Familial Pseudoxanthoma Elasticum and Valvular Heart Disease

By Jay D. Coffman, M.D., and Sheldon C. Sommers, M.D.

The clinical and pathologic findings are presented of a patient with pseudoxanthoma elasticum leading to fatal valvular heart disease. The literature concerning the involvement of the heart by this disease is reviewed and reveals that valvular heart disease has not been described as a clinical problem heretofore. The occurrence of the condition in the relatives of the patient is described.

PSEUDOXANTHOMA ELASTICUM has been described as a systemic disease that affects the skin, the eyes, and the blood vessels. That it may directly involve the heart and cause significant valvular disease is not so well known. Histologic changes in the endocardium and heart valves have been described but valvular heart disease has not been a clinical problem in these cases. After studying the following familial cases of pseudoxanthoma elasticum, especially case 1 who died in severe congestive heart failure due to mitral stenosis, it was considered that another differential diagnosis must be added to the uncommon causes of valvular heart disease.

Case I. Mrs. M. K. (MMH 390-037), a 68-year-old white housewife of Portuguese extraction, entered the Massachusetts Memorial Hospitals because of shortness of breath. Three years prior to admission she developed irregular heart action and symptoms of congestive heart failure that were controlled by digitalis and diuretics. During the previous month she became dyspneic and was confined to bed, the legs and abdomen became swollen, and the urinary output decreased. She denied chest pain or knowledge of high blood pressure.

Past history included an attack of "influenza" in 1918, following which a heart murmur was heard. There were no other episodes suggestive of rheumatic fever.

Physical examination revealed an obese dyspneic woman. The temperature was 101 F., and respirations were 30; the blood pressure was 140 mm. Hg systolic and 80 diastolic. The skin was pale, loose, dry, and scaly, with wide ecchymoses on the forearms. The neck veins were distended.

There were fine rales over the left lower lung field posteriorly. Cardiac dullness extended from the left anterior axillary line to 3 cm. to the right of the sternal border in the fifth interspace. The rhythm was grossly irregular. The first heart sound was accentuated and an opening snap was heard. A grade-II, low-pitched, rumbling mid-diastolic murmur was localized to the apex. A grade-III, rough, blowing systolic murmur was loudest at the apex and radiated to the axilla. The pulmonic component of the second heart sound was louder than the aortic. A fluid wave and shifting dullness were noted in the abdomen. The liver was firm, not tender, and pulsating 5 cm. below the right costal margin. There was pitting edema of the entire lower extremities.

The hemoglobin was 6.3 Gm. per 100 ml. and the hematocrit level was 22 per cent; the red blood cell count was 2.76 million per mm. The icteric index was 5. The serum sodium was 143 mEq., the potassium 5.3 mEq., the chloride 110 mEq., and the carbon dioxide 19.8 mEq. per liter. The fasting blood sugar was 121 mg., the total protein 6.1 Gm., the albumin 3.8 Gm., and the globulin 2.3 Gm. per 100 ml. The protein-bound iodine was 4.2 μg., the total iodine 4.2 μg., and the serum iron 9 μg. per 100 ml. Urinalysis was negative except for 1+ albumin.

A chest x-ray film showed a markedly enlarged heart with a contour suggesting pericardial effusion. An electrocardiogram revealed atrial fibrillation with a ventricular rate of 90, occasional ventricular premature beats, right axis deviation, and ST-T abnormalities attributed to digitalis.

The morning after admission, the patient suddenly became very dyspneic, vomited a small amount of material, and died.

Gross and microscopic findings of the autopsy showed unusual changes in the heart, kidney, and blood vessels. The abdominal cavity contained about 2,000 ml. and the pericardial cavity 200 ml. of serous fluid. The empty heart weighed 750 Gm.; there was hypertrophy, mostly of the left ventricle, and dilatation of all chambers. The left
atrium had a wrinkled, white and yellow, opaque endocardium. The mitral valve was narrowed and fish-mouthed in appearance, with thickening and localized calcification at the leaflet margins. The chordae tendineae were normal (fig. 1). The other cardiac valves and coronary arteries were within normal limits for the patient's age. Microscopically, the heart valves, including the mitral valve, were not vascularized and there was endocardial and valvular thickening by dense connective tissue. No inflammation or Aschoff bodies were observed.

Special stains for elastic tissue showed that the elastic fibers in the thickened endocardium were abnormally increased in number, coarse, fragmented, and locally palisaded perpendicular to the surface (fig. 2). In the mitral valve, and to a
Fig. 5 *Top left.* Aortic media at higher magnification showing extremely peculiar alterations of black-stained elastic fibers and hydropic degeneration of the intervening gray-stained muscle. Verhoeff-van Gieson stain, × 250.

Fig. 6 *Bottom left.* Small artery in the gastric submucosa is shown, with nearby accessory glands of the cardia. Marked degeneration of the internal elastic membrane is present. Hematoxylin and eosin stain, × 250.

Fig. 7 *Top right.* Kidney of case 1, with elastic tissue stained black, to illustrate the unusual degenerative changes found in the arterial and arteriolar elastic. Verhoeff-van Gieson stain, × 90.

Fig. 8 *Bottom right.* Skin specimen from case 1. The epidermis is wrinkled, and the black-stained elastic tissue of the upper dermis appears normal. The lower dermis and insert contain coarse degenerated, dermal elastic fibers, curled and broken, typical of pseudoxanthoma elasticum. Verhoeff-van Gieson stain, × 20; insert × 40.

In aorta and pulmonary artery there were intimal hilly hocks that contained fine fibers lightly stained by elastic-tissue technic; below this level the elastic tissue of the media was unusually abundant, coarse, and fragmented (fig. 4). The muscle of the aortic media appeared hydropic (fig. 5).

The lungs weighed 900 Gm. together, the spleen 500 Gm., and the liver 1,450 Gm.; all showed chronic passive congestion. There were petechial
hemosus in the gastric mucosa, and microscopically occasional small arteries showed extreme thickening and degeneration of the internal elastic lamina, unlike that seen in arteriosclerosis (fig. 6).

Each adrenal gland weighed 9 G.m. and each kidney 150 G.m. The renal capsules stripped with some difficulty, leaving a pitted, diffusely granular, pale tan surface. The cortices were poorly demarcated and measured 0.6 cm. in width. Microscopically there were extreme localized thickening, reduplication and fragmentation of elastic tissue in the small renal arteries and in some arterioles. Glomeruli were large and rather ischemic, with nonspecific sclerotic changes and a slight increase in the number of nuclei. Focal interstitial chronic inflammation was seen, consistent with pyelonephritis (fig. 7).

Grossly the skin appeared wrinkled and pale with induration and brownish discoloration over the legs. Microscopically in the deep corium, with routine stain, the connective tissue appeared abnormally coarse and slightly basophilic. This tissue stained green like collagen with the Masson trichrome method. The elastic-tissue stain showed a striking degeneration of elastic fibers deep in the corium, with fragmentation, coalescence, thickening, and curling of elastic tissue, typical of pseudoxanthoma elasticum (fig. 8).

Incedental findings included cholelithiasis, endometrial hyperplasia, chronic cystic mastitis with intraductal papillomas, ovarian stromal hyperplasia, and cavernous hemangioma of a lumbar vertebra.

Death was attributed to congestive heart failure in the presence of pseudoxanthoma elasticum involving the heart, kidney, aorta, pulmonary artery, small blood vessels, and skin.

Case 2. E. B. (M.M.H. 389-706), a 46-year-old daughter of case 1 (fig. 9) entered the Massachusetts Memorial Hospitals for extraction of teeth. At age 9 she was told by the school physician that she had a heart murmur. She remembered no episode resembling rheumatic fever. No cardiac symptoms were present until exertional dyspnea developed 3 years prior to admission. Two years after this she experienced a transient loss of motor power of the right leg for 1 day. Six months later she developed numbness of the left side of her face and of her left hand. These symptoms gradually improved.

There were no indications of a bleeding tendency from any system; her menstrual history was normal. Symptoms of peripheral vascular disease, except as noted above, were absent. She had had blurred vision in her right eye since birth.

She had had 2 thyroid operations, 14 and 12 years previously, for symptoms of hyperthyroidism and exophthalmus. Ten years prior to admission she was given thyroid medication for “low thyroid activity.” She stopped taking it because it made her nervous.

Physical examination revealed a well developed, middle-aged woman in no distress. Pulse was 70 and respirations were 16 per minute. Blood pressure was 110 systolic mm. Hg and 78 diastolic. The skin was dry and of fine texture; a 2 by 3 cm.
atrophic, wrinkled area was present on the lower back. There was marked exophthalmos. The right fundus could not be visualized because of a cataract; the left fundus was normal. The neck veins were distended but the lungs were clear to auscultation and percussion. A grade-III rough blowing systolic murmur was heard loudest at the aortic area and transmitted to the neck and axilla. A grade-II, high-pitched, soft, blowing diastolic murmur was present at the aortic area and in the third left interspace parasternally. The pulmonic component of the second heart sound was louder than the aortic. The rhythm was regular. Pulses below the femorals were absent in the legs; the radial pulses were of normal amplitude. There was weakness of the left facial muscles.

Blood urea nitrogen, fasting sugar, electrolytes, and total protein were normal. A serum cholesterol was 383 mg. per 100 ml. Urinalysis revealed 1+ albumin. The basal metabolic rate was +1 per cent.

Cardiac fluoroscopy showed the heart to be enlarged in all diameters with no specific chamber enlargement. The barium-filled esophagus was displaced posteriorly. There was generalized diminution of cardiac pulsations. The lung fields showed increased prominence of the bronchovascular pattern. An electrocardiogram revealed nonspecific T-wave abnormalities and late U waves, which were inverted over the left precordium.

The patient was given thyroid extract and digitalis, and she improved considerably.

Skin biopsy from the atrophic, wrinkled, lumbar area was diagnosed as pseudoxanthoma elasticum. The deeper layers of dermis appeared abnormally basophilic and were composed of curled heavy connective-tissue strands with the hematoxylin and eosin stain. With Verhoeff-van Gieson stain for elastic tissue, the elastica of the superficial dermis was practically normal, but in the lower dermis the elastic fibers were coarse, broken, curled, and irregular both in distribution and in the appearance of individual fibers.

Case 3. M. K., the second eldest daughter of case 1 who was 36 years of age, was examined for evidence of pseudoxanthoma elasticum. She had been healthy all her life. There were no symptoms of bleeding from any system and her menstrual history was normal. She stated that small ecchymoses of the legs developed very easily. She denied cardiac or peripheral vascular symptoms except for palpitation and a tightness in the anterior chest when nervous. There were no visual difficulties. Past history failed to reveal any episode resembling rheumatic fever.

The fundi and skin were normal. A grade-II, rough, blowing, systolic murmur was heard precordially but loudest in the right supraclavicular fossa; it was not transmitted to the axilla. The aortic component of the second basal heart sound was louder than the pulmonic. The rhythm was regular. The blood pressure was 150/80. This murmur was considered most consistent with aortic stenosis. Peripheral pulses were of normal amplitude.

Chest films and cardiac fluoroscopy showed the heart to be normal in size and contour. There was minimal but normal posterior indentation of the barium-filled esophagus in the region of the atria. No intracardiac calcification was seen. An electrocardiogram showed sinus arrhythmia and prominent U waves.

A skin biopsy showed localized abnormalities of the lower dermis with fragmentation of elastic fibers, consistent with mild pseudoxanthoma elasticum.

Case 4. H. P. (MMH 507-115), a 31-year-old daughter of the patient of case 1 entered the hospital for repair of a hernia. She had had a heart murmur since childhood and was restricted in sports at school. There was no history of an illness resembling rheumatic fever. Symptoms of heart failure were absent. Except for the appearance of small ecchymoses on her legs without known trauma, there was no bleeding tendency. Menstrual history was normal; she had had 4 miscarriages and 3 normal pregnancies. No visual or peripheral vascular symptoms were present.

The fundi and skin were normal except for a small ecchymosis on the right upper arm. The cardiac impulse was very forceful 2 cm. to the left of the midclavicular line in the fifth interspace. A systolic thrill was felt over this area. There was a grade-IV, rough, blowing systolic murmur, loudest at the apex and transmitted to the axilla but not to the neck. The aortic component of the second basal heart sound was louder than the pulmonic. A third heart sound was heard in early diastole at the lower left sternal border. The rhythm was regular at a rate of 72. The blood pressure was 120/68. The findings were considered most consistent with mitral insufficiency. There were many nonpigmented striae on the abdomen and a large right lower quadrant sear with a bulging hernia. A firm, nontender liver was felt 3 cm. below the right costal margin. The right dorsalis pedis pulse was of small amplitude compared to the left.

Laboratory data were normal, including total cholesterol and protein-bound iodine values.

An electrocardiogram revealed ST-T abnormalities in the left precordial leads suggestive of left ventricular hypertrophy. A chest film showed the heart to be above the normal limits in size with a cardiothoracic ratio of 15.5 to 29.5. The pulmonary artery segment and left atrium were prom-
inquent. Cardiac fluoroscopy showed an indentation on the barium-filled esophagus in the region of the left and right atria. No intra-cardiac calcifications were seen. Findings were consistent with mitral valvular disease.

As in cases 1 and 2, skin biopsy showed coarse basophilic connective tissue in the deeper corium. With Verhoeff stain, the deep corium was partly composed of heavy, irregular, curled and broken elastic fibrils, considered pseudoxanthoma elasticum.

Case 5. J. K., a 39-year-old son of case 1 was admitted to another hospital at age 29 for paresthesias and weakness of the left extremities. A complete neurologic study including 3 lumbar punctures that showed 10 to 15 lymphocytes, a first-zone colloidal gold curve, and normal protein resulted in a diagnosis of probable multiple sclerosis. A myelogram was unrevealing. He recovered almost completely and had no further episodes.

He was seen at Massachusetts Memorial Hospitals following his mother's death. His history was negative for symptoms of pseudoxanthoma elasticum. Positive physical findings included a scaly rash of the left elbow present for many years, old acne scars of the back and chest, a blood pressure of 164 systolic, 110 diastolic, and arteriovenous nicking and arteriolar tortuosity of the fundic vessels.

A skin biopsy from the lower back showed that the epidermis was mildly hydropic. The dermis appeared negative, except that the deeper corium had a somewhat basophilic coloration with hematoxylin and eosin, and Verhoeff stain showed exaggerated swelling, coalescence, fragmentation, and curling of elastic fibers. Changes were consistent with mild pseudoxanthoma elasticum.

Case 6. L. K., a 41-year-old son of case 1 had no symptoms or physical findings of pseudoxanthoma elasticum. His only positive physical findings were signs indicating a moderate degree of emphysema. Skin biopsy of the lower back showed mild basophilia of collagen fibers deep in the dermis, associated with abnormal swelling and fragmentation of elastic tissue. These degenerative changes were considered consistent with pseudoxanthoma elasticum.

D. K. (MMH 508534), the 71-year-old Irish husband of case 1 had no symptoms or physical findings suggestive of pseudoxanthoma elasticum. A skin biopsy from the lower back was of normal appearance except for atrophic changes attributable to age. No abnormalities of elastic tissue, resembling those described above were identified with the Verhoeff-van Gieson stain.

A third son of case 1 was not available for examination.

**Discussion**

Pseudoxanthoma elasticum has been the subject of many papers reviewing the typical skin appearance and the retinal angioid streaks (Grönblad-Strandberg syndrome), the systemic findings, and the pathologic picture. Revell and Carey have provided the following list of systemic symptoms and signs in order of their frequency: hypertension, inequality and changes in pulses, intermittent claudication or angina, calcification of peripheral vessels, abnormal bleeding into the gastrointestinal tract, uterus, bladder and brain, psychic disturbances, and epilepsy.

Signs and symptoms of heart disease are quite common. Left ventricular hypertrophy associated with hypertension and angina pectoris due to coronary arterial involvement by the disease are often present. Pathologic changes in the heart due to pseudoxanthoma elasticum have rarely been encountered. The opinion has been expressed that involvement of the heart would not be expected, since it contains only a small amount of elastic tissue. In his original description of this disease in a 49-year-old man without evidence of clinical heart disease, Balzer described a whitish yellow surface over the greater part of the endocardium of the right atrium as well as plaques of the same color on the ventricular trabeculae and pericardium. Histologically, degeneration of the elastic elements, the same pathologic picture as seen in the corium of the skin, was present at these sites.

McKusiek described interesting findings at postmortem examination in a case of pseudoxanthoma elasticum with a loud blowing apical systolic murmur as the only manifestation of heart disease. The heart was not enlarged, weighing 325 Gm. There was a yellowish thickening of the endocardium of the right atrium and a nodular thickening over the trabecular ridges. The posterior leaflet of the tricuspid valve had a smooth, thickened, firm, rolled edge without excrescences. The aortic leaflet of the mitral valve was similarly thickened at the edge and there was marked calcific change at its attachment. Histologically the subendocardial tissue of the right atrium
showed the same changes as described in the skin of pseudoxanthoma elasticum.

Reiner\(^3\) presented the case of a 27-year-old woman with pseudoxanthoma elasticum at the New England Society of Pathologists in 1955. The only cardiac symptom was palpitation. At autopsy the endocardium of the right and left atria and the left ventricle was dull, thickened, and opaque. The histologic picture of the endocardium was typical of pseudoxanthoma elasticum.

Clinically our first patient was believed to have rheumatic heart disease with mitral stenosis and tricuspid insufficiency. Histologically, changes of pseudoxanthoma elasticum were present in the skin, blood vessels, kidney, and heart. The endocardium of the left atrium was thickened and whitish yellow in color. The mitral valve had a hard, rolled ridge along the closure line and was definitely stenotic. Microscopic studies revealed far-advanced degeneration of the elastic fibers in the endocardium. Lack of vascularization of the valves, the normal chordae tendineae, and absence of Aschoff bodies ruled against this being inactive rheumatic heart disease. The patient had shown no obvious skin changes except for the subcutaneous hemorrhages that have also been described in pseudoxanthoma elasticum.\(^6\) The eye grounds were not visualized, so we cannot say if angioid streaks were present in case 1, but the patient had no history of visual difficulties.

Other patients with pseudoxanthoma elasticum have been described as having heart disease, but histologic proof that this disease involved the elastic tissue of the heart was lacking. Prick\(^9\) presented a 48-year-old woman with pseudoxanthoma elasticum, whose heart was hypertrophied at autopsy. The mitral valve presented a thickened edge with some yellowish white patches, but microscopically only fatty infiltration of the heart muscle was described. This patient had dyspnea on exertion, an enlarged heart with a faint systolic precordial murmur, and an accentuated second aortic heart sound. Von Trannenhain\(^10\) reported a case of pseudoxanthoma elasticum in which the postmortem diagnosis included chronic mitral endocarditis and chronic myocarditis, but histologic studies of the heart were not presented. Small yellowish white deposits were found on the aortic and mitral valves in 1 other case,\(^4\) but microscopic study was again lacking. Systolic murmurs have been heard frequently in patients with pseudoxanthoma elasticum and there has been 1 reported case\(^11\) with the murmur of mitral stenosis.

Five of the 6 children of the patient of case 1 showed the changes of pseudoxanthoma elasticum in skin biopsy, and 3 presented evidence of heart disease (fig. 9). There were no clinical skin lesions in these patients except for an atrophic area of skin in case 2 and an elbow rash in case 5. The history of ecchymosis formation without provocation in the daughters was suggestive. It is not unusual to find the pathologic changes of this disease in normal-appearing skin.\(^5\),\(^1\)

Each of the daughters also had clinically significant heart findings, and there was no history of rheumatic fever. It has been found that about 60 to 70 per cent of those with rheumatic heart disease will have had a known episode of rheumatic fever, if carefully questioned.\(^1\) Whether the heart lesions in the daughters are the result of pseudoxanthoma elasticum cannot be said at this time. In case 2 thyroidectomy had been performed for thyrotoxicosis, which has been believed to have some relationship to pseudoxanthoma elasticum.\(^6\) This daughter also had absent peripheral pulses in the legs. One of the sons had an elevated blood pressure, a common accompaniment of this disease.

Inheritance of pseudoxanthoma elasticum is usually as an autosomal recessive, but rarely is it transmitted as a dominant.\(^2\),\(^4\),\(^1\) Parental consanguinity is common in the latter case. Microscopic study of the skin from 5 of the 6 children of case 1 revealed changes consistent with pseudoxanthoma elasticum. The patient and her husband were of different racial backgrounds and a skin biopsy from the husband failed to reveal evidence of pseudoxanthoma elasticum. McKusick\(^2\) was able to find only 8 cases of direct transmission of
this disease in his survey of the literature; however, it has been rare that skin biopsies were examined from offspring who did not show evident clinical manifestations of the disease. Perhaps when more such studies are performed, the dominant mode of transmission will be found in pedigree studies, as has already been postulated by Weidman, Anderson, and Ayres.14

This paper does not pretend to review the controversy regarding the basic lesion of this disease, whether it is really an elastic or a connective tissue degeneration, except to point out that the most recent analytic work with histochemistry, electron microscopy, and enzymes seems to indicate a primary elastic tissue disorder.7–15, 16

Summary

The clinical and postmortem findings in a patient with pseudoxanthoma elasticum, who died in congestive heart failure due to mitral stenosis, are presented. Histologic examination of the heart revealed elastic-tissue degeneration in the endocardium of the left atrium and in the valves and no evidence for rheumatic heart disease. The skin, blood vessel, and kidney sections also showed the changes of pseudoxanthoma elasticum.

Five of the patient’s 6 children were available for skin biopsies, and all demonstrated some degree of elastic-tissue change consistent with pseudoxanthoma elasticum. Three of the children also had evidence of valvular heart disease. A skin biopsy from the patient’s husband was normal, indicating a dominant mode of inheritance, which has been considered rare.

In the 3 previously reported cases of pseudoxanthoma elasticum with histologic cardiac involvement, valvular heart disease was not a clinic problem. It is thought that pseudoxanthoma elasticum must be added to the list of uncommon causes of valvular heart disease. When a patient with the findings of valvular heart disease lacks a history of rheumatic fever, pseudoxanthoma elasticum should be considered.

Summary in Interlingua

Es presentate le constatationes clinica necroptic in un patiente con pseudoxanthoma elastic, qui moriva in congestive disfallimento cardiae causate per stenosis mitral. Le examine histologic del corde revelava degeneration de hist elastic in le endocardio del atrio sinistre e in le valvulas. Esseva trovate nulle signo de rheumatic morbo cardiae. Le alteraciones characteristic de pseudoxanthoma elastic esseva etiam presente in le pelle, le vasos faint systolic precordial murmur, and an ae-sanguine, e sectiones renal.

Le patiente habeva 6 filios. Cinque de illes esseva disponibile pro biopsias cutanee, e omne istes monstrava un certe grado de alteration del histos elastic, de character compatible con un diagnose de pseudoxanthoma elastic. Tres de illes habeva etiam signos de morbo de valvula cardiae. Un biopsia cutanea ab le sposo del patiente esseva normal. Isto indica que le transmission representava le modo dominante, un phenomeno que ha essite considerate como rar.

In le 3 previamente reportate cases de pseudoxanthoma elastic con affection histologic del corde, morbo de valvula cardiae non esseva un problema clinic. Es opinate que pseudoxanthoma elastic debe esser addite al lista del causas incommun de morbo de valvula cardiae. Quando un patiente con indicios de morbo de valvula cardiae es sin historia de febre rheumatic, le possibilitate de pseudoxanthoma elastic deberea esser prendite in consideration.

References


Only 1 instance of myocardial infarction was found among 521 thyrotoxic patients aged 40 years or older seen at the Rikshospitalet in Oslo during the 20 years prior to 1956. This patient was a 46-year-old woman who had had severe angina pectoris for about 2½ years before developing the symptoms of thyrotoxicosis. According to Norwegian Life Insurance statistics, 2 myocardial infarctions would have been expected in a group of this size. Three hundred and seventy-eight of these patients had serum cholesterol measurements averaging 160 mg. per cent, which is significantly lower than the 255 mg. per cent average found in normal persons of the same ages. The 15 autopsied thyrotoxic patients showed less than average coronary and aortic atherosclerosis. The authors suggest that thyrotoxicosis may afford some protection against the development of atherosclerosis.

Rogers
Familial Pseudoxanthoma Elasticum and Valvular Heart Disease
JAY D. COFFMAN and SHELDON C. SOMMERS

Circulation. 1959;19:242-250
doi: 10.1161/01.CIR.19.2.242
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1959 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/19/2/242

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/