic muscle, taking into account the relative size of the lesion.43 The age of lesions showing myocytolysis was estimated depending on the severity of degeneration.44 More advanced lesions were considered to be less than 3–4 months old if they showed immature, relatively avascular fibrous tissue and over 3–4 months old if they were composed of mature, relatively acellular scar tissue.45 46

Results
Clinicopathologic findings in the 52 patients are summarized in tables 1–7. We evaluated 59 clinical events by 99mTc-PYP myocardial scintigraphy in the 52 patients (tables 1 and 2). Clinicopathologic observations allowed separation of the 59 events into four categories: acute myocardial infarction, unstable angina pectoris, ischemic heart disease without clinical acute myocardial infarction or unstable

TABLE 4. 99mTc-PYP Scintigraphic Findings for 59 Clinical Events in 52 Patients

<table>
<thead>
<tr>
<th></th>
<th>Normal (0–1+)</th>
<th>Poorly localized 2+ activity</th>
<th>Localized activity* 2+</th>
<th>3+</th>
<th>4+</th>
<th>Totals</th>
</tr>
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<tbody>
<tr>
<td>Acute myocardial infarct (AMI) (N = 31)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transmural AMI</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>9†</td>
<td>4†</td>
<td>16</td>
</tr>
<tr>
<td>Subendocardial AMI</td>
<td>2</td>
<td>1</td>
<td>8</td>
<td>3</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Unstable angina pectoris (UAP) (N = 10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multifocal necrosis/fibrosis</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>No associated lesion</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Ischemic heart disease without AMI or UAP (N = 12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multifocal necrosis/fibrosis</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>No associated lesion</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Other heart disease (N = 6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multifocal necrosis/fibrosis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>No associated lesion</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Totals</td>
<td>18</td>
<td>2</td>
<td>18</td>
<td>16</td>
<td>5</td>
<td>59</td>
</tr>
</tbody>
</table>

*In the 27 clinical events with two or more 99mTc-PYP myocardial scintigrams, the most intense scan grade is reported.
†Six of these scintigrams showed the doughnut pattern characterized by marked activity peripherally around a central area of relatively decreased activity.
angina pectoris, and other non-atherosclerotic forms of heart disease. There was clinicopathologic evidence of previous or subsequent myocardial infarcts in relation to 34 (57.6%) of the 59 clinical events (table 3); however, additional myocardial infarcts were documented in only eight of the 19 events in which the interval between scintigraphic studies and death or operation was longer than 5 weeks (table 3). Two or more $^{99m}$Tc-PYP myocardial scintigrams were performed for 27 (46%) of the 59 clinical events, including 17 of the 31 acute myocardial infarcts, five of the 10 cases of unstable angina pectoris, four of the 12 cases of chronic ischemic heart disease and one of the six cases of other heart disease; single $^{99m}$Tc-PYP myocardial scintigrams were performed in the other cases. Of the 27 instances of multiple scintigraphic studies, the initial $^{99m}$Tc-PYP myocardial scintigram was positive in 19 and negative in eight, with a change to an abnormal pattern on the repeat scintigram in four of the eight initially negative studies. Forty-one of the 59 clinical episodes were associated with one or more abnormal $^{99m}$Tc-PYP scintigraphic studies (tables 1 and 4), with definite evidence of myocardial infarcts in 29 of the 41 cases and evidence of multifocal myocardial damage associated with unstable angina pectoris in five cases and recurrent ischemic heart disease without clinical acute infarction or unstable angina pectoris in seven cases.

**Acute Myocardial Infarction**

Of the 59 clinical events in the 52 patients, 31 corresponded to acute myocardial infarcts which were 1 day to less than 2 weeks old at the time of $^{99m}$Tc-PYP scintigraphic studies. One or more positive $^{99m}$Tc-PYP myocardial scintigrams were obtained in 29 of the 31 instances of acute myocardial infarction in 30 patients (tables 1 and 5). Of the 30 patients, 29 had evidence of severe coronary artery disease and one patient with congenital heart disease had a myocardial infarction which may have been related to a coronary

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**FIGURE 1.** $^{99m}$Tc-PYP myocardial scintigrams and gross pathologic findings in a patient with clinical and laboratory evidence of an acute inferior subendocardial infarct 7 months before death. The scintigram shows intense (3+) activity localized to the inferior and posterior regions of the heart (arrow) as well as activity in sternum (S).

**FIGURE 2.** At necropsy, a single, healed, subendocardial infarct was identified (arrows) in the heart of the patient described in figure 1. Although the infarct occupied a relatively small area of each ventricular slice, the infarct extended from apex to base of the posterior left ventricle.
TABLE 6. Clinicopathological Findings in 10 Patients with Coronary Artery Disease and Unstable Angina Pectoris

<table>
<thead>
<tr>
<th>Pt no.</th>
<th>Myocardial infarcts before UAP</th>
<th>Interval between onset of UAP and death or operation</th>
<th>99mTc-PYP scans during UAP</th>
<th>Interval between scan and death or operation</th>
<th>Multifocal myocardial lesions associated with UAP</th>
<th>Possible correspondence of acute damage to scan</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 MI - 3 years old and 6 weeks old</td>
<td>6 weeks</td>
<td>2+ apical anterior</td>
<td>2 days</td>
<td>Myocytolysis</td>
<td>Yes</td>
<td>Shock 1 day postop</td>
</tr>
<tr>
<td>2</td>
<td>1 MI - 3 months old</td>
<td>3 months</td>
<td>2+ apical, inferior</td>
<td>11 days</td>
<td>Myocytolysis, fibrosis</td>
<td>Yes</td>
<td>Shock 10 days postop</td>
</tr>
<tr>
<td>3</td>
<td>1 MI - years old</td>
<td>1 month</td>
<td>2+ apical</td>
<td>20 days</td>
<td>Myocytolysis, organizing coagulation necrosis, fibrosis</td>
<td>Yes</td>
<td>Operative specimen</td>
</tr>
<tr>
<td>4</td>
<td>None</td>
<td>5 months</td>
<td>2+ inferior, posterior</td>
<td>5 months</td>
<td>Fibrosis</td>
<td>Yes</td>
<td>Arrhythmias 1 day postop</td>
</tr>
<tr>
<td>5</td>
<td>None</td>
<td>12 months</td>
<td>2+ apical, posterior</td>
<td>12 months</td>
<td>Fibrosis</td>
<td>Yes</td>
<td>Acute MI</td>
</tr>
<tr>
<td>6</td>
<td>None</td>
<td>2 months</td>
<td>Negative (4 scans)</td>
<td>8 days</td>
<td>Organizing coagulation necrosis, fibrosis</td>
<td>Yes</td>
<td>Acute MI 12 hours postop</td>
</tr>
<tr>
<td>7</td>
<td>3 MI - 2, 2 and 1 months old</td>
<td>1 month</td>
<td>Negative</td>
<td>13 days</td>
<td>3-week-old extension of older MI</td>
<td>=</td>
<td>Shock 1 day postop</td>
</tr>
<tr>
<td>8</td>
<td>None</td>
<td>2 months</td>
<td>Negative</td>
<td>5 days</td>
<td>Fibrosis</td>
<td>No</td>
<td>Shock hours postop</td>
</tr>
<tr>
<td>9</td>
<td>4 MI - years to months old</td>
<td>3 months</td>
<td>Negative</td>
<td>1 day</td>
<td>Fibrosis</td>
<td>No</td>
<td>Shock hours postop</td>
</tr>
<tr>
<td>10</td>
<td>None</td>
<td>6 months</td>
<td>Negative</td>
<td>8 days</td>
<td>Fibrosis</td>
<td>No</td>
<td>Shock hours postop</td>
</tr>
</tbody>
</table>

Abbreviations: MI = myocardial infarct; UAP = unstable angina pectoris.

Embolus. The acute myocardial infarcts occurred after one or more prior myocardial infarcts in 12 of 31 cases (table 3). Abnormal 99mTc-PYP myocardial scintigrams were observed with all 16 acute transmural infarcts and in 13 of 15 acute subendocardial infarcts (figs. 1 and 2, tables 4 and 5). The anatomic location of the infarcts generally agreed with areas of increased uptake on the 99mTc-PYP scintigrams. Of the 31 acute myocardial infarcts, 13, including eight transmural and five subendocardial infarcts, were fatal; and 18, including eight transmural and 10 subendocardial infarcts, were associated with recovery with subsequent demise due to a myocardial infarct, arrhythmia or cardiac failure.

For the 18 clinical events with negative 99mTc-PYP scintigraphic studies, no evidence of a corresponding grossly obvious myocardial infarct of appropriate age and location was found in 16 cases. Myocardial infarcts not detected by 99mTc-PYP scintigraphy were documented in two cases; both infarcts were small subendocardial lesions estimated at less than 3 g. The 18 negative scintigraphic studies were obtained in 17 patients, including 11 with and six without coronary artery disease.

Unstable Angina Pectoris

Ten patients had 99mTc-PYP myocardial scintigraphic studies related to clinical episodes of unstable angina pectoris recognized by significant alteration in their stable pattern; five of the 10 patients had 2-3+
positive scintigrams and five had negative scintigrams (tables 1, 4 and 6). None of the 10 patients with unstable angina pectoris had electrocardiographic or serum enzyme changes diagnostic of acute myocardial infarction during the episodes of unstable angina pectoris. All had significant coronary artery disease with more than 75% narrowing of the luminal areas of two or three major coronary arteries. Tissue for pathological examination was obtained at operation in one patient and at autopsy in nine patients. Seven of the nine autopsy patients died within 1 day after cardiac surgery, one died 10 days after cardiac surgery, and one died with a 2-day-old myocardial infarct (table 6).

Pathological examination revealed left ventricular lesions in each of the 10 patients. These lesions were small and multifocal, and were not classified as discrete, grossly obvious myocardial infarcts. Relatively acute multifocal lesions consisted of coagulation necrosis or myocytolysis (fig. 3).\(^{43-46}\) Older lesions were characterized by replacement fibrosis (fig. 4). Correlation of the timing of myocardial scintigraphy with histologic findings indicated that the age of the myocardial lesions was consistent with the possibility of acute myocardial injury at the time of \(^{99m}\)Tc-PYP scintigraphy in all five patients with positive myocardial scintigrams (table 6). The three patients who died within 14 days of scintigraphic study had active myocardial lesions which clearly antedated healed myocardial infarcts (fig. 3). The two patients who died later than 2 months after scintigraphic study had multifocal fibrosis in the absence of clinical or pathological evidence of discrete regional myocardial infarction (fig. 4). Two patients with negative \(^{99m}\)Tc-PYP scintigrams had small, healing myocardial lesions which could have been in an acute state of necrosis at
also had evidence of healed myocardial infarcts which antedated the onset of unstable angina pectoris.

Ischemic Heart Disease Without Acute Myocardial Infarction or Unstable Angina Pectoris

Myocardial scintigrams were performed in 12 patients with coronary artery disease during periods which were not associated with clinical evidence of acute myocardial infarction and were not judged clinically to represent unstable angina pectoris (tables 1–4). Myocardial scintigrams were positive in seven and negative in five of the 12 patients. The positive myocardial scintigrams in these individual fulfilled the criteria for persistently positive scintigrams, since these scintigrams were obtained 2.5–9 months after clinically suspected episodes of acute myocardial infarction without definitive clinical evidence of new infarction (fig. 5).13, 14, 30 All seven patients with persistently positive scintigrams had significant recurrent episodes of angina pectoris, but only one of the five patients with scintigrams that evolved to negative following infarction had significant angina.

Tissue for pathological examination was obtained at operation in four patients (three with positive and one with negative scintigrams) and at autopsy in eight patients (four with positive and four with negative scintigrams). All seven patients with persistently positive scintigrams showed evidence of multifocal coagulation necrosis, myocytolysis or fibrosis consistent with acute damage at the time of scintigraphic study (fig. 6). With the possible exception of one patient, we found no evidence of acute damage at the time of scintigraphic study in the five patients with negative 99mTc-PYP scintigrams.

Sensitivity and Specificity

For the 59 clinical events in this series, 41 were associated with abnormal PYP scintigrams out of 46 instances in which there was active necrosis estimated to correspond to the time of scintigraphy. The scintigrams were negative in 18 events. In five of these instances, however, there was evidence of necrosis which was felt to correspond potentially to the time of the
FIGURE 6. Foci of severe myocytolysis and fibrosis in a patient with persistently positive $^{99m}$Tc-PYP myocardial scintigrams who died within a few hours after developing an acute subendocardial infarct. A) Focus of myocytolysis (M) has progressed to complete loss of many muscle cells with retention of a loose connective tissue stroma. Previous episodes of injury have resulted in fibrosis (F). B) Fragments of necrotic muscle cells (arrows) blend into scar tissue. A) Masson trichrome stain × 140; B) Masson trichrome stain × 350.

Discussion

This study demonstrates the clinicopathological correspondence of abnormal $^{99m}$Tc-PYP myocardial scintigrams with the presence of irreversible myocardial damage. In individuals with clinically documented acute myocardial infaracts, appropriately timed and performed $^{99m}$Tc-PYP myocardial scintigrams were abnormal in every instance of transmural anterior, inferior and posterior myocardial infarction, and in all but two acute subendocardial myocardial infarcts. In addition, histopathological evidence of multifocal irreversible damage was observed in all patients with abnormal $^{99m}$Tc-PYP myocardial scintigrams associated with unstable angina pectoris or symptomatic ischemic heart disease after myocardial infarction. Previous experimental studies have shown that $^{99m}$Tc-PYP myocardial scintigrams were consistently abnormal in canine models with permanent coronary occlusion and acute myocardial infarcts larger than 3 g.5,18-21 Our findings in patients are compatible with the experimental observations, since the only negative scintigraphic tests in the present study in the setting of acute myocardial damage occurred with very small subendocardial myocardial infarcts in two patients and with multifocal myocardial lesions in two patients with unstable angina pectoris and one patient with chronic ischemic heart disease. In the other individuals with normal $^{99m}$Tc-PYP myocardial scintigrams in whom there was clinical concern...
that myocardial infarction might have occurred, there was no evidence of myocardial damage corresponding to the time of the negative \(^{99m}\text{Tc-PYP}\) scintigram and the clinical event.

Our clinicopathologic findings are based in part on the use of standard gross and histologic criteria for the estimation of the age of myocardial damage. Previous work has indicated that infarcts less than 1 week old can be dated accurately to within 24 hours, those in the second week to within 36–48 hours, and infarcts up to approximately 6 weeks old to within 7 days.\(^{45, 44}\) The morphological criteria become less accurate as the infarcts enter an advanced healing phase, and they cannot be used for determination of the age of completely healed lesions.\(^{43, 44}\) However, the interval between onset of necrosis and pathological examination for most clinical events in the present study was within the interval when morphological criteria may provide useful information (table 2). The morphological criteria for aging also were correlated with clinical timing of onset and electrocardiographic and enzymatic evidence of acute infarction. Furthermore, the location of abnormal \(^{99m}\text{Tc-PYP}\) myocardial uptake corresponded well with electrocardiographic and morphological localization of the infarcts. In the patients with unstable angina pectoris and chronic ischemic heart disease, evidence for acute necrosis at the time of scintigraphy was based necessarily only on the morphological findings. In every case of positive scintigraphy, however, the morphological findings were consistent with the possibility of acute damage at the time of the study. In those subjects with previous myocardial infarcts, the histopathologic changes also were indicative of damage which was more recent than the original infarcts. In the two patients with unstable angina pectoris and one patient with chronic ischemic heart disease who had histological evidence of possible active myocardial damage associated with negative \(^{99m}\text{Tc-PYP}\) scintigrams, the discrepancy may have been related to limitations in determination of the exact age of healing lesions as well as to involvement of relatively small amounts of myocardium.

Our clinicopathologic findings in patients are supported by extensive evidence in animal models that a positive \(^{99m}\text{Tc-PYP}\) myocardial scintigram is dependent upon the presence of acute necrosis, with selective concentration of the agent in acutely necrotic and severely damaged tissue with increased calcium accumulation and residual blood flow.\(^{16, 27, 46}\) This has been demonstrated in animal models by assays of regional tissue radioactivity\(^{16, 27, 46}\) and by autoradiography.\(^{20}\)

Although our current practice is to perform serial \(^{99m}\text{Tc-PYP}\) myocardial scintigraphy whenever necessary, the present retrospective study extended to a period before our protocols for serial imaging were formalized. In this study, two or more \(^{99m}\text{Tc-PYP}\) myocardial scintigrams had been performed for 27 (45.8\%) of the 59 clinical events; however, only eight of the 27 instances of serial scintigraphy had negative initial scans, but four of these eight changed to an abnormal pattern on repeat scintigraphic study. We repeated scintigraphy in the 19 clinical events with initially abnormal scintigrams to follow the evolution of the abnormal scintigraphic pattern. Localization of damage over time could be identified in every patient except for one, in whom \(^{99m}\text{Tc-PYP}\) uptake remained poorly localized. This individual had diffuse and patchy myocardial injury throughout the subendocardium. Our current procedure is to obtain at least one additional scintigram 48–72 hours after admission if the initial scan within the first 24 hours after admission is negative or equivocal. If the initial scintigram obtained within the first 24 hours of admission is abnormal, repeat scintigrams are obtained at 48–72 hours and at 7–14 days to evaluate serial changes in intensity of myocardial uptake.

Although the results of this study represent a select autopsy series, they are similar to those of our larger clinical series.\(^{2, 4}\) Emphasis on serial myocardial imaging may explain the higher incidence of abnormal \(^{99m}\text{Tc-PYP}\) myocardial scintigrams obtained for acute subendocardial infarcts at our institution compared with the experience of some other workers.\(^{32, 44}\)

Several patients with unstable angina in this study and previous studies\(^{2, 32}\) had abnormal \(^{99m}\text{Tc-PYP}\) myocardial scintigrams without electrocardiographic or enzymic evidence of acute myocardial infarcts. In the two patients with unstable angina who had undergone myocardial scintigraphy over 2 months before death, histologic examination showed evidence of multifocal myocardial fibrosis in the absence of clinical or pathological evidence of discrete regional myocardial infarction. The other three patients had histories of previous myocardial infarction; however, these patients had evidence of active myocardial necrosis which had a temporal correlation with the abnormal \(^{99m}\text{Tc-PYP}\) scintigrams obtained within 14 days of tissue sampling. The irreversible myocardial damage occurred as coagulation necrosis or myocyte lysis.\(^{43, 46}\) In one patient in whom tissue was obtained at operation and in the other two in whom specimens were obtained shortly after operation, the lesions were judged to have antedated the operations and to correspond to the time of positive scintigraphy. Multifocal myocardial lesions also were identified in the five patients with unstable angina pectoris and negative \(^{99m}\text{Tc-PYP}\) myocardial scintigrams. In three patients the active lesions clearly antedated the timing of the scans; but, as discussed previously, there was some question about the relationship between the exact timing of the scintigrams and the onset of necrosis in two of these patients. Thus, the findings indicate that multifocal myocardial necrosis leading to replacement fibrosis may develop in patients with coronary heart disease in the absence of definitive evidence of acute myocardial infarction obtained by electrocardiographic or standard serum enzyme tests. This is not a new observation and has been described repeatedly in previous clinicopathologic studies.\(^{19–32}\) Our results also are in accord with the work of Jaffe and associates, who found a correlation between ab-
Our study also shows that multifocal myocardial necrosis occurs in patients with chronic coronary artery disease who retain persistently abnormal myocardial scintigrams after myocardial infarction without clinical evidence of new infarction. Persistently abnormal scintigrams after acute myocardial infarcts appear to be associated with a subsequently difficult clinical course characterized by recurrent episodes of angina and readmissions to the hospital with chest pain. The scintigrams in these patients are generally weakly positive. Some patients retain more intensely abnormal scintigrams, and these individuals tend to have associated congestive heart failure as well. Olsen, Aronow and associates have also found that persistently abnormal myocardial scintigrams are associated with an increased incidence of severe angina, acute myocardial infarcts, cardiac death and congestive heart failure compared with patients whose scintigrams return to normal after myocardial infarction. Many patients with persistently abnormal myocardial scintigrams must be followed, but these patients appear to need frequent examination and vigorous but individually appropriate therapeutic intervention. Ventricular aneurysms, dystrophic myocardial calcification, or metastatic myocardial calcification as occurs in patients with severe renal disease also may be associated with abnormal myocardial scintigrams.

Our results indicate that the myocardial scintigraphic pattern alone does not provide an absolute separation of patients with clinical and laboratory evidence of acute myocardial infarction from patients with multifocal necrosis associated with clinical unstable angina pectoris or previous myocardial infarction (table 4). The diagnosis of clinical acute myocardial infarction, however, can still be made with a high probability of accuracy on the basis of a single 3+ positive myocardial scintigram; but even in these patients it is best to document evolution to either a decrease in or loss of abnormal myocardial activity by serial myocardial imaging. Currently, we do not make a diagnosis of classical acute myocardial infarction in patients who exhibit the same 2+ intensity of uptake on three or more myocardial scintigrams obtained over 12 days without other diagnostic evidence of acute myocardial infarction. When clinically indicated, we have also proceeded with diagnostic evaluation and coronary bypass surgery in this group of patients. Further study, however, is needed to determine optimal clinical management for patients with myocardial scintigraphic evidence of limited myocardial necrosis without other evidence of classical acute myocardial infarction.

In summary, the results of this clinicopathologic study demonstrate that abnormal myocardial scintigraphy is a very sensitive indicator of myocardial necrosis. Abnormal myocardial uptake may result from discrete myocardial infarcts as well as from multifocal myocardial damage that may be clinically undetected otherwise.

Acknowledgments

The authors acknowledge the essential contributions of present and previous house officers on the Medicine, Pathology and Nuclear Medicine services of Parkland Memorial Hospital, as well as the excellent technical assistance of Norman Vance, Kenneth Graham and their associates in the Nuclear Medicine Department.

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Circulation. 1979;59:257-267
doi: 10.1161/01.CIR.59.2.257

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