Asymptomatic Coronary Artery Disease: Angiographic Assessment of Diabetics Evaluated for Renal Transplantation

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SUMMARY Twenty-one insulin-dependent diabetics with azotemic nephropathy were evaluated for renal transplantation by selective coronary angiography and cine left ventriculography. All had hypertension, retinopathy, neuropathy, and required salt restriction plus diuretics for volume overload. There was no clinical or electrocardiographic evidence of ischemic coronary artery disease in twenty.

Ten patients (five males, five females; mean age 29.3 years; mean duration of diabetes 18.9 years; mean serum cholesterol 264 mg%) had no significant coronary artery disease and no ventricular wall motion abnormalities.

Nine patients (seven males, two females; mean age 38.7 years; mean duration of diabetes 21.9 years; mean serum cholesterol 239 mg%) had significant coronary artery disease, seven demonstrating focal abnormalities in left ventricular wall motion.

Two patients (one male, one female; mean age 36.5 years; mean duration of diabetes 28.5 years; mean serum cholesterol 250 mg%) had no significant coronary artery disease, but demonstrated diffusely abnormal left ventricular wall motion with diminished ejection fraction.

Thirty-eight percent had significant coronary artery disease unpredictable by electrocardiographic or clinical data. The finding of no significant coronary artery disease in 52% of a group with severe renahypertensive complications of diabetes is surprising. Two patients may have a demonstrated cardiomyopathy.

ATHEROSCLEROTIC CARDIOVASCULAR disease is the most common cause of death among patients with severe renal disease.1 In a group of diabetic patients under evaluation for renal transplantation, the major non-renal cause of morbidity and mortality would be ischemic cardiovascular complications. In order to clarify the risks of surgery in those diabetic patients in whom severe coronary artery replacement with a ball-valve prosthesis. Circulation 29 (suppl 1): I-36, 1964

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Transplantation Committee of the New England Deaconess Hospital and included comprehensive metabolic, renal, urological, vascular, ophthalmological, socioeconomic, psychiatric and ministerial services, in addition to noninvasive and invasive cardiac investigations.

**Methods**

Right and left heart catheterization, cine left ventriculography and selective coronary angiography were performed by standard Sones' technique with fluoroscopic, electrocardiographic and pressure monitoring. Left and right heart pressures were obtained in a resting state. Cardiac output was measured both by the Fick technique and by thermodilution. Hemodynamic measurements were repeated in selected patients during straight leg raising exercise on the catheterization table. After hemodynamic determinations, the patient was rested for 15 minutes in order to return to basal status. At this point cine left ventriculography was performed in the right anterior oblique position using 50 ml of Renografin 76 (methylglucamine diatrizoate 66% and sodium diatrizoate 10%) by pressure injector. Selective coronary angiography was then performed with 50–250 ml of Renografin 76 via small hand injections. Patients were studied in the postabsorptive state after a split insulin dose and while receiving intravenous fluids. No patient was dehydrated, although loop diuretics were frequently required. Each patient was premedicated with both diazepam and pentobarbital sodium. The presence of peripheral neuropathy and proliferative retinopathy severely hampered adequate exercise testing. Further, the fluid overload state may have precluded accurate echocardiographic interpretation of wall motion. Gated and ungated radioisotopic scanning for ventricular wall motion was not available at the time of this study.

Films and tracings were reviewed independently by each of three cardiologists and rated for this study as greater than 50% obstruction, less than 50% obstruc-

**Table 1. Characteristics of Population Studied**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex</th>
<th>Diabetes</th>
<th>Hypertension</th>
<th>Azotemia</th>
<th>Cholesterol (mg/dl)</th>
<th>Urate (mg/dl)</th>
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<tr>
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<td>22</td>
<td>F</td>
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</tr>
<tr>
<td>3</td>
<td>27</td>
<td>M</td>
<td>23</td>
<td>3</td>
<td>4</td>
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</tr>
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<td>4</td>
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<td>F</td>
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<td>3</td>
<td>2</td>
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</tr>
<tr>
<td>6</td>
<td>37</td>
<td>M</td>
<td>25</td>
<td>3</td>
<td>3</td>
<td>281</td>
</tr>
<tr>
<td>7</td>
<td>31</td>
<td>M</td>
<td>20</td>
<td>5</td>
<td>5</td>
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</tr>
<tr>
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<td>24</td>
<td>F</td>
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<td>2</td>
<td>2</td>
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<td>30</td>
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<td>17</td>
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<td>10</td>
<td>41</td>
<td>M</td>
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<tr>
<td>11</td>
<td>42</td>
<td>M</td>
<td>20</td>
<td>3</td>
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<td>15</td>
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<tr>
<td>14</td>
<td>46</td>
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<td>15</td>
<td>44</td>
<td>M</td>
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<tr>
<td>16</td>
<td>27</td>
<td>F</td>
<td>21</td>
<td>1</td>
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</tr>
<tr>
<td>17</td>
<td>36</td>
<td>M</td>
<td>20</td>
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</tr>
<tr>
<td>18</td>
<td>36</td>
<td>M</td>
<td>33</td>
<td>11</td>
<td>11</td>
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<td>19</td>
<td>48</td>
<td>M</td>
<td>20</td>
<td>?</td>
<td>?</td>
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<tr>
<td>20</td>
<td>32</td>
<td>M</td>
<td>31</td>
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</tr>
<tr>
<td>21</td>
<td>41</td>
<td>F</td>
<td>26</td>
<td>?</td>
<td>?</td>
<td>163</td>
</tr>
<tr>
<td>Means</td>
<td></td>
<td></td>
<td>34 ± 7.7</td>
<td>13 M, 8 F</td>
<td>21.1 ± 4.9</td>
<td>3.4 ± 2.5</td>
</tr>
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</table>

**Table 2. Relationship of Coronary Artery Disease to Clinical Findings**

<table>
<thead>
<tr>
<th>Clinical findings</th>
<th>No significant coronary artery disease, groups A and C (n = 12)*</th>
<th>Significant coronary artery disease, group B (n = 9)*</th>
</tr>
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<tbody>
<tr>
<td>A. Cardiac examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Cardiomegaly</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>2. Gallops</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>3. Murmurs</td>
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<td></td>
</tr>
<tr>
<td>S, S1</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>4. Diastolic regurgitant</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>B. Electrocardiogram</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Normal</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>2. Left ventricular hypertrophy</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>3. Non-specific STT abnormality</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>C. Chest x-ray</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Normal</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>2. Cardiomegaly</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>D. Cardiac echo (n = 5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Pericardial effusion</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2. LVDD†</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*P = Not significant by chi square for each observation category.

Abbreviation: LVDD = left ventricular internal diameter in diastole.
Table 3. Hemodynamic Data (mean ± s.d.)

<table>
<thead>
<tr>
<th>Creatinine (mg%)</th>
<th>Hgb (gm%)</th>
<th>Mean BP (mm Hg)</th>
<th>Pulse beats/min</th>
<th>PRA (ng/ml/He)</th>
<th>LVEDP (mm Hg)</th>
<th>SV (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>rest/exercise</td>
<td>rest/exercise</td>
<td></td>
</tr>
</tbody>
</table>

A. No significant coronary disease
1. With AV fistula
1. 7.1 7.9 133 102 2.0 2.8 15 27 70 102
2. 5.1 7.3 93 100 2.0 1.8 15 11 100 --
3. 8.1 9.9 100 90 9.8 10.6 4 7 56 68
4. 7.6 7.5 110 92 18 17 185 237
5. 9.1 5.6 105 116 12 15 112 --
6. 8.1 8.1 110 -- 7.9 11 132 --
7. 6.1 6.1 100 74 9 11 111 136
Mean (n = 7) 7.3 7.5 107.3 95.7 11 15 111 136

B. Significant coronary disease
1. With AV fistula
11 8.1 9.6 120 90 2.2 1.6 8 19 104 150
12 7.9 7.5 105 102 2.2 1.6 10 17 132 --
11 11.0 7.1 111 92 2.2 1.6 30 10 108 138
14 10.5 9.7 110 89 2.6 4.2 12 17 84 73
16 9.8 9.4 100 -- 12 17 84 73
17 8.2 11.5 105 89 2.6 4.2 12 17 84 73
Mean (n = 7) 8.2 9.0 109.4 92.7 20 24 104 114

2. Without AV fistula
18 14.1 6.5 100 -- 8 19 104 150
19 5.3 11.2 112 81 2.2 1.6 8 19 104 150
Mean (n = 2) 9.7 8.9 106 -- 20 -- -- --
10 6.2 ± 3.0 ± 1.8 ± 129 ± 19.8 ± 4 ± 7 ± 46 ± 89
Mean (n = 9) 8.5 8.9 108.7 91 20 25 99 108
11 3.1 ± 6.7 ± 6.3 ± 10 ± 14 ± 16 ± 34

C. Myocardial dysfunction
20 14.2 8.1 100 86 -- 24 -- 109 --
21 13.6 8.0 98 108 -- 21 40 48 83
Mean (n = 2) 13.9 8.1 99 97 -- 23 -- 79 --
12 ± 0.4 ± 1.4 ± 15.6 ± 2 ± 43

*Comparing groups A and B, P < 0.05 by unpaired t test.
Abbreviations: PRA = plasma renin activity; LVEDP = left ventricular end-diastolic pressure; SV = stroke volume; SI = stroke index; CO = cardiac output; CI = cardiac index; LVEDV = left ventricular end-diastolic volume; SVR = systemic vascular resistance; EF = ejection fraction.

Results

The 21 insulin-dependent diabetic patients were divided into three groups: 1) no significant coronary artery disease; 2) significant coronary artery disease; 3) no significant coronary artery disease, but diffuse left ventricular dysfunction.

The 10 patients in group A included five males and five females with a mean age of 29.3 years (range 22-37 years), mean duration of diabetes of 18.9 years (range 14-25 years), mean duration of hypertension of 2.6 years (range 1-5 years), mean serum cholesterol concentration of 264 mg% (range 157-351 mg%), and mean serum uric acid concentration of 8.3 mg% (range 6.1-11.7 mg%). In this group there were no ventricular wall motion abnormalities.

The nine patients in group B included seven males and two females with a mean age of 38.7 years (range 27-48 years), mean duration of diabetes of 21.9 years (range 15-33 years), mean duration of hypertension of 4.1 years (range 1-11 years), mean serum cholesterol
concentration of 239 mg% (range 131–481 mg%), and mean serum uric acid concentration of 8.1 mg% (range 5.7–13.8 mg%). In this group with significant coronary artery disease, four patients demonstrated involvement of three major vessels and five patients exhibited two-vessel coronary artery disease. Regional abnormalities of ventricular wall motion were seen on cine left ventriculography in each of seven patients in whom adequate films were obtained. In each instance the ventricular wall motion abnormality corresponded (hypokinesis in four; akinesis in three; akinesis and dyskinesis in one) regionally with a significant coronary arterial occlusive lesion. The anatomic distribution of coronary occlusive findings was similar to those reported for symptomatic nondiabetics.5

The two patients in group C included one male and one female with a mean age of 36.5 years (range 32–41 years), mean duration of diabetes of 28.5 years (range 26–31 years), mean duration of hypertension of 3 years, mean serum cholesterol concentration of 253 mg% (range 163–338 mg%), and mean serum uric acid concentration of 10.5 mg% (range 10.4–10.6 mg%). These two patients had diffusely abnormal cine left ventriculograms.

Within the three groups there were no statistically significant differences in age, duration of diabetes or hypertension, and serum concentration of cholesterol or uric acid. Mean age of males in group B was 40.1 years (range 36–48 years), compared with 32.5 years (range 27–41 years) in groups A and C. Mean age of females in group B was 28.5 years (range 27–30 years), compared with 28.3 years (range 22–41 years) in groups A and C.

Table 2 reveals that no clinical noninvasive modality was useful in predicting the presence or absence of significant coronary artery disease in these patients.

Table 3 lists hemodynamic data in the three groups.
which were comparable with regard to degree of anemia, severity of azotemia, level of blood pressure, and presence or absence of surgically created arteriovenous fistula. Comparison of groups A and B showed no statistically significant differences in left ventricular end-diastolic pressure, stroke volume, stroke index, cardiac output, cardiac index, left ventricular end-diastolic volume and systemic vascular resistance. Ejection fractions were significantly different, though within the normal range. Group C demonstrated the highest left ventricular end-diastolic pressure and the lowest determinations of stroke volume, stroke index, cardiac output, cardiac index and ejection fraction. The normal control values in this laboratory are: ejection fraction 72.4 ± 6.5%, and end-diastolic volume index 77.4 ± 13.2 ml/m².

Discussion

Severe coronary artery disease was found in nine of 21 juvenile-onset diabetics under evaluation for renal transplantation. As a group, these patients did not differ statistically from the 12 who demonstrated no significant coronary artery disease in terms of age, sex distribution, duration of diabetes, duration or severity of hypertension, and concentration of hemoglobin, cholesterol, creatinine or uric acid.

Cardiac catheterization was prospectively begun in this group of 21 consecutive patients. All had had interstitial pulmonary edema, but only one had typical angina pectoris. Given the insensitivity of noninvasive techniques in differentiating the patients with fluid overload from those with true myocardial ischemia in the setting of known accelerated atherosclerotic vascular disease, coronary angiography was used to assess long-term survival and to clarify the risks of surgery in those patients in whom asymptomatic coronary artery disease might raise serious doubts as to the wisdom of transplantation.

While this study was prospective and consecutive, the incidence of coronary artery disease in the study is subject to several selection biases, limiting its validity within other populations of patients with diabetes, azotemia or hypertension. In the context of proposed renal transplantation among diabetic patients, general restrictions have included age limitations; prior cardiac, cerebrovascular or peripheral vascular events; proven susceptibility to urinary tract or skin infections; and major psychiatric disorders. In contrast, only minor restrictions are associated with blindness due to diabetic retinopathy, paralysis due to diabetic neuropathy and weakness due to diabetic gastroenteropathy. The results do not apply to the general group of diabetics, including adult-onset hyperglycemic patients whose disease does not necessarily parallel the juvenile-onset group. Nevertheless, since the patients studied represented a group in whom the risks of renal transplantation were being seriously considered, this kind of study does have some practical applicability within the population of insulin-dependent diabetics with severe renal insufficiency. It is not surprising that patients with myocardial dysfunction had only mildly depressed ejection fractions, since marked clinical cardiac disease would have excluded patients from consideration for renal transplantation.

Insulin-dependent diabetics followed prospectively tend to fall into two groups. The first group develops severe renal insufficiency with hypertension within 20 years of diabetes. About 10% of these patients suffer a major cardiac or cerebrovascular event before the requirement for chronic dialysis or renal transplantation. The patients in our present study fall into this general category in terms of duration of diabetes, age of onset, etc. Yet, 43% had severe coronary artery disease. A high incidence of myocardial infarction would be expected after transplantation surgery with high-dose glucocorticoid immunosuppression or during the course of maintenance dialysis with ultrafiltration-induced hypotension. A second group, surviving 30–40 years of insulin-dependent diabetes, suffers a majority of the cardiac and cerebrovascular events found among diabetics before the onset of severe renal insufficiency. Seventy-five percent of this second group die of major vessel disease. Data concerning patients in the present study would not apply to this second group.

Diabetics not only have an increased number of ischemic attacks, but also enhanced susceptibility to congestive heart failure, myocardial rupture and death after documented myocardial infarction. Our study found the two-year survival post-myocardial infarction to be greater than 70% among nondiabetics, compared with less than 50% among diabetics. A recent study documented more coronary artery disease in diabetics who underwent coronary arteriography after chest pain than in a similar group of nondiabetics. For these reasons, we investigated for asymptomatic coronary artery disease before undertaking renal transplantation from living donors. However, in view of the unreliability of noninvasive cardiac tests, it was necessary to use coronary angiography as a means of assessing expected long-term survival given “normal” renal function.

Although Framingham and other studies have shown a reversal of the usual coronary artery disease sex distribution statistics with a significantly increased prevalence for premenopausal insulin-dependent women, the present small series showed a male preponderance of coronary artery disease similar to that in the general population. Other risk factors for the development of coronary artery disease may be difficult to analyze in these azotemic patients since hypertension, hyperlipidemia, and hyperuricemia may be secondary to underlying renal disease. Although accelerated atherosclerosis has been associated with maintenance hemodialysis, it is not known whether normalization of renal function with allograft transplantation will modify the progression of coronary artery disease.

Ventriculography was enlightening in several in-
stances in which diffuse hypokinesis was found in the absence of significant coronary artery disease, suggesting the diagnosis of myocardiopathy. Based on autopsy studies, there is pathologic and histochemical data for intimal infiltration of small myocardial arterioles. The initial process appears to be interstitial deposition of glycoprotein-like material (PAS positive) in a periarteriolar location with localized fibrosis which may form a dense collagen network, destroying myofibers.21-26 Biochemical analysis of cardiac muscle in these patients revealed increased triglyceride and cholesterol concentrations without changes in phospholipid.27,28 The pathogenesis of the myocardial dysfunction in these complex patients is not known at this time and may well be multifactorial. The impact of myocardial dysfunction on the long-term survival of diabetics after renal transplantation has not been studied. Reversibility of myocardial dysfunction has been reported after control of underlying cause, i.e., ethanol,29 volume overload, hypertension and uremia.30 We do not know if renal transplantation will also be shown to reverse myocardial dysfunction and change prognosis.

Several previous studies have attempted to relate the stress of specific hemodynamic factors, including surgical arteriovenous fistula, anemia, azotemia, hypertension, and dialysis-induced fluid shifts to increased demands for cardiac work.31-34 However, since none of these studies included coronary angiography, it has not been possible to correlate hemodynamic data with coronary arterial supply. The present study is the first to do so.

The results showed no reliability of noninvasive clinical or laboratory methods in detecting severe coronary artery disease among asymptomatic diabetic patients with severe renal insufficiency despite multiple hemodynamic factors producing increased cardiac output. Since these patients may be expected to be undergoing renal transplantation or maintenance hemodialysis, this baseline information will be of value in subsequent follow-up evaluation.35 Radiographic contrast studies in the azotemic diabetic carry a high risk of precipitating further renal failure.36 Therefore, the risks involved in these studies should be weighed against the possibility of obtaining useful information.6

References

A Conductive Catheter to Improve Patient Safety During Cardiac Catheterization

MARTIN J. LIPTON, M.D., ALLEN K. REAM, M.D., AND BRUCE H. HYNDMAN, M.S.

SUMMARY A 60 Hz current, as small as 20 μA (rms) is capable of causing ventricular fibrillation when directly applied to the heart. Significant cost and engineering effort has been spent to construct monitoring equipment which satisfies the safety regulations requiring maximum leakage currents below this value. Patients undergoing cardiac catheterization are particularly at risk from electrical hazards, primarily because catheters are made from nonconductive materials. A conductive catheter should allow externally applied currents to leak through its walls before reaching the catheter tip. A new electrically conductive catheter was compared with a standard nonconductive catheter.

Five dogs were studied, with 81 attempts to cause fibrillation. Sixty-hertz voltage between the catheter and an external electrode was increased until fibrillation occurred or 130 V was reached. Eight states were studied in randomized sequence: conductive or nonconductive catheter, guidewire or saline-filled and tip touching wall, or free in left ventricle (verified by fluoroscopy and cineangiography). The saline-filled conductive catheter was safer in that fibrillation never occurred, while fibrillation nearly always occurred with the nonconductive catheter. A conductive guidewire negates the protection of the conductive catheter. The application of conductive catheters could reduce instrumentation costs in laboratories and intensive care units and improve patient safety.

ADVANCES IN BIOMEDICAL ENGINEERING have resulted in a progressive increase in the number and complexity of hospital electrical monitoring devices. These devices are particularly available in specialized centers, such as intensive care and cardiac catheterization units. Such devices are important in the provision of health care, but have brought about an increased danger of accidental electrocution. This hazard has received attention in the past few years, but the incidence of electrical complications in hospitals remains a very controversial issue. Such electrocutions may be far more common than realized.1, 2 because proof of such incidents is very difficult to obtain. However, incidents of ventricular fibrillation and hospital deaths from electrocutions have been documented during cardiac catheterization and also in patients with myocardial pacemakers.3-11 Studies have shown that 60 Hz alternating currents of as little as 80 μA, with typical values below 1 mA, can produce ventricular fibrillation in humans.12-15 Considerable effort has been spent to construct monitoring equipment which draws maximum leakage currents of less than the established safety standard threshold of 10 μA16-20 The increasing importance of such safety is immeasurable. One common opportunity for fibrillation with minimum current is provided by intracardiac catheters used during cardioangiographic studies and monitoring.2, 15, 21

Macroshock and Microshock

There are two modes of possible electric shock in hospitals. Macroshock is due to externally applied currents and can cause ventricular fibrillation with currents > 100 mA. Hence, direct or commercial alternating power frequencies with 75–120 V are dangerous. All hospital patients may be exposed to such macroshock hazards, just as they would be in their own homes— for example, from a defective electrical appliance.
Asymptomatic coronary artery disease: angiographic assessment of diabetics evaluated for renal transplantation.
L Weinrauch, J A D'Elia, R W Healy, R E Gleason, A R Christleib and O S Leland, Jr

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