IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

| | |
|---|---|
| IN RE DIET DRUGS (Phentermine/ Fenfluramine/Dexfenfluramine) PRODUCTS LIABILITY LITIGATION | MDL Docket No. 1203 |
| THIS DOCUMENT RELATES TO: | |
| SHEILA BROWN, SHARON GADDIE, VIVIAN NAUGLE, QUINTIN LAYER, and JOBY JACKSON-REID, Individually and all others similarly situated, | |
| Plaintiffs, | |
| v. | C.A. NO. 99-20593 |
| AMERICAN HOME PRODUCTS CORPORATION, | JURY TRIAL DEMANDED |
| Defendant. | |

## DECLARATION OF DEAN G. KARALIS, M.D.

### A. General Background

I, Dean G. Karalis, M.D., hereby declare as follows:

1. I am a medical doctor who is board certified in the specialty of internal medicine and the subspecialty of cardiology. From 1990 through the present, I have occupied the position of Assistant Professor of Medicine at Hahnemann University Hospital, Philadelphia, Pennsylvania and have served as an attending cardiologist in the Echocardiography Laboratory at that institution. Although my practice involves general cardiology, I have a special interest in the diagnosis and treatment of valvular heart disease and echocardiography. A copy of my most recent curriculum vitae, which accurately summarizes my training and experience as a cardiologist, is attached to this Declaration as Exhibit "A."

2. I have been engaged in connection with the instant matter by the Plaintiffs' Management Committee ("PMC") and Class Counsel to provide consulting services with respect to those areas falling within my expertise as a cardiologist. The PMC and Class Counsel have agreed to pay for my services on an hourly basis at the rate of $400.00 per hour plus reimbursement of all proper out-of-pocket costs.

3. Aside from a previous deposition which I provided in MDL Docket No. 1203, I have not testified as an expert at trial or by deposition within the four years proceeding the date of this Declaration.

**B. <u>The Anatomy and Physiology of the Heart</u>**

4. The human heart has four chambers. The upper chamber on the right side of the heart, the right atrium, functions to receive deoxygenated blood from the body. The lower chamber of the right side of the heart, the right ventricle, pumps the deoxygenated blood through the pulmonary artery into the lungs where carbon dioxide is removed from the blood and replaced with oxygen. The upper chamber on the left side of the heart receives and collects oxygenated blood which has been pumped from the lungs to the heart through the pulmonary veins. The lower chamber on the left side of the heart, the left ventricle, pumps oxygenated blood from the heart through the aorta and into the arterial system.

5. Just as the heart has four chambers, it also has four valves. The valve structures function to assure that blood moves through the heart in a forward direction and that effective blood flow is maintained.

6. The valve located between the right atrium and the right ventricle is the tricuspid valve. The valve between the right ventricle and the pulmonary artery is the pulmonic valve. The valve located between the left atrium and the left ventricle is the mitral valve. The valve located between the left ventricle and the aorta is the aortic valve.

7. The valves are composed of either two or three leaflets, sometimes referred to as "cusps". The mitral valve has two leaflets. It is attached to the heart by thin fibrous cords called chordae tendenae that arise from the valve leaflets and connect to the papillary muscles. The papillary muscles are in turn anchored to the muscular wall of the left ventricle. The aortic valve has three leaflets or cusps which are attached to the heart by a fibrous ring or annulus.

C. Valvular Heart Disease

8. Valvular heart disease ("VHD") is a group of different conditions which cause a disruption in the normal structure and/or function of the heart valves. When a patient suffers from VHD, blood which is supposed to move in a forward direction through the heart leaks backward or "regurgitates" through the diseased valve.

9. The existence of VHD and the extent of regurgitation associated with it can be diagnosed with echocardiography in which ultrasound waves are used to image cardiac structure and blood flow in the heart.

10. Apart from VHD related to the use of diet drugs (which is described below) the following conditions are the principal causes of valvular regurgitation in the left side of the heart:

| | Condition | Description |
|---|---|---|
| 1. | Unicuspid, Bicuspid valve or Quadricuspid aortic valve | Congenital abnormalities in which the number of valve leaflets varies from the normal 3 leaflet structure of the aortic valve |
| 2. | Ventricular Septal defect | Congenital abnormality in which part of the ventricular septum below the aortic valve is absent |
| 3. | Aortic Dissection involving the aortic root and/or aortic valve | A tear in the aortic wall that interferes with aortic valve function |
| 4. | Aortic Sclerosis | An abnormal hardening of the aortic valve |
| 5. | Aortic Root Dilation greater than 5.0 cm | An enlargement of the aortic root at its junction with the aortic valve |
| 6. | Aortic Stenosis with an aortic valve area less than 1.0 square centimeter by the Continuity Equation | An abnormal narrowing of the aortic valve opening |
| 7. | Parachute valve | A congenital abnormality of the mitral valve |
| 8. | Cleft of the mitral valve associated with atrial septal defect | A congenital abnormality of the mitral valve |
| 9. | Mitral Valve Prolapse | Contemporary standards define mitral prolapse as a condition where the echo-cardiogram includes the parasternal long axis view and shows displacement of one or both mitral leaflets greater than two millimeters above the atrial ventricular border during systole (ph) (*i.e.*, contraction of the heart), and greater than 5 mm. leaflet thickening during diastole (ph) (relaxation of the heart) |
| 10. | Chordae tendinea rupture, papillary rupture or acute myocardial infarction associated with acute mitral regurgitation | Disruption of the subvalvular structures that support the mitral valve leaflets |
| 11. | Mitral annular calcification | Calcification of the mitral valve opening |
| 12. | Rheumatic Mitral Valve | A condition associated with a history of rheumatic heart fever where there is doming of the anterior leaflet and/or anterior motion of the posterior leaflet and/or commissural fusion |
| 13. | Valvular abnormalities of a type associated with systemic lupus erythematosus | Valve disease associated with lupus, which typically includes diffuse valvular thickening of the aortic and mitral valves, decreased leaflet mobility, and presence of Libman-Sacks vegetations, usually less than one cm. in diameter |
| 14. | Valvular abnormalities of a type associated with rheumatoid arthritis | Disease of the mitral valve associated with rheumatoid arthritis which typically includes rheumatoid nodules usually less than 0.5 centimeters in diameter which may occur at any location on the valve leaflets |

Each of the above conditions may be diagnosed by an echocardiogram in accordance with accepted, objective criteria.

11. The levels of valvular regurgitation caused by the varying conditions underlying VHD vary in severity. The degree of valvular regurgitation is measured by an echocardiogram in accordance with standardized techniques and criteria. For mitral valvular regurgitation ("MR"), the severity of valvular regurgitation is normally measured in any "apical" view[1] by the ratio of the regurgitant jet area ("RJA") to the left atrial area "(LAA"). The severity of aortic valvular regurgitation ("AR") is typically measured in the so-called "parasternal long axis view"[2] or in the "apical long axis view"[3] by the ratio between the regurgitant jet height ("JH") and the left ventricular out flow height ("LVOH").

12. Using these techniques of measurement, the degree of valvular regurgitation is characterized as trace, mild, moderate or severe in accordance with the criteria set forth in the following table:

| Grades | MR | AR |
|---|---|---|
| Absent | - | - |
| Trace | w/in 1 cm of valve | JH/LVOH < 10% |
| Mild | RJA/LAA < 19% | 10%-24% |
| Moderate | 20%-40% | 25%-49% |
| Severe | >41% | >50% |

*See* J.P. Singh, et al., "Prevalence and Clinical Determinants of Mitral, Tricuspid and Aortic Regurgitation (The Framingham Heart Study)," *American J. Cardiology*, 83:897-902 (1999).

1 The differing "views" which may be obtained during an echocardiogram are dependent upon the placement of the echocardiogram transducer and are illustrated and described with particularity at p. 29 of the "Green Form" appended hereto as Exhibit "B."

2 *See* f.n. 1, *supra*.

3 *See* f.n. 1, *supra*.

13. Mild or greater AR and moderate or greater MR is frequently referred to as "FDA positive regurgitation" based on the FDA's observation that "[m]inimal degrees of regurgitation (*i.e.*, trace mild mitral regurgitation [MR] or trace aortic regurgitation [AR]) are relatively common in the general population and are not generally considered abnormal." *See Morbidity and Mortality Weekly Report* 1997; 46:1061.12.

14. Although progression in severity of valvular regurgitation has not been subject to rigorous clinical investigation, it is generally accepted that VHD is potentially progressive in nature; that is, once valvular regurgitation exists, it tends to beget more severe regurgitation in a significant subset of patients. This is true for several reasons. First, many of the underlying conditions which cause valvular regurgitation are progressive in nature. Hence, the regurgitation associated with these conditions will progress as well. Second, even if the condition which initiates valvular regurgitation is not itself progressive in nature, the hemodynamics of regurgitation which are characterized by turbulent blood flow within the heart and increased stress on the valves and their supporting structures can be a mechanical cause for progression in the degree of regurgitation. Finally, the valves tend to undergo degenerative changes with aging which may contribute the progression of valvular regurgitation.

15. Although there are a few good studies on the issue, clinical experience tends to suggest that the risk of progression of valvular regurgitation is related to the severity of regurgitation in the first instance, with trace to mild forms of regurgitation tending to progress less and moderate to severe levels of regurgitation tending to be more likely to progress more.

16. Trace AR and mild MR are relatively common conditions while more severe forms of regurgitation tend to be less common in the general population. The *Framingham Study*, an extremely well regarded longitudinal epidemiology study, recently reported the incidence of varying degrees of valvular regurgitation in the population, stratified by age and sex, as follows:

**Prevalence of Valvular Regurgitation Stratified by Age and Severity in Men**

| | Age (yr.) | | | | |
|---|---|---|---|---|---|
| | 26-39 | 40-49 | 50-59 | 60-69 | 70-83 |
| Mitral regurgitation | (n=91) | (n=351) | (n=432) | (n=372) | (n=90) |
| None (%) | 14.4 | 13.3 | 11.3 | 12.7 | 9.0 |
| Trace (%) | 76.7 | 72.9 | 74.6 | 60.3 | 51.7 |
| Mild (%) | 8.9 | 13.5 | 12.5 | 24.6 | 28.1 |
| ≥Moderate (%) | 0.0 | 0.8 | 1.6 | 2.4 | 11.2 |
| Tricuspid regurgitation | (n=77) | (n=289) | (n=320) | (n=260) | (n=66) |
| None (%) | 14.3 | 17.8 | 19.0 | 18.3 | 16.7 |
| Trace (%) | 72.7 | 72.5 | 71.5 | 59.8 | 47.0 |
| Mild (%) | 13.0 | 9.4 | 9.2 | 21.9 | 25.8 |
| ≥Moderate (%) | 0.0 | 0.3 | 0.3 | 0.0 | 1.5 |
| Aortic regurgitation | (n=91) | (n=352) | (n=433) | (n=359) | (n=91) |
| None (%) | 96.7 | 95.4 | 91.1 | 74.3 | 75.6 |
| Trace (%) | 3.3 | 2.9 | 4.7 | 13.0 | 10.0 |
| Mild (%) | 0.0 | 1.4 | 3.7 | 12.1 | 12.2 |
| ≥Moderate (%) | 0.0 | 0.3 | 0.5 | 0.6 | 2.2 |

| Prevalence of Valvular Regurgitation Stratified by Age and Severity in Women | | | | | |
|---|---|---|---|---|---|
| | Age (yr.) | | | | |
| | 26-39 | 40-49 | 50-59 | 60-69 | 70-83 |
| Mitral regurgitation | (n=93) | (n=452) | (n=515) | (n=395) | (n=90) |
| None (%) | 14.0 | 8.6 | 9.0 | 7.2 | 5.6 |
| Trace (%) | 76.3 | 75.0 | 74.0 | 66.5 | 70.8 |
| Mild (%) | 9.7 | 15.5 | 16. | 24.0 | 23.6 |
| ≥Moderate (%) | 0.0 | 0.9 | 1.0 | 2.3 | 0.0 |
| Tricuspid regurgitation | (n=84) | (n=371) | (n=414) | (n=300) | (n=71) |
| None (%) | 20.5 | 16.0 | 14.5 | 10.4 | 14.1 |
| Trace (%) | 65.1 | 70.0 | 70.7 | 62.2 | 56.4 |
| Mild (%) | 13.2 | 13.5 | 14.1 | 25.7 | 23.9 |
| ≥Moderate (%) | 1.2 | 0.5 | 0.7 | 1.7 | 5.6 |
| Aortic regurgitation | (n=93) | (n=451) | (n=515) | (n=390) | (n=90) |
| None (%) | 98.9 | 96.6 | 92.4 | 86.9 | 73.0 |
| Trace (%) | 1.1 | 2.7 | 5.5 | 6.3 | 10.1 |
| Mild (%) | 0.0 | 0.7 | 1.9 | 6.0 | 14.6 |
| ≥Moderate (%) | 0.0 | 0.0 | 0.2 | 0.8 | 2.3 |

*See* J.P. Singh, et al., "Prevalence and Clinical Determinants of Mitral, Tricuspid and Aortic Regurgitation (The Framingham Heart Study)," *American J. Cardiology*, 83:897-902 (1999).

**D. Symptoms and Management of VHD**

17. The existence and degree of symptoms caused by VHD and the medical care required to manage such disease vary significantly depending upon the degree of valvular regurgitation which the patient presents.

18. Trace AR, trace MR, and mild MR are completely asymptomatic conditions which do not impose any limitations on a patient's ability to function normally. Without some

additional factor, such as valve thickening or impaired leaflet mobility, patients with trace AR, trace MR and mild MR, do not require medical management or treatment.

19. Mild AR is an asymptomatic condition which does not impose any limitation on an individual's ability to function normally. However, mild AR poses two distinct health risks. First, the abnormal aortic valve is susceptible to bacteria introduced into the blood stream through invasive procedures such as surgery or normal dental hygiene. This, in turn, creates an increased risk of the patient suffering an infection of the heart valve and surrounding heart muscle known as "bacterial endocarditis." Bacterial endocarditis is an extremely serious and often fatal condition. Patients suffering from bacterial endocarditis can develop severe regurgitation or peripheral emboli which, in turn, can lead to stroke, loss of an extremity or major organ failure. Second, mild AR can progress to more severe levels of valvular regurgitation which can impair the functioning of the heart.

20. Given these risks, the accepted regimen of medical management for patients with mild AR is the prescription of antibiotic prophylaxis in connection with invasive procedures such as surgery or normal dental hygiene and periodic examination and periodic evaluation by a cardiologist to determine if the degree of valvular regurgitation in the patient is progressing.

21. Typically, the regimen for following such asymptomatic patients is a yearly examination by a cardiologist and serial echocardiographic testing. Since the risk of progression of valvular regurgitation in diet drug VHD is unknown, an echocardiogram should be performed one year after the diagnosis of the valvular regurgitation is made. If the aortic regurgitation remains mild or the mitral regurgitation remains moderate then follow-up echocardiograms should be performed every two to three years to screen for progressive valvular regurgitation or left ventricular

dilatation. If the valvular regurgitation is found to be more severe on follow-up echocardiographic studies then the echocardiogram should be performed yearly.

22. Severe AR and severe MR are conditions in which the percentage of blood ejected from the heart (*i.e.*, the "ejection fraction") can fall significantly below normal. In chronic severe aortic and mitral regurgitation patients are often asymptomatic at first and become symptomatic when the heart function begins to fail.

23. When such patients are symptomatic, their symptoms will include shortness of breath, fatigue and/or diminished exercise capacity. These symptoms are frequently staged in accordance with the New York Heart Association (NYHA) Functional Classification System as follows: (I) Asymptomatic; (II) Symptoms with exercise; (III) Symptoms with activities of daily living; and (IV) Symptoms at rest.

24. Severe valvular regurgitation leads to a volume overload of the heart. The size of the left atrium and/or left ventricle tends to increase in response to the volume overload created by severe regurgitation. This phenomenon is described as LV and/or LA "dilatation." In addition, the thickness of the walls of the atrium and/or ventricle also tends to increase in response to the volume overload created by severe regurgitation. This process is known as left ventricular hypertrophy and/or left atrial hypertrophy. Over time heart function will deteriorate and as the left ventricular ejection fraction decreases the pressure within the left ventricle increases. This in turn will lead to an increase in the pulmonary venous pressures and an increase in the pulmonary artery pressure. This secondary pulmonary hypertension is a marker of significant cardiac dysfunction and may not return to normal even after valve surgery. In addition the hypertrophy and dilatation may

also be permanent conditions which may not be corrected medically or surgically following valve repair or replacement.

25. The existence of left-sided dilatation and hypertrophy are assessed by reference to standardized measurements of left heart chamber size which include:

- Left ventricular end systolic dimension -- the dimensions of the left ventricle measured at the end of the contraction of the heart;
- Left ventricular end diastolic dimension -- the dimensions of the left ventricle measured at the end of the relaxation of the heart;
- Left atrial supero-inferior systolic dimension -- a measure of the dimensions of the left atrium when the heart has contracted; and
- Left atrial antero posterior systolic dimension -- a measure of the dimensions of the left atrium when the heart has contracted.

A description of the techniques for measuring these dimensions and the criteria for assessing any abnormalities is set forth in the Appendix to the Green Form which is attached to this Declaration as Exhibit "B."

26. When dilatation and/or hypertrophy progress to a sufficient level of abnormality, the patient is exposed to the following risks, among others:

- The patient is at risk of developing chronic atrial fibrillation in the case of severe MR which can lead to a stroke or peripheral embolus;
- The patient is at risk of developing ventricular fibrillation or ventricular tachycardia, dangerous arrhythmias which can precipitate the patient's sudden death;
- The patient has a high risk of developing congestive heart failure, an often fatal condition;
- The patient is at risk of developing permanent pulmonary hypertension which can lead to persistent symptoms of shortness of breath, fatigue, congestive heart failure and death.

27. Drug therapies can be used in the treatment of severe AR and severe MR particularly before the patient develops symptoms, hypertrophy, dilatation, and/or pulmonary hypertension. These include drugs that increase the strength or the contractility of the heart and drugs that decrease the afterload of the heart to allow the heart to beat more easily.

28. However, where a patient with severe MR or severe AR exhibits significant symptoms, or begins to exhibit hypertrophy, dilatation and/or PH, surgery is usually the treatment of choice. Such surgery involves the operative repair of the diseased valve, if possible, or the replacement of the diseased valve with either a mechanical valve or a porcine valve.

29. Valvular repair/replacement surgery in properly selected patients is a safe procedure. The morbidity/mortality associated with valvular repair/replacement surgery during the intra-operative and post-operative period in low risk patients is between 2 and 4 percent with a long-term morbidity/ mortality for such patients averaging about 5 percent per year. *See* Scott, et. al. "Determinants of Operative Mortality for Patients Undergoing Aortic Valve Replacement" *Journal of Thoracic Cardiovasc. Surg.* 1985;89:400-413; Di Lello, et. al., "Improved Early Results After Aortic Valve Replacement; Analysis By Surgical Time Frame," *Ann Thorac Surg.* 1989;47:51-56; Morris, et. al. "Determinants of Survival and Recovery of Left Ventricular Function After Aortic Valve Replacement," *Ann Thor. Surg.* 1993;56:22-29; Lindblom, et. al. "Long-Term Survival Rates After Heart Valve Replacement," *J. Am. Coll. Cardiology* 1990;15;566-573; Klodas, et. al. "Surgery for Aortic Regurgitation in a Women" *Circulation*, 1996;94;2472-2478. Atkins et al., "Mitral Valve Reconstruction Versus Replacement For Degenerative or Ischemic Mitral Regurgitation." *Ann Thorac Surg.* 1994;58:668. Galloway et al. "A Comparison of Mitral Valve

Reconstruction With Mitral Valve Replacement: Intermediate Term Result." *Ann Thorac Surg.* 1989;47:655.

30. Patients who undergo valve repair or replacement surgery are normally able to resume their activities of daily living without significant restriction or disability.

31. However, valvular repair or replacement surgery is not without risk. Patients who receive metallic prosthetic valves must take blood thinning agents for the rest of their lives. The use of such blood thinners reduce the risk of stroke but increase the risk of major bleeding to the patients who take them. Although tissue valves do not require blood thinners they are less durable than metallic valves and over one-third of patients with tissue valves will have valve failure within 11 years of operation. Hammermeister et al, "A comparison of outcomes in men 11 years after heart-valve replacement with a mechanical valve or bioprosthesis." *N Engl J Med.* 1993;328:1289-1296. Valve repair/replacement surgery creates the risk of stroke, peripheral embolus with severe impairment to the kidneys, abdominal organs, or extremities, renal failure, quadriplegia or paraplegia resulting from cervical spine injury, and post-operative infection.

32. Therefore, the decision to perform valve repair or replacement surgery involves striking a balance between the risks of such surgery and the risks of severe regurgitation. The criteria for striking this balance are set forth in R.O. Bonow, et al, "Guidelines for the Management of Patients with Valvular Heart Disease: A Report in the American College of Cardiology/American Heart Association Task Force on Practice Guidelines" (Committee on Management of Patients with Valvular Heart Disease), *JACC* 32:1510-14 & 1533-35. According to these guidelines, the criteria which are generally accepted as absolute indications for valvular

repair/replacement surgery in patients suffering from severe AR or MR (*i.e.*, "Class I indications") are as follows:

| Recommendations for Aortic Valve Replacement in Chronic Severe Aortic Regurgitation | | |
|---|---|---|
| | INDICATION | CLASS |
| 1. | Patients with NYHA functional Class III or IV symptoms and preserved LV systolic function, defined as normal ejection fraction at rest (ejection fraction ≥ 0.50). | 1 |
| 2. | Patients with NYHA functional Class II symptoms and preserved LV systolic function (ejection fraction ≥ 0.50 at rest) but with progressive LV dilatation or declining ejection fraction at rest on serial studies or declining effort tolerance on exercise testing. | 1 |
| 3. | Patients with Canadian Heart Association functional Class II or greater angina with or without CAD. | 1 |
| 4. | Asymptomatic or symptomatic patients with mild to moderate LV dysfunction at rest (ejection fraction 0.25 to 0.49) | 1 |
| 5. | Patients undergoing coronary artery bypass surgery or surgery on the aorta or other heart valves. | 1 |

| Recommendations for Mitral Valve Surgery in Nonischemic Severe Mitral Regurgitation | | |
|---|---|---|
| | INDICATION | CLASS |
| 1. | Acute symptomatic MR in which repair is likely | 1 |
| 2. | Patients with NYHA functional Class II, III or IV symptoms with normal LV function defined as ejection fraction >0.60 and end-systolic dimension <45mm. | 1 |
| 3. | Symptomatic or asymptomatic patients with mild LV dysfunction, ejection fraction 0.50 to 0.60, and end-systolic dimension 45 to 50 mm. | 1 |
| 4. | Symptomatic or asymptomatic patients with moderate LV dysfunction, ejection fraction 0.30 to 0.50, and/or end-systolic dimension 50 to 55mm. | 1 |

33. Given the above, the regimen to be followed in the management of patients suffering from severe AR and severe MR consists of:

- Prescribing antibiotic prophylaxis in connection with any invasive procedures such as surgery or dental hygiene which are required by the patient;
- Frequent examination and evaluation of the patient by a cardiologist, including frequent use of echocardiograms, to assess the degree of regurgitation, the presence and extent of LV/LA dilatation, the presence and extent of LV/LA hypertrophy, the patient's ejection fraction, the patient's pulmonary artery pressure, the patient's NYHA symptom status, and other cardiovascular parameters;
- Treatment with medication; and
- Surgery, where indicated.

34. Moderate MR and Moderate AR are asymptomatic conditions which do not impair an individual's ability to function normally. Typically, these conditions pose the same risk and require the same regimen of medical management as that which is appropriate for the management of mild AR. However, when moderate MR and/or moderate AR approach the level of severe regurgitation, the patient can begin to develop PH, LV/LA dilatation, and LV/LA hypertrophy. When such conditions develop, it is appropriate to treat the patient in the same manner as one would treat a patient who had severe regurgitation with such findings.

**E. <u>The Use of Diet Drugs and VHD</u>**

35. According to documents supplied to me by counsel, during the period from December, 1989 through September 1997 the drug Fenfluramine was marketed by American Home Products, Inc. ("AHP") under the trade name "Pondimin."

36. According to documents supplied to me by counsel, during the period from June, 1996 through September 15, 1997 the drug Dexfenfluramine was co-promoted by Interneuron Pharmaceuticals, Inc. and AHP under the trade name "Redux."

37. Fenfluramine is an appetite suppressant (*i.e.*, an anorectic agent) which affects blood levels of the neuro-transmitter, Serotonin. As the "d-isomer" of Fenfluramine, the drug Dexfenfluramine is chemically related to Fenfluramine and acts as an appetite suppressant by stimulating the release of Serotonin from the nerve cells in the brain which control appetite, by reducing the re-uptake of the released Serotonin and may act directly on the serotonergic receptors in the brain.

38. Experience with other drugs and conditions which effect serum serotonin levels should have caused AHP to investigate whether or not Fenfluramine and/or Dexfenfluramine could cause valvular heart disease. Specifically, it has been known for a number of years that carcinoid disease, which produces increased levels of serotonin in the blood, is associated with the development of plaque-like encasements of the valve leaflets and chordal structures on the left side of the heart which produce significant degrees of valvular regurgitation. Similarly, certain drug preparations used to treat headaches, methysergide and egotamines, affect serotonin metabolism and have been associated with left-sided valvular regurgitation in patients who use these drug preparations continuously for extended periods of time.

39. In March of 1997, researchers at the Mayo Clinic in Rochester, Minnesota began observing an association between the use of Fenfluramine and/or Dexfenfluramine and a particular type of VHD. This type of VHD was characterized by an unusual valvular morphology in which the valves had a glistening white appearance with a plaque-like encasement of the valve

leaflets and chordal structures. Eventually, the Mayo Clinic researchers observed this unusual form of VHD in 24 women who had used Fenfluramine in combination with the drug Phentermine. The findings of the Mayo Clinic researchers were first brought to the attention of the public in a July 8, 1997 press release and were eventually published on August 28, 1997 in *The New England Journal of Medicine*. *See* Connelly, et al, "Valvular Heart Disease Associated With Fenfluramine-Phentermine," *N.Engl.J.Med.* 1997, August 28; 337(9):581-588.

40. Subsequent studies confirmed that individuals who used Fenfluramine or Dexfenfluramine had an increased risk of left-sided valvular heart disease (MR or AR) as compared with similarly situated individuals who did not use these appetite suppressants and that this risk increased in proportion to the duration for which patients ingested such appetite suppressants. *See, e.g.*, Kahn, et al, "The Prevalence of Valvular Insufficiency Assessed by Transthoracic Echocardiography in Obese Patients Treated with Appetite Suppressant Drugs," *N.Engl.J.Med.* 1998, September 10; 339(11):713-8; Jick, et al "A Population Based Study of Appetite-Suppressant Drugs and the Risk of Cardiac-Valve Regurgitation," *N.Engl J.Med.* 1998, September 10; 339(11):719-24; Weisman, et al, "An Assessment of Heart-Valve Abnormalities in Obese Patients Taking Dexfenfluramine, Sustained Released Dexfenfluramine, or Placebo," *N.Engl.J.Med.* 1998, September 10; 339(11):725-32.39.

41. I have reviewed the report of Steven N. Goodman, M.D., M.H.S., PhD. regarding the epidemiology of diet drug induced valvular heart disease. Based on the information reflected in that report, it is medically appropriate that all patients who have taken Dexfenfluramine or Fenfluramine for more than 60 days undergo a complete echocardiographic evaluation for valvular pathology. Such a program of diagnostic evaluation will allow the early diagnosis and

treatment of cardiac valvulopathies in patients who have taken the diet drugs Fenfluramine and Dexfenfluramine and will undoubtedly save lives.

42. There is no reason to believe that there is a potential "latent period" of any significance between the termination of diet drug exposure and the onset of valvular regurgitation. There is nothing in the experience with carcinoid disease, use of ergotamines and methyasergides or in the published literature which suggests the possibility of such latency.

43. In contrast, a number of articles have addressed the likelihood of progression (worsened severity) vs. regression (lessened severity) of regurgitation over time. Generally, these studies suggest that regurgitation attributable to diet drug induced VHD remains stable or regresses in a substantial portion of the exposed population but that there may be progression of the severity of the disease among five to ten percent of those individuals who have developed FDA positive levels of VHD after being exposed to diet drugs. *See, e.g.*, Eichelberger, et al "Fifteen-year Outcome Data on Patients Treated with Fenfluramine/ Phentermine Combination," *Journal of the American Society of Echocardiography* (*JASE*) May, 1999; 12:355(7C); Fisher, et al "Valvular Regurgitation in Subjects Receiving Anti-Obesity Agents: A Consecutive Series with Follow-up, *JASE*, May, 1999; 12:370(102P); Hensrud, et al, "Echocardiographic Improvement Over Time After Cessation of Use of Fenfluramine and Phentermine, *Mayo Clinic Proceedings*, 1999; 74:1191-1197; Shively, et al, "Prevalence and Determinants of Valvulopathy in Patients Treated with Dexfenfluramine," *Circulation* 1999; 100:2161-2167; Mast, et al, "The Natural History of Fenfluramine-Associated Valvulopathy Assessed by Echocardiography," *Supplement to The American Journal of Cardiology*, February, 2000, 35(2), Supplement A:523.

44. As a general matter, if a patient presents (a) with FDA positive regurgitation, (b) with a history of ingesting Pondimin and/or Redux, particularly for a long duration, (c) without any echocardiographic evidence for the alternative causes of valvular regurgitation described in paragraph 8 of this Declaration, (d) without a history of valvular heart disease predating the use of diet drugs, and (e) without any history of chronic ergotamine or methysergide use or having a carcinoid tumor, then it is likely that the use of diet drugs caused the patient's valvular heart disease. Conversely, where a patient presents with objective evidence of any of the alternative causes for valvular regurgitation set forth in paragraph 8 of this Declaration or with a history of valvular heart disease predating diet drug use or with a history of taking methysergide or egotamines for a continuous period of longer than 120 days, or with a history of a carcinoid tumor of a type associated with aortic and/or mitral valve lesions, it is unlikely that the consumption of diet drugs by that patient was the cause of left-sided valvular heart disease in the patient.

45. By the Fall of 1997, a number of individuals throughout the country initiated litigation against AHP claiming either that (a) they were entitled to "medical monitoring" in the form of echocardiograms to determine if they suffered from valvular heart disease as a result of ingesting Pondimin and/or Redux and/or (b) they were entitled to recover damages on account of VHD which they claimed was the causal result of ingesting Pondimin and/or Redux.

46. In April of 1999, AHP entered into settlement negotiations with Plaintiffs' Management Committee in MDL 1203 and with Class Counsel in certain state actions. Those negotiations ultimately led to the execution of a Memorandum of Understanding on October 6, 1999 and to a Settlement Agreement which was executed on November 18, 1999.

47. I was one of the physicians with whom the plaintiffs consulted during the course of those negotiations. Among other things, I provided substantial medical input with regard to the development of the settlement matrices, insofar as they involve medical issues. The settlement matrices and matrix criteria are set forth in the "Green Form" which is appended to this Declaration as Exhibit "B."

48. The settlement matrices correspond with well-recognized medical distinctions which are summarized elsewhere in this Declaration.

F. **Medical Principles Underlying the Funding of the Settlement Matrix**

49. Finally, I have been asked to provide information to counsel concerning the progression of valvular heart disease in individuals who qualify for matrix benefits under the Settlement Agreement in order to make an estimate of the probable cost of funding benefits under the settlement matrices. Based upon the information set forth elsewhere in this Declaration, I believe that the following "assumptions" concerning the progression of valvular heart disease are reasonable:

(a) Of the class members who show evidence of FDA positive valvular regurgitation as of the close of the period for medical screening, five to ten percent may have sufficient progression in the degree of regurgitation from which they suffer to qualify for payment on the settlement matrices (*See* Paragraph 43 above);

(b) Each year, on the average, 4.3 percent of the individuals in matrix level 1 will progress to matrix level 3 based upon the information summarized and reported upon in R.O. Bonow et al, "Guidelines for the Management of

Patients with Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines," (Committee on Management of Patients with Valvular Heart Disease), *JACC*, 32:1510, 1505-06 (citing seven published studies);

(c) Two to four percent of the individuals in matrix level 3 will progress to matrix level 4 or 5 within one year for the reasons set forth in paragraph 29 above; and

(d) Overall, approximately 30 percent of the individuals in matrix level 3 will progress to matrix level 5 over 10 years, given the general prognosis for otherwise relatively healthy individuals who undergo valvular repair and/or replacement surgery. *See* Carabello, Aortic Regurgitation in Women, *Circulation*, 1996;94:2355-57 (Citing references).

Dated: 3/29/00

DEAN G. KARALIS

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# EXHIBIT "A"

# CURRICULUM VITAE

## Dean G. Karalis, M.D., F.A.C.C.


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Malvern, Pa 19355
(610) 722-0682

OFFICE ADDRESS: 227 North Broad Street
Suite 200
Philadelphia, Pa 19107
(215) 564-3050
(215) 564-3398 FAX


EDUCATION:

1980-1984, M.D.,Albany Medical College
Albany, NY

1978-1979, Columbia University
New York, NY

1974-1978, B.S., Trinity College
Hartford, CT

POSTGRADUATE TRAINING AND FELLOWSHIP APPOINTMENTS:

| | |
|---|---|
| 1987 - 1990 | Fellow in Cardiology<br>Likoff Cardiovascular Institute<br>Hahnemann University Hospital<br>Philadelphia, PA |
| 1985 - 1987 | Resident in Medicine<br>The Cornell Hospitals, Program B<br>North Shore University Hospital<br>Manhasset, NY<br>Memorial Sloan-Kettering Cancer Center<br>New York, NY |

| | |
|---|---|
| 1984 - 1985 | Intern in Medicine<br>The Cornell Hospitals, Program B<br>North Shore University Hospital<br>Manhasset, NY<br>Memorial Sloan-Kettering Cancer Center<br>New York, NY |

EMPLOYMENT HISTORY:

| | |
|---|---|
| 1990 to Present | Cardiology Consultants of Philadelphia<br>227 North Broad Street<br>Philadelphia, PA 19107<br><br>1703 S. Broad Street<br>Philadelphia, PA 19148 |

FACULTY APPOINTMENTS & POSITIONS:

| | |
|---|---|
| 1990 to Present | Assistant Professor of Medicine<br>Hahnemann University Hospital<br>Philadelphia, PA |

HOSPITAL APPOINTMENTS:

| | |
|---|---|
| 1988 - 1989 | Chief Cardiology Fellow<br>Likoff Cardiovascular Institute<br>Hahnemann University Hospital<br>Philadelphia, PA |
| 1986 - 1987 | Assistant Chief Resident In Medicine<br>North Shore University Hospital<br>Manhasset, NY |
| 1990 to Present | Attending Cardiologist<br>Hahnemann University Hospital<br>Philadelphia, PA |
| 1991 to Present | Attending Cardiologist<br>St. Agnes Medical Center<br>Philadelphia, PA |

| | |
|---|---|
| 1994 to Present | Attending Cardiologist<br>Roxborough Memorial Hospital<br>Philadelphia, PA |
| 1994 to Present | Attending Cardiologist<br>Methodist Hospital<br>Philadelphia, PA |

SPECIALTY CERTIFICATION:

| | |
|---|---|
| 1990 | Cardiovascular Medicine |
| 1987 | Internal Medicine |

LICENSURE: Pennsylvania (MD-038166-E)

AWARDS

| | |
|---|---|
| 1993 | Teacher of the Year Award<br>(Department of Medicine) |
| 1991- 1992 | Commendation for outstanding teaching<br>of medical interns and residents |

MEMBERSHIP IN PROFESSIONAL SOCIETIES:

| | |
|---|---|
| 1991 | Fellow, Council on Clinical Cardiology,<br>American Heart Association |
| 1990 | American Heart Association |
| 1990 | American Society of Echocardiography |
| 1990 | Delaware Valley Cardiac Ultrasound Society |
| 1987 | American College of Physicians, Associate |
| 1987 | American College of Cardiology, Fellow |
| 1987 | Pennsylvania Medical Society |
| 1984 | American Medical Association |

## PROFESSIONAL COMMITTEES AND ADMINISTRATIVE SERVICE

| | |
|---|---|
| 1998 - present | Member, Medical Executive Committee, Hahnemann University Hospital |
| 1995 - 1997 | Chairman, Outcomes Management Steering Committee |
| 1995 - 1997 | Chairman, Cardiology Outcomes Management Committee |
| 1995-1997 | Member, Hospital Ethics Committee |
| 1993 to Present | Course Director, Introduction to Clinical Medicine, Cardiology: For Second-Year Medical Students |

## MANUSCRIPT REVIEWER

1. American Journal of Cardiology
2. Journal of the American College of Cardiology
3. Journal of the American Society of Echocardiography
4. Catheterization and Cardiovascular Diagnosis
5. Annals of Internal Medicine

## CLINICAL TRIALS

1. PRAISE II: Prospective Randomized Amlodipine Survival Evaluation II. (Principle Investigator) Sponsor: Pfizer.

2. LET: Losartan effectiveness and tolerability. (Principle Investigator) Sponsor: Merck.

3. EXCITE: Efficacy and safety of Xemilofiban Hydrochloride to patients undergoing coronary angioplasty or stent placement. (Principle Investigator) Sponser: Searle.

4. CHALLENGE: A multicenter six week randomized open-label parallel arm study comparing the efficacy of once daily Atorvastatin to Simvistatin in hypercholesterolemic patients. (Principle Investigator) Sponsor: Parke-Davis and Pfizer.

5. CAPRICORN: Study to determine the effects of Carvedilol on mortality in patients with left ventricular dysfunction, post myocardial infarction. (Principle Investigator) Sponsor: Smith Kline Beecham.

6. PRESTO: *Prevention of restenosis by Tranilast and its outcomes.* (Principle Investigator) Sponsor: Smith Kline Beecham.

7. CHARM: Candesartan (Atacand) in heart failure assessment of reduction in mortality and morbidity. (Principle Investigator) Sponsor: Astra-Zeneca.

8. OVERTURE: Omapatrilat versus Enalapril randomized trial of utility in reducing events. (Principle Investigator) Sponsor: Bristol-Myers Squibb.

9. SAGE: A prospective randomized double-blind, multi-center study comparing the effects of aggressive lipid lowering with moderate lipid lowering on the reduction of total duration of myocardial ischemia in the elderly as measured by Holter monitoring by comparing the maximal doses of two statins: Study assessing goals in the elderly. (Principle Investigator) Sponsor: Parke-Davis and Pfizer.

10. ACES: Azithromycin and Coronary Events Study. (Co-Investigator) Sponsor: NIH.

11: A to Z Trial: Aggrastat to Zocor Trial. (Co-Investigator). Sponsor: Merck

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ARTICLES IN MEDICAL JOURNALS


1. **Karalis DG**, Parris T. Coronary angioplasty in cardiogenic shock: a bridge to coronary artery surgery. J Inv Cardiol 1989; 1:231-237.

2. **Karalis DG**, Wahl JM, Mintz GS, Chandrasekaran K. Severe stenosis involving a congenitally bicuspid aortic valve in the tenth decade of life. Am J Cardiol 1990;65:264-265.

3. Ross JJ, **Karalis DG**, Chandrasekaran K, Mintz GS. Echocardiographic detection of a mobile mass in the left main coronary artery. J Inv Cardiol 1990;2:77-79.

4. **Karalis DG**, Chandrasekaran K, Wahl JM, Ross JJ, Mintz GS. Transesophageal echocardigraphic recognition of mitral valve abnormalities associated with aortic valve endocarditis. Am Heart J 1990;119:1209-1211.

5. Pina IL, **Karalis DG**. Comparison of four exercise protocols using anaerobic threshold measurement of functional capacity in congestive heart failure. Am J Cardiol 1990:65:1269-1271.

6. **Karalis DG**, Chandrasekaran K, Victor MF, Mintz GS. Prolonged survival despite severe cyanosis in an adult with right ventricular hypoplasia and atrial septal defect. Am Heart J 1990; 120:701-703.

7. **Karalis DG**, Nydegger C, Porter RS, Carver J, Pina IL, Kutalek SP, Michelson EL. Effects of encainide and metabolizer phenotype on ventricular conduction during exercise. Am J Cardiol 1990;66:1393-1396.

8. **Karalis DG**, Chandrasekaran K, Victor MF, Ross JJ, Mintz GS. The recognition and embolic potential of intraaortic atherosclerotic debris. J Am Coll Cardiol 1991:17:73-78.

9. **Karalis DG**, Blumberg EA, Vilaro JF, Covalesky VA, Wahl JM, Chandrasekaran K, Mintz GS. Prognostic significance of valvular regurgitation in patients with infective endocarditis. Am J Med 1991;90:193-197.

10. Frohwein SC, **Karalis DG**, McQuillan JM, Ross JJ, Mintz GS, Chandrasekaran K. Preoperative detection of pericardial angiosarcoma by transesophageal echocardiography. Am Heart J 1991; 122: 874-875.

11. **Karalis DG**, Chandrasekaran K, Ross JJ, Mintz GS. The role of transesophageal echocardiography in infective endocarditis. Video Journal of Echocardiography 1991:1:49-55.

12. Ayala K, Chandrasekaran K, **Karalis DG**, Parris TM, Ross JJ. Diagnosis of superior vena caval obstruction by transesophageal echocardiography. Chest 1992; 101:874-876.

13. **Karalis DG**, Chandrasekaran K, Mintz GS. Correspondence: The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. N Engl J Medicine 1991;325:130.

14. **Karalis DG**, Blumberg EA, Covalesky VA, Vilaro JF, Wahl JM, Chandrasekaran K, Mintz GS. Clinical importance of valvular regurgitation in infective endocarditis. Cardiology Board Review 1992; 2: 55-63.

15. **Karalis DG**, Chandrasekaran K, Victor MF, Ross JJ, Mintz GS. Thoracic aortic atherosclerotic debris: a cause of embolism. Cardiology Board Review 1991; 12: 68-74.

16. Davis GA, Saverisen S, Chandrasekaran K, **Karalis DG**, Ross JJ, Mintz GS. Subclinical traumatic aortic injury diagnosed by transesophageal echocardiography. Am Heart J 1992; 123: 534-536.

17. **Karalis DG**, Bansal RC, Hauck AJ, Ross JJ, Applegate PM, Jutzy KR, Mintz GS, Chandrasekaran K. Transesophageal echocardiographic recognition of subaortic complications in aortic valve endocarditis: clinical and surgical implications. Circulation 1992;86: 353-362.

18. **Karalis DG**, Chandrasekaran K, Ross JJ, Mcklin A, Brown BM, Ren JF, Mintz GS. Single plane transesophageal echocardiography for assessing function of mechanical or bioprosthetic valves in the aortic valve position. Am J Cardiol 1992:69: 1310-1315.

19. Ren JF, Tulchinsky M, Davis GA, Chandrasekaran K, Kimbiris D, **Karalis DG**, Pennock RS, McAllister M. Frankl WS. Interrelationship of regional systolic wall motion with changes in left ventricular diastolic filling and global systolic function following coronary angioplasty. J Cardiovasc Technology 1992; 10:147-156.

20. Singer R, **Karalis DG**, Procacci PM, Naide D, Ross JJ, Chandrasekaran K. Transesophageal echocardiography for the evaluation of thoracic aortic atherosclerosis. Am J Roentgenol 1992; 159: 285-286.

21. **Karalis DG**, Chandrasekaran K. Intraaortic atherosclerotic debris by transesophageal echocardiography. Am Heart J 1992;124:1664

22. Walsh DV, Uppal JA, **Karalis DG**, Chandrasekaran K. The role of transesophageal echocardiography in the acute onset of paraplegia. Stroke 1992; 23: 1660-1661.

23. Ren JF, Tulchinsky M, Chandrasekaran K, Ross JJ, Foley RV, **Karalis DG**, Pennock RS, Frankl WS. A color Doppler guided echocardiographic technique for evaluation of left ventricular diastolic filling: validation by radionuclide angiography. A J Noninvas Cardiol 1993;7: 1-6.

24. **Karalis DG**, Victor MF, Davis GA, McAllister M, Covalesky VA, Ross J, Foley R., Kerstein M., Chandrasekaran K. The role of echocardiography in blunt chest trauma: A transthoracic and transesophageal echocardiographic study. J Trauma 1994; 36: 53-58.

25. Ross JJ, D'Adamo AJ, **Karalis DG**, Chandrasekaran K. Three-Dimensional imaging of the descending thoracic aorta. Am J Cardiol 1993;71:1000-1002.

26. Goldberg SP, **Karalis DG**, Ross JJ, Chandrasekaran K. Severe right ventricular contusion mimicking cardiac tamponade: the value of transesophageal echocardiography in blunt chest trauma. Ann Emerg Med 1993;22:745-747.

27. Kasper KJ, Chandrasekaran K, Bowman R, **Karalis DG**, Young NA, Owens JS. Left ventricular out-flow tract to left atrial communication secondary to perforation of the mitral-aortic intervalvular fibrosa from isolated mitral valve and mitral ring endocarditis. Am Heart J 1993; 125: 1792-1797.

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29. Duch PM, Chandrasekaran K, **Karalis DG**, Ross JJ. Improved diagnosis of co-existing type II and III aortic dissection with multiplane transesophageal echocardiography. Am Heart J 1994; 127:699-701.

30. Quinn VJ, Baloch Z, Chandrasekaran K, Ross JJ, **Karalis DG**. Coronary artery aneurysm masquerading as a paracardiac mass on transesophageal echocardiography. Am Heart J 1994; 127: 441-443.

31. Blumberg EA, **Karalis DG**, Chandrasekaran K, Wahl JM , Vilaro J, Covalesky VA, Mintz GS. Endocarditis associated paravalvular abscesses: Do clinical parameters predict the presence of abscess? Chest 1995; 107: 898-903.

32. Warnick WC, Ross JJ, **Karalis DG**. Stress echocardiography in clinical practice. Hahnemann University Monograph Series, Winter 1996; 6:1-6.

33. **Karalis DG**, Quinn VJ, Victor MF et al. Risk of catheter related emboli in patients with atherosclerotic debris in the thoracic aorta. Am Heart J 1996; 131:1149-55.

34. Hyman LR, **Karalis DG**, Ross JJ, Victor MF, Morris R. Pulmonary embolism from in situ right atrial thrombus following coronary artery bypass surgery. J Am Soc Echo 1997; 10: 760-762.

35. **Karalis DG**, Ross JJ. Left ventricular thromboembolism. Circulation 1998; 97:498.

36. **Karalis DG**, Hypertension and the ARBS: Commentary. Cardiology Review. December 1999.

BOOK CHAPTERS

1. Chandrasekaran K, Brown B, Bansal RC, Davis G, **Karalis DG**, Ren JF. Transesophageal Pulsed and Color Flow Doppler Echocardiography in Doppler Echocardiography: 2nd Edition. Navin C. Nanda M.D. (Ed). Lea and Febiger, Philadelphia 1992

2. **Karalis DG**, Chandrasekaran K, Ross JJ. Transesophageal echocardiography in Valvular Heart Disease. In Valvular Heart Disease: Comprehensive Evaluation and Treatment. Albert N. Brest, M.D. (Ed) F.A. Davis Company, Philadelphia 1992.

3. **Karalis DG**, Ross JJ, Chaudhry FA. Echocardiography in Chest Trauma. In Surgical Management of Thoracic Trauma. Westaby and Odell (Ed). Arnold, London 1999.

ABSTRACTS

1. **Karalis, DG.** Inaccuracy of predicted oxygen uptake values to evaluate patients with coronary artery disease: altered oxygen kinetics. Presented at the Merck, Sharp and Dohme Fifth Annual Health Science Associate Research Conference in Cardiovascular Disease, King of Prussia, PA. *September, 1988.*

2. Pina I, **Karalis DG**, Zack R, Frankl WS. Comparison of exercise protocols; evaluation of oxygen uptake kinetics in heart failure. Presented at the 38th Annual Scientific Session of the American College of Cardiology. Anaheim, CA, March, 1989. J. Am Coll Cardiol. 1989; 13:242A.

3. Blumberg E, **Karalis DG**, Covalesky VA, Wahl J., Vilaro J, Mintz GS, Chandrasekaran K. Preoperative diagnosis of myocardial abscess in infective endocarditis. Presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy. Dallas, TX, September, 1989.

4. **Karalis DG**, Nydegger C, Porter RS, Carver J, Pina IL, Kutalek SP, Michelson EL. Phenotypic expression of encainide metabolism and use-dependence. Presented at the 62nd Scientific Sessions of the American Heart Association. New Orleans, LA, November, 1989. Circulation 1989:80 (Suppl II) II-430.

5. **Karalis DG**, Chandrasekaran K, Victor MF, Ross JJ, Mintz GS. The recognition and embolic potential of intraaortic atherosclerotic debris. *Presented at the 63rd Scientific Sessions of the American Heart* Association Dallas, TX, November 1990. Circulation 1990;82 (Suppl III) III-246.

6. **Karalis DG**, Covalesky VA, Blumberg EA, Vilaro JF, Wahl JM, Chandrasekaran K, Mintz GS. Prognostic significance of valvular regurgitation in infective endocarditis. Presented at the American Federation for Clinical Research, Southern Section, New Orleans, LA, January, 1991. Clinical Research 1990;38:919A.

7. Brown BM, **Karalis DG**, Ross JR, Mintz GS, Chandrasekaran K. Limited value of single plane transesophageal echocardiography in prosthetic aortic valve malfunction. Presented at the 2nd Annual Scientific Sessions of the American Society of Echocardiography, Arlington VA, June 1991. J Am Soc Echo, 1991;4:284.

8. Tulchinsky M, Ren JF, Davis G, Chandrasekaran K, **Karalis DG**, Pennock RS, Frankl WS. Relationship of diastolic and regional systolic function in coronary artery disease: Effect of percutaneous transluminal coronary angioplasty. Presented at the 2nd Annual Scientific Sessions of the American Society of Echocardiography, Arlington, VA, June 1991. J Am Soc Echo 1991; 4:299.

9. Ren JF, Ahern T. Dreifus L, Chandrasekaran K, **Karalis DG**, Ross JJ, Frankl WS, Kutalek S. Effect on changing heart rate on mitral flow velocity dynamics in patients with atrioventricular (AV) sequential pacing. Presented at the Sixth World Congress of Ultrasound in Biology and Medicine, Denmark, September, 1991.

10. Bansal CR, Chandrasekaran K, **Karalis DG**, Applegate PM, Jutzy KR, Ross JJ. Transesophageal echocardiographic recognition of subaortic complications of aortic valve endocarditis. Presented at the 64th Scientific Sessions of the American Heart Association, Anaheim, CA, November 1991. Circulation 1991;84 (Suppl II) : II-129.

11. Ayala K, Chandrasekaran K, Otto J, **Karalis DG**, Quinn VJ, Ross JJ, Bansal R, Pandian N. Are the Doppler characteristics of the entry site of an intimal flap useful in the evaluation and follow up of aortic dissection? Presented at the 41st Annual Scientific Session of the American College of Cardiology, Dallas TX, March 1992. J Am Coll Cardiol 1992; 19:279A.

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14. Parmet JL, Pharo G, Orlando D, **Karalis DG**, Horrow JC. ST segment depression during LIMA dissection: artifact or ischemia? Presented at the Society of Cardiovascular Anesthesiologists, Boston MA, April 1992.

15. **Karalis DG**, Quinn V, Polansky M., Ross JJ, Victor MF, Chandrasekaran K, Hahnemann University Hospital. Clinical profile of patients with intraaortic atherosclerotic debris: implications regarding invasive aortic procedures. Presented at the 3rd Annual Scientific Meeting of the American Society of Echocardiography, Boston, MA, June, 1992. J Am Soc Echo 1992;5:310.

16. Chandrasekaran K, Quinn V. Ross JJ, Ayala Kn, **Karalis DG**, Parris T. Kimbiris D. Diagnostic utility and clinical applicability of intra-vascular ultrasonography in the evaluation of aortic disorders: initial experience in 48 patients. Present at the 65th Scientific Sessions of the American Heart Association, New Orleans, LA, November, 1992. Circulation 1992;86 (Suppl I):I-364.

17. Ross JJ, D'Adamo AJ, **Karalis DG**, Chandrasekaran K. Three-Dimensional intravascular ultrasonic reconstruction of the descending thoracic aorta. Presented at the 42nd Annual Scientific Session of the American College of Cardiology, Anaheim, CA, March, 1993. J. Am. Coll Cardiolol 1993; 21:449A.

18. Chandrasekaran K, Walsh DV, Ross JJ, Duch PM, **Karalis DG**. Multiplane transesphageal echocardiography increases diagnostic capability beyond biplane transesophageal echocardiography. Presented at the 42nd Annual Scientific Session of the American College of Cardiology, Anaheim CA, March, 1993. J. Am Coll Cardiol 1993; 21:487A.

19. Chandrasekaran K, Aurangzeb A. Singer RA, Davis GA, **Karalis DG**, Kerstein MD. Improved diagnosis of thoracic aortic injury by transesophageal echocardiography in patients with blunt chest trauma. Presented at the 66th Annual Scientific Sessions of The American Heart Association, Atlanta, GA, November 1993. Circulation 1993; 88 (Suppl II): I-56.

20. Brode SE, Dourdoufis PJ, Mandal SK, Ross JJ, Blumberg EA, **Karalis DG**, Bansal RC, Chandrasekaran K. Transesophageal echocardiography in patients with endocarditis limited to the mitral valve. Presented at the 5th Annual Scientific Sessions of the American Society of Echocardiography, San Francisco, CA, June, 1994. J Am Soc Echo 1994; 7: S55.

21. Ross JJ, Chandrasekaran K, **Karalis DG**, Scharf GR, Victor MF. Pulse repetition frequency significantly alters color flow Doppler assessment of regurgitant lesions. Presented at the 5th Annual Scientific Sessions of the American Society of Echocardiography, San Francisco, CA, June, 1994. J Am Soc Echo 1994; 7: S53.

22. **Karalis DG**, Davis GA, McAllister MPJ, Victor MF, Covalesky VA, Ross JJ, Foley RV, Kerstein MD, Chandrasekaran K. Are patients with myocardial contusion at risk for late cardiac complications? Presented at the 5th Annual Scientific Sessions of the American Society of Echocardiography, San Francisco CA, June 1994. J Am Soc Echo 1994; 7:S60.

23. Samuels LE, Sharma S, Rodriguez-Verga JR, Morris RJ, Karetu RML, Grunewald KE, **Karalis DG**, Brockman SK. Diagnosis and management of traumatic aorto-right ventricular fistulas. Presented at the 1996 Annual Meeting of the Pennsylvania Association for Thoracic Surgery, Farmington, PA, September 1996.

24. Dhawan R, Ahmar W, Galatro K, Ren J, Jyotinagaraim M, **Karalis DG**, Chaudhry FA. Prognostic implications of mobile vs. complex aortic plaque: a transesophageal echocardiographic study. Presented at the 9th Annual Scientific Sessions of the American Society of Echocardiography, San Francisco, CA, June 1998. J Am Soc Echo 1998.

25. **The LET investigators.** A community based study on the effectiveness and tolerability of a losartan-based regimen versus usual care for the treatment of hypertension. Presented at the American Society of Hypertension, New York, NY, May 1998.

## PRESENTATIONS

BY INVITATION

1. Cardiology Grand Rounds. "Exercise Echocardiography". October 11, 1990, Hahnemann University Hospital, Philadelphia.

2. Medicine Grand Rounds. "Transesophageal Echocardiography and Cardiac Sources of Emboli". October 17, 1990, Hahnemann University Hospital, Philadelphia.

3. "Noninvasive Evaluation of Prosthetic Valves". February 18, 1991, Cardiology Associates, Cherry Hill, NJ.

4. Medicine Grand Rounds. "Transesophageal Echocardiography". March 27, 1991. St. Agnes Hospital, Philadelphia.

5. Surgical Grand Rounds. "Cardiac Trauma". May 1, 1991, Hahnemann University Hospital, Philadelphia.

6. Trauma Topics Day, Division of Trauma. "Cardiac Contusion in Blunt Chest Injury". September 9, 1991, Hahnemann University Hospital, Philadelphia.

7. Transesophageal Echocardiography Conference. "The Role of Transesophageal Echocardiography in Infective Endocarditis". September 28, 1991, Toshiba America Medical Systems, Philadelphia.

8. "Role of TEE in Systemic Embolism". November 6, 1991, Delaware Valley Cardiac Ultrasound Society, Lankenau Hospital, Philadelphia.

9. Medical Seminar Series: Antithrombotic Therapy in Coronary Artery Disease. "Peri MI Embolism". January 22, 1992, Hahnemann University Hospital, Philadelphia.

10. Medicine Grand Rounds. "Transesophageal Echocardiography in Clinical Practice". January 29, 1992, St. Agnes Hospital, Philadelphia.

11. "Transesophageal Echocardiography". April 3, 1992, Bridgeton Division, Southern Jersey Hospital.

12. Crozer-Keystone Educational Symposium. "Role of Transesophageal Echocardiography in Unexplained Stroke and Arterial Embolism". April 8, 1992, Crozer-Chester Medical Center, Upland, Pennsylvania.

13. Cardiology Ground Rounds. "Transesophageal Echocardiography and Cardiac Sources of Emboli". August 17, 1992, Franklin Square Hospital, Philadelphia.

14. Medical Grand Rounds. "Hyercholesterolemia: Diagnosis and Management". January 6, 1993, St. Agnes Hospital, Phildelphia.

15. Medical Grand Rounds. "Echocardiography and Stroke: When is it Useful?". April 8, 1993, Chester County Hospital, West Chester, Pennsylvania.

16. Advances in Echocardiography for Clinical Practice. "Echocardiography in the Evaluation of Systemic Embolism". April 14, 1993, Hahnemann University Hospital, Philadelphia.

17. USTMAATS 11th Annual Scientific Seminary. "Hypertension in the Elderly". May 8, 1993, Atlantic City, New Jersey.

18. Medical Grand Rounds. "Modern Management of Acute Myocardial Infarction". July 15, 1993, Community Medical Center, Toms River, New Jersey.

19. Medical Grand Rounds. "Hypertension in the Elderly". October 13, 1993, Nazarath Hospital, Philadelphia, Pennsylvania.

20. New Trends in Cardiac Ultrasound. "Systemic Embolism". November 20, 1993, Valley Forge, Pennsylvania.

21. Medical Grand Rounds. "Stress Echocardiography and the Evaluation of Coronary Artery Disease". December 4, 1993, Delaware County Memorial Hospital, Drexel Hill, Pennsylvania.

22. Office Management of Heart Disease for the Generalist. "Echocardiography in the Office". March 2, 1994, Hahnemann University Hospital, Philadelphia, Pennsylvania.

23. Cardiovascular Disease in the 90's. Moderator: "Prevention of Coronary Artery Disease by Risk Factor Modification". May 7, 1994, Lafayette Hill, Pennsylvania.

24. The Philadelphia County Medical Society. "CHF, Angina and Hypertension in the Elderly, May 18, 1994, Philadelphia, Pennsylvania.

25. Office Management of Heart Disease: A Primare Care Perspective. "Echocardiography in the Office; How can it Help?" June 11, 1994, Atlantic City, NJ.

26. Medical Grand Rounds: "Transesophageal Echocardiography in Clinical Practice," October 18, 1994. Roxborough Memorial Hospital Philadelphia, PA.

27. Medical Grand Rounds: "Hypertension in the Elderly," October 26, 1994. Holy Redeemer Hospital, Philadelphia, PA.

28. Clinical Advances: Conference on Diseases of the Aorta and Peripheral Vasculature: "Aortic Debris and Atheroembolism," February 8, 1995. Hahnemann University Hospital, Philadelphia, PA.

29. Medical Grand Rounds: "Stress Echocardiography," May 5, 1995. Bridgeton Division, Southern Jersey Hospital, Bridgeton, NJ.

30. Second Annual Medical Staff Educational Seminar: "Blood Pressure, ECG, Stress Test; June 7, 1995. Elkins Park Hospital, Philadelphia, PA.

31. Office Management of Heart Disease: A Primary Care Perspective: "Exercise Echocardiography - Is This The Cost Effective Approach

For The Future," June 10, 1995, Atlantic City, NJ.

32. Cardiac Auscultation for the Generalist and Office Practice; Course Co-Director. December 6, 1995. Hahnemann University Hospital, Philadelphia, PA.

33. Cardiology Grand Rounds: "Echocardiography and Source of Embolism." January 24, 1996. Presbyterian Hospital, Philadelphia, PA.

34. Medical Grand Rounds: "Modern Approach To Treating Hypertension." March 12, 1996, Mercy-Haverford Hospital, Haverford, PA.

35. "Hypertension Update: Facts vs Fiction in Treatment Options". At the 3rd Annual office Management of Heart Disease - A Primary Care Perspective. June 8, 1996, Lafayette Hill, PA.

36. "Calcium Channel Blocker; Relevance of Research in Clinical Practice." Issues in Cardiovascular Care, June 29, 1996, Lafayette Hill, PA.

37. "Evaluation of the Acute Trauma Patient." Echo-Philadelphia '96, September 7, 1996, Philadelphia, PA.

38. "What is the Optimal Imaging Technique in Aortic Dissection?" Echo-Philadelphia '96, September 8, 1996, Philadelphia, PA.

39. Medical Grand Rounds. "Hypertension and Its Complications". April 15, 1997, Methodist Hospital, Philadelphia, PA.

40. Clinical Frontiers in Cardiology. "Treating Hypertension in Calcium Antagonists: A Plan of Action". May 17, 1997, Lafayette Hill, PA.

41. Medical Grand Rounds. "Coronary Artery Disease and Hypertension: Calcium Channel Blockers." October 8, 1997, Paoli Hospital, Paoli, PA.

42. Echo Philadelphia 1997. "Evaluation of Acute Trauma Patients." October 6, 1997, Philadelphia, PA.

43. Echo Philadelphia 1997. "TTE and TEE for Aortic Disease." October 8, 1997, Philadelphia, PA.

44. Medical Grand Rounds. "Hypertension in the Elderly." February 4, 1998, Allegheny University Hospitals, Bucks County, PA.

45. Cardiology Grand Rounds. "Evaluation of the Acute Trauma Patient." February 23, 1998, Hershey Medical Center, Hershey, PA.

46. Medical Grand Rounds. "Hypertension and its Complications." February 24, 1998. St. Luke's Hospital, Bethlehem, PA.

47. Fifth Annual Office Management of Heart Disease. "Custom Tailoring the Approach to Hypertension." September 27, 1998, Philadelphia, PA.

48. Cardiac Auscultation for the Generalist in Office Practice. December 9, 1998, Hahnemann University Hospital, Philadelphia, PA.

49. "Treating Hypertension". The JNC VI Recommendations. February 24, 1999, Hershey Medical Center, Hershey, PA.

50. Sixth Annual Office Management of Heart Disease: A Primary Care Perspective. "Treating Hypertension: Making sense of the Clinical Trials". October 24, 1999, Philadelphia, PA.

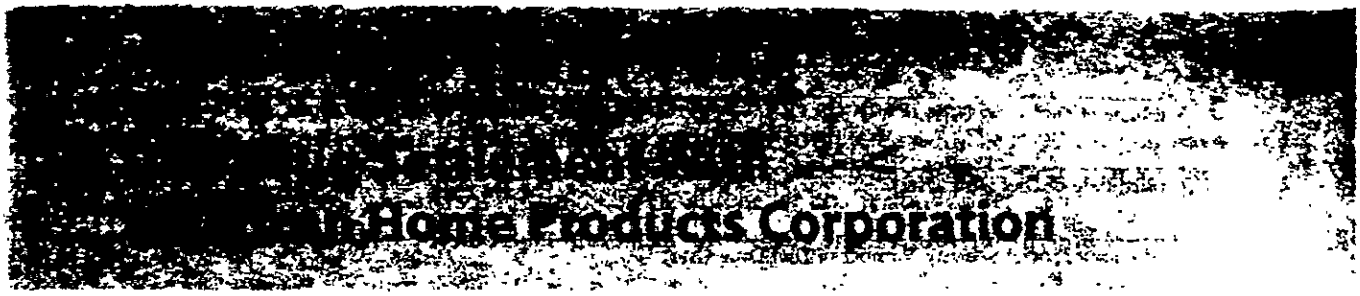
51. Cardiovascular Consultants' Meeting. "Modifying Cardiovascular Risk Factors Throughout the Cardiovascular Continuum". December 11, 1999. Washington, D.C.

52. Cardiac Auscultation for the Generalist in Office Practice, Course Co-Director. January 19, 2000. Hahnemann University Hospital, Philadelphia, PA.

53. Medical Grand Rounds. "Changing the Natural History of Coronary Disease: Aggressive Cholesterol Reduction." January 26, 2000. St. Agnes Hospital, Philadelphia, PA.

updated 2/00

# EXHIBIT "B"




**Part I:** Matrix Compensation Benefits Claim Form
*(to be completed by Claimant or Claimant's Representative)*

**Part II:** Doctor's Evaluation Form
(to be completed by Physician)

**Part III:** Claimant's Lawyer Statement
(to be completed if you are represented by an Attorney)

**Appendix:** Settlement Matrix Compensation Benefits Guide for Physicians, Attorneys and Class Members

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To receive Matrix Compensation Benefits, you must complete either the PINK FORM (if you choose the Accelerated Implementation Option) or the *BLUE FORM* (if you choose to register for Settlement Benefits) in addition to this form.

## Part I — To the Claimant(s):

1. *This form should be used if you believe that you are entitled to Matrix Compensation Benefits* under the Diet Drug Settlement Agreement with American Home Products Corporation. These benefits are described generally in the Notice of Settlement which you have received and in the "Matrix Compensation Benefits Guide for Physicians, Attorneys and Class Members," which is an Appendix to this form.

   If you are the individual who used the diet drugs Pondimin® (Fenfluramine) and/or Redux™ (Dexfenfluramine) and who has a condition which you believe qualifies for a Matrix Payment, state your name, birthdate, social security number and, if known, your Diet Drug Settlement Claim number which you have received from the Settlement Claims Administrator.

   If you are making this claim as the guardian, executor, administrator, or other legal representative of a living person or the estate of a deceased person, or as a Derivative Claimant, such as a spouse, child, dependent, parent, other relative or "significant other" of the person who used the diet drugs Pondimin® ("Fenfluramine") and/or Redux™ ("Dexfenfluramine") and who has (or had) a condition which you believe qualifies for a Matrix Payment, state the name, birthdate, social security number of the person who used the diet drugs and, if known, the Diet Drug Settlement Claim number received from the Settlement Claims Administrator relating to the Diet Drug User.

| |
|---|
| Remove label from mailing envelope and affix here. |

Please return this form to:
Diet Drug Settlement
P.O. Box 7939
Philadelphia, PA 19101

(Name of Diet Drug User)

(Birthdate of Diet Drug User)

(If known, Social Security Number of Diet Drug User)

(If known, Diet Drug Settlement Claim Number)

2. **Individuals who qualify for Matrix Compensation Benefits may file for such compensation benefits by using this "GREEN FORM" as and when they have a medical condition that qualifies them.**

Individuals who have qualified for Matrix Compensation Benefits at one level are entitled to "step up" to higher levels of compensation on the applicable matrix in the event that their condition progresses. If you have previously submitted an Original Matrix Compensation Benefits Claim Form ("GREEN FORM") to make a claim and your condition has progressed to a level that entitles you to "stepped-up" or increased benefits because of a change in the physical condition of the individual who used the diet drugs Pondimin® and/or Redux™, you can use this form to supplement a prior claim.

If this claim form is used to supplement a prior claim, the entire claim form does not have to be completed again in full. Only changes to information previously provided needs to be submitted. Additionally, if this is a supplemental Matrix Benefits Claim, the physician responsible for completing Part II of the claim form should complete only those portions of the form which reflect a change in condition from the condition described in the original or prior supplemental claim form.

**Please check below whether this is an original claim form (the first Matrix Compensation Benefits Claim Form which you have submitted) or a supplemental Matrix Benefits Claim Form (a second, third, or fourth claim form which you have completed in order to "step up" to higher compensation levels in the Settlement Matrices).**

❒ *This is an Original Claim Form* ❒ *This is a Supplemental Matrix Benefits Claim Form*

3. **If you are submitting this form as the Representative of the estate of the Diet Drug Recipient, or on behalf of a Diet Drug Recipient who has become incapacitated, and have already provided all of the information requested below, and that information has not changed, check below:**

❒ I have already provided the requested information and a copy of my authority to act previously or on another form and there is no change.

If this question applies to you and you have not yet provided the following information, or there is a change in that information, please fill out the information below:

(First Name) (Middle Initial) (Last Name)

(Street Address)

(City) (State) (Zip Code)

( ) ( )
(Daytime Phone Number & Area Code) (Evening Phone Number & Area Code)
— —

(E-mail Address, if any)

(Legal Relationship to Diet Drug Recipient [trustee, power of attorney, etc.])

PLEASE NOTE—You must attach or include a copy of your court approval or other authorization to represent the Diet Drug Recipient in this Settlement with your completed GREEN FORM if you have not previously provided the approval or other authorization to the Claims Administrators or are providing it with another form you are submitting. Check whichever box is applicable:

☐ I have already provided the requested documentation previously or on another form and there is no change.

☐ A copy of my court approval or other authorization to represent the Diet Drug Recipient is attached.

**If you are submitting this form as a Derivative Claimant, (*i.e.*, a spouse, parent, child, dependant, relative, or "significant other" of a Diet Drug Recipient) and all of the information on all Derivative Claimants requested below has already been provided to the Claims Administrator, and that information has not changed, check here:**

☐ The requested information is supplied on another form or has been already provided and there is no change.

**a. If this question applies and you have not yet provided the following information, or there is a change in that information, please fill out the information below:**
**(PLEASE NOTE—Current and correct information is required for all Derivative Claimants. If there is information or changes for more than one Derivative Claimant, check here ☐ and then use a blank piece of paper or a photocopy of this question to provide the information for each applicable Derivative Claimant. Please staple that paper to this form.)**

(First Name) (Middle Initial) (Last Name)

(Street Address)

(City) (State) (Zip Code)

(_____) — (_____) —
(Daytime Phone Number & Area Code) (Evening Phone Number & Area Code)

(E-mail Address, if any)

(Birth Date — Month, Day, Year) (Social Security Number)

**b. Please specify the relationship of the Derivative Claimant to the Diet Drug Recipient.**

☐ Spouse ☐ Dependent, please specify _____
☐ Parent ☐ Other relative, please specify_____
☐ Child ☐ Significant other, please specify_____

**c. If you selected "spouse" above, what is the current status of the relationship of the Derivative Claimant to the Diet Drug Recipient?**

☐ Married ☐ Divorced ☐ Separated ☐ Widowed

Date of the marriage (Month/Day/Year): _____

d. If the Derivative Claimant is currently estranged from the Diet Drug Recipient, please state the date of separation and/or divorce.

Date: _____

(Please provide evidence of the date of separation or divorce, i.e., separation agreement or divorce decree).

e. Please identify the basis on which the Derivative Claimant is claiming "derivative" benefits.

❒ Loss of Consortium/Per Quod (e.g., loss of marital services and relationship)
❒ Loss of Support
❒ Loss of Service
❒ Other, please explain: _____

_____

5. Check which matrix level you believe you currently qualify for:

❒ Level I ❒ Level III ❒ Level V
❒ Level II ❒ Level IV

6. Check which Matrix you believe you qualify for:

❒ Matrix A-1 (the full compensation Matrix)
❒ Matrix B-1 (the reduced compensation Matrix)

NOTE: If you are completing this questionnaire as a Representative or Derivative Claimant, the following questions using the term "You" refer to the "Diet Drug Recipient."

7. State your age and the date on which you were diagnosed with the condition or experienced the event (e.g., date of surgery) which you believe qualifies you for payment at the Matrix Level set forth in answer to question #5:

Date of diagnosis/event: _____ Age at diagnosis/event: _____

8. To the best of your knowledge, did you have the condition which you believe qualifies you for payment at the Matrix Level before you took Pondimin® or Redux™?

❒ Yes ❒ No ❒ Don't Know

9. Are you represented by any lawyer in connection with this claim?

❒ Yes ❒ No

If you checked the box marked "Yes," please have your lawyer complete the Claimant's Lawyer Statement (Part III of this GREEN FORM).

10. To complete the application, you must provide (a) hospital reports of admitting history and physical examinations, (b) cardiac catheterization reports, (c) hospital discharge summaries, (d) operation or surgery reports, (e) pathology reports, and (f) the written report and videotape or disk of the Echocardiogram results which relate to the condition for which you seek compensation. You can either provide the medical records if they are in your possession or, alternatively, you can provide the name of the physician(s), clinics or hospitals whose records document or support the claim and sign the attached "Medical Records Authorization" form.

Please check one of the boxes:

❒ I am supplying medical records.

❒ I am signing a medical authorization to enable the Claims Administrators to obtain the medical records. The following physician(s), clinics or hospitals have the above records:

| Name of Physician, Clinic or Hospital | Address of Physician, Clinic or Hospital | Date(s) of Treatment, Service or Admission |
|---|---|---|
| | | |
| | | |
| | | |

If there are additional physicians, clinics or hospitals, check here ☐ and use an additional sheet to list them. Please remember to attach that sheet to this form.

11. **The undersigned hereby consents to the disclosure of the information contained herein to the extent necessary to process claims for Settlement Benefits. The person(s) signing below acknowledges and understands that this form is an official document sanctioned by the Court that presides over the Diet Drug Settlement, and submitting it to the Claims Administrators is equivalent to filing it with a Court. After reviewing the information which has been supplied on this form by a Board-Certified Physician (Part II) and, if applicable, by an attorney (Part III). Each person declares under penalty of perjury that all of the information provided in this form is true and correct to the best of his/her knowledge, information and belief.**

(Signature of Diet Drug Recipient, if Living) (Date)

(Signature(s) of all Legal Representative(s) of Diet Drug Recipient, if any) (Date)

(Signature(s) of Claiming Spouse, Parent, Child, Dependent, Other Relative, or "Significant Other," if any) (Date)

## Important Information to Claimants Regarding Part II of This Form

**art II of this form must be completed by a Board-Certified Cardiologist or Cardiothoracic Surgeon.** owever, if the claim is based upon the Diet Drug User developing endocardial fibrosis, then you may, if you refer, have a Board-Certified Pathologist complete Part II regarding the existence of the pathological crite- a for endocardial fibrosis. If the claim is based upon the determination of the functional outcome that a )iet Drug Recipient has or had 6 months after a stroke, then, if you prefer, a Board-Certified Neurologist or Neurosurgeon may also complete the questions in Part II of the form that concern that outcome.

# Medical Records Authorization

This will authorize you to furnish copies of all echocardiographic recordings and reports in your possession (including written reports and Echocardiographic video tapes and disks), hospital reports of admitting history and physical examinations, cardiac catheterization reports, hospital discharge summaries, operation or surgery reports, pathology reports, concerning:

_____
(Name of Diet Drug Recipient)

whose date of birth is _____
(Date of Birth of Diet Drug Recipient)

and whose social security number is _____
(Social Security Number of Diet Drug Recipient)

You are authorized to release the above records/recordings to the Trustees and/or Claims Administrators in the Diet Drug Settlement. The entity requesting the records will pay reasonable charges made by you to supply copies of such records/or disks.

Please forward the above records to:
**Claims Administrators**
**Diet Drug Settlement**
**P.O. Box 7939**
**Philadelphia, PA 19101**

This authorization does not authorize you to disclose anything other than the items referenced above to anyone.

_____
(Date) (Claimant or Claimant's Legal Representative)

# Part II—To the Board-Certified Physician

Part I of this form identifies an individual who was prescribed and ingested the diet drugs Pondimin® ("Fenfluramine") and/or Redux™ ("Dexfenfluramine") and who has a condition which may qualify the patient, his or her legal representatives and/or members of the family for payment as part of the nationwide Class Action Settlement reached with American Home Products Corporation.

In order to qualify for such payment, a Board-Certified Cardiologist or Cardiothoracic Surgeon must certify that the diet drug user either does or does not have conditions which are relevant to the determination of the amount of compensation payable. (However, with respect to the information required in response to question No. F(11), the response may be supplied by a Board-Certified Neurologist or Neurosurgeon, or based upon information supplied by such specialists. With respect to the information required in response to question No. L(6), the response may be supplied by a Board-Certified Pathologist, or based upon information supplied by such specialists.)

These conditions are defined by reference to well-accepted, published criteria which are excerpted in the Settlement Matrix Compensation Benefits Guide for Physicians, Attorneys and Class Members which should have been provided to you with this form as an Appendix.

In completing the form you may consider, rely upon and use the patient's echocardiograms, medical records and reports, hospital records or reports, the patient's medical history or other sources of information you regularly and routinely use in your practice.

Please certify below that the patient either has or does not have a given condition to a reasonable degree of medical certainty. For this purpose a claimant who qualifies for a particular Matrix payment, by virtue of a properly interpreted Echocardiogram showing the required levels of regurgitation and/or complicating factors, after exposure to fenfluramine and/or dexfenfluramine, shall not be disqualified from receiving that Matrix payment in the event that a subsequent Echocardiogram shows that the required levels of regurgitation and/or complicating factors are no longer present.

If this form is a "supplemental" claim form, you only need to provide information which relates to a condition that has changed since the date on which any original or prior supplemental claim form was completed.

A. **Medical Background:** What is your name, office address, and telephone number?

_____
(Name)

_____
(Office Address)

_____
(City) (State) (Zip Code)

(_____) _____
(Telephone Number & Area Code)

Check whether you are:

☐ A Board-Certified Cardiologist ☐ A Board-Certified Cardiothoracic Surgeon

☐ Other _____

Check whether you have level 2 training in echocardiography as specified in the "Recommendations of the American Society of Echocardiography Committee on Physician Training in Echocardiography."[1]

☐ Yes ☐ No

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[1] Pearlman AS, Gardin JM, Martin RP, Parsi AF, Popp RL, Quinones MA, *et al.*, *Guidelines for optimal physician training in echocardiography. Recommendations of the American Society of Echocardiography Committee for Physician Training in Echocardiography*, 60 Am. J. Cardiol. 158-163 (1987).

B. Patient Information:
State the name of the patient (Diet Drug Recipient) for whom you are providing the information contained in this form.

_____
(Diet Drug Recipient's Name)

C. 1. Did the above named patient have an Echocardiogram which was conducted in accordance with the standards and criteria as outlined in Feigenbaum[2] (1994) or Weyman[3] (1994)?

❒ Yes ❒ No

2. If the answer to the preceding is "Yes," state the date when the Echocardiogram was performed.

Date: _____

3. Based on your review of the Echocardiogram, does the above-named Diet Drug Recipient have the following conditions as defined by Singh[4]? (Check each which applies):

A. For mitral regurgitation, the following determined in any apical view:

❒ Mild mitral regurgitation, defined as (1) either the Regurgitant Jet Area/Left Atrial Area ("RJA/LAA") ratio is more than 5% or the mitral regurgitant jet height is greater than 1 cm from the valve orifice, and (2) the RJA/LAA ratio is less than 20%.

❒ Moderate mitral regurgitation, defined as regurgitant jet area in any apical view equal to or greater than 20% of the left atrial area but less than 40% (20% - 40 % RJA/LAA).

❒ Severe mitral regurgitation, defined as > 40% RJA/LAA.

❒ None of the above.

B. For aortic regurgitation, the following determined in the parasternal long-axis view or in the apical long-axis view, if the parasternal long-axis view is unavailable:

❒ Mild aortic regurgitation, defined as regurgitant jet diameter equal to or greater than 10% but less than 25 % of the outflow tract diameter ("10%-24% jet height ("JH")/left ventricular out flow tract ("LVOTH")").

❒ Moderate aortic regurgitation, defined as 25% - 49% JH/LVOTH.

❒ Severe aortic regurgitation, defined as > 50% JH/LVOTH.

❒ None of the above.

D. **Based on your review of the Echocardiogram (or the results of any cardiac catheterization or surgical examination), does the above-named Diet Drug Recipient have any of the following conditions:**

1. Congenital Aortic Valve Abnormalities: Unicuspid, Bicuspid or Quadricuspid aortic valve; ventricular septal defect associated with aortic regurgitation?

❒ Yes ❒ No

2. Aortic dissection involving the aortic root and/or aortic valve?

❒ Yes ❒ No

3. Aortic sclerosis at the time that the Diet Drug Recipient was first diagnosed with mild or greater aortic regurgitation if he or she was 60 or older at that time?

❒ Yes ❒ No

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[2] H. Feigenbaum, *Echocardiography* 68-133 (5th ed. 1994).
[3] A. E. Weyman, *Principles and Practice of Echocardiography* 75-97 (2d ed. 1994).
[4] J. P. Singh, *et al., Prevalence and Clinical Determinants of Mitral, Tricuspid and Aortic Regurgitation (The Framingham Heart Study)*, 83 American Journal of Cardiology 897-902 (1999).

4. Aortic root dilation >5.0 cm?

   ❒ Yes ❒ No

5. Aortic stenosis with an aortic valve area <1.0 square centimeter by the Continuity Equation?

   ❒ Yes ❒ No

6. Congenital mitral valve abnormalities: Parachute valve or cleft of the mitral valve associated with atrial septal defect?

   ❒ Yes ❒ No

7. Mitral valve prolapse defined as a condition where (a) the Echocardiogram video tape or disk includes the parasternal long-axis view and (b) that Echocardiographic view shows displacement of one or both mitral leaflets >2 mm above the atrial-ventricular border during systole, and >5 mm leaflet thickening during diastole, as determined by a Board-Certified Cardiologist[5]?

   ❒ Yes ❒ No

8. Chordae tendinae rupture or papillary muscle rupture, or acute myocardial infarction associated with acute mitral regurgitation?

   ❒ Yes ❒ No

9. Mitral annular calcification?

   ❒ Yes ❒ No

10. M-Mode and 2-D Echocardiographic evidence of rheumatic heart valves (doming of the anterior leaflet and/or anterior motion of the posterior leaflet and/or commissural fusion), except where a Board-Certified Pathologist has examined mitral valve tissue and determined that there was no evidence of rheumatic valve disease?

    ❒ Yes ❒ No

E. **To the best of your knowledge, has the above-named Diet Drug Recipient had the following:**

1. Heart valve surgery to repair or replace the mitral valve prior to Pondimin® and/or Redux™ use?

   ❒ Yes ❒ No

2. Heart valve surgery to repair or replace the aortic valve prior to Pondimin® and/or Redux™ use?

   ❒ Yes ❒ No

3. Bacterial endocarditis prior to Pondimin® and/or Redux™ use?

   ❒ Yes ❒ No

4. Mild or greater aortic regurgitation confirmed by echocardiography prior to Pondimin® and/or Redux™ use?

   ❒ Yes ❒ No

5. Moderate or greater mitral regurgitation confirmed by echocardiography prior to Pondimin® and/or Redux™ use?

   ❒ Yes ❒ No

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[5]Lisa A. Freed, *et al., Prevalence and Clinical Outcomes of Mitral Valve Prolapse,* 341 New Eng. J. Med. (1999).

6. Carcinoid tumor of a type associated with aortic and/or mitral valve lesions?

   ❒ Yes ❒ No

7. History of daily use of methysergide or ergotamines for a continuous period of longer than 120 days?

   ❒ Yes ❒ No

8. A diagnosis of Systemic Lupus Erythematosus and valvular regurgitation and/or abnormalities of a type associated with Systemic Lupus Erythematosus?[6]

   ❒ Yes ❒ No

9. A diagnosis of rheumatoid arthritis and valvular regurgitation and/or abnormalities of a type associated with rheumatoid arthritis?[7]

   ❒ Yes ❒ No

F. **To the best of your knowledge, has the above-named Diet Drug Recipient developed the following conditions <u>after</u> the date on which the patient first used Pondimin® and/or Redux™ as reported above:**

1. Mild or greater aortic regurgitation and/or moderate or greater mitral regurgitation with bacterial endocarditis?

   ❒ Yes ❒ No

2. Pulmonary Hypertension secondary to severe aortic regurgitation with a peak systolic pulmonary pressure >40 mm Hg[8] measured by cardiac catheterization or with a peak systolic pulmonary artery pressure >45 mm Hg measured by Doppler Echocardiography, at rest, utilizing standard procedures[9, 10] *assuming a right atrial pressure of 10 mm Hg?*

   ❒ Yes ❒ No

3. *Pulmonary Hypertension secondary to moderate or greater mitral regurgitation with peak systolic* pulmonary artery pressure >40 mm Hg measured by cardiac catheterization or with a peak systolic pulmonary artery pressure >45 mm Hg[11] measured by Doppler Echocardiography, at rest, utilizing standard procedures assuming a right atrial pressure of 10 mm Hg?

   ❒ Yes ❒ No

4. Abnormal left ventricular end-systolic dimension >50 mm[12] by M-mode or 2-D Echocardiography or abnormal left ventricular end-diastolic dimension >70[13] mm as measured by M-mode or 2-D Echocardiography?

   ❒ Yes ❒ No

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6 Harrison's Principles of Internal Medicine (14th ed. 1998) 1878.

7 Harrison's Principles of Internal Medicine (14th ed. 1998) 1885.

8 Braunwald, *Heart Disease. Textbook of Cardiovascular Medicine* 796-98 (1997).

9 Feigenbaum, J. *Echocardiography,* Baltimore, Williams & Wikins, pp. 201-02 (5th ed. 1994).

10 Chan, K-L., *et al., Comparison of Three Doppler Ultrasound Methods in the Prediction of Pulmonary Artery Disease,* J. Am. Coll. Cardiol., 9:549-554 (1987).

11 Braunwald, *supra.*

12 Bonow RO, Carabello B, de Leon Jr A, Edmunds Jr LH, Fedderly BJ, Freed MD, *et al.,* Guidelines for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Valvular Heart Disease), *J Am Coll. Cardiol.,* 32:1510-14 (1998).

13 *Id.*

5. Abnormal left atrial supero-inferior systolic dimension >5.3 cm[14] (apical four chamber view) or abnormal left atrial antero-posterior systolic dimension >4.0 cm (parasternal long axis view) measured by 2-D directed M-mode or 2-D Echocardiography with normal sinus rhythm using sites of measurement recommended by the American Society of Echocardiography?[15]

   ❒ Yes ❒ No

6. Abnormal left ventricular end-systolic dimension greater than or equal to 45 mm[16] by M-mode or 2-D Echocardiogram?

   ❒ Yes ❒ No

7. Arrhythmias, defined as chronic atrial fibrillation/flutter that cannot be converted to normal sinus rhythm, or atrial fibrillation/flutter requiring ongoing medical therapy, either of which are associated with left atrial enlargement, (abnormal left ventricular end-systolic dimension >50 mm by M-Mode or 2-D Echocardiography or abnormal left ventricular end-diastolic dimension > 70 mm as measured by M-Mode or 2-D Echocardiography)?

   ❒ Yes ❒ No

8. Ejection fractions as follows:[17]

| | | | | | |
|---|---|---|---|---|---|
| 50% - 60% | ❒ Yes | ❒ No | 30% - 34% | ❒ Yes | ❒ No |
| 40% - 49% | ❒ Yes | ❒ No | <30% | ❒ Yes | ❒ No |
| 35% - 39% | ❒ Yes | ❒ No | | | |

9. Surgery to repair or replace the aortic and/or mitral valve(s) **after** use of Pondimin® and/or Redux™?

   ❒ Yes ❒ No

10. Severe regurgitation and the presence of ACC/AHA Class I indications for surgery to repair or replace the aortic[18] and/or mitral[19] valve(s) where such surgery was not performed?

    ❒ Yes ❒ No

    a. Was valvular repair/replacement surgery medically indicated but the patient declined to consent to surgery?

    ❒ Yes ❒ No

    b. Was valvular repair/replacement surgery medically contra-indicated?

    ❒ Yes ❒ No

    **If your answer to 10 was "Yes"—Please supply (at end of form) or attach a written statement from the attending Board-Certified Cardiologist or Cardiothoracic Surgeon supported by medical records regarding the recommendation made to the patient concerning valvular surgery with the reason that surgery was not performed.**

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[14] Weyman, A. E. *Principles and Practice of Echocardiography*, Philadelphia, Lea & Febiger. pp. 1290-1292 (1994).

[15] Henry, W.L. *et. al.*, Report of the American Society of Echocardiography Committee on Nomenclature and Standards in Two-dimensional Echocardiography, *Circulation*, 62:212-17 (1980).

[16] Bonow, 1275 *supra* at 32:1533-35.

[17] Bonow, *supra*.

[18] *Id.* at 32:1510-14.

[19] *Id.* at 32:1533-35.

11. Stroke due to (a) bacterial endocarditis contracted after use of Pondimin® and/or Redux™, or (b) chronic atrial fibrillation with left atrial enlargement as defined above, or (c) valvular repair and/or replacement surgery which has resulted in a permanent condition which meets the criteria for the following functional levels of the AHA Stroke Outcome Classification System,[20] determined six months after the event:

a. Functional Level II ☐ Yes ☐ No
b. Functional Level III ☐ Yes ☐ No
c. Functional Level IV ☐ Yes ☐ No
d. Functional Level V ☐ Yes ☐ No

12. A peripheral embolus due to Bacterial Endocarditis and/or as a consequence of atrial fibrillation with left atrial enlargement as defined above which resulted in:

a. Severe impairment to the kidneys, defined as chronic severe renal failure requiring hemodialysis or Continuous Abdominal Peritoneal Dialysis for more than six months.

☐ Yes ☐ No

b. Severe impairment to the abdominal organs, defined as impairment requiring intra-abdominal surgery.

☐ Yes ☐ No

c. Severe impairment to the extremities, defined as impairment requiring amputation of a major limb.

☐ Yes ☐ No

**G. Does the above named Diet Drug Recipient have New York Heart Association Functional Class symptoms as follows:**

1. Class I ☐ Yes ☐ No
2. Class II ☐ Yes ☐ No
3. Class III ☐ Yes ☐ No
4. Class IV ☐ Yes ☐ No

**H. Did the above-named Diet Drug Recipient have valvular repair or replacement surgery and have one more of the following complications either during surgery, within 30 days after surgery, or during the same hospital stay as surgery:**

1. Renal failure, defined as chronic, severe renal failure requiring regular hemodialysis or Continuous Abdominal Peritoneal Dialysis (CAPD) for greater than six months following aortic and/or mitral valve replacement surgery?

   ☐ Yes ☐ No

2. Peripheral embolus following surgery resulting in severe permanent impairment of the kidneys, abdominal organs, or extremities?

   ☐ Yes ☐ No

3. Quadriplegia or paraplegia resulting from cervical spine injury during valvular heart surgery?

   ☐ Yes ☐ No

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[20] *The American Heart Association Stroke Outcome Classification*, approved by the American Heart Association Science Advisory and Coordinating Committee, 29 Stroke 1274-80, 1275 (1998).

Did the above-named Diet Drug Recipient have valve repair or replacement surgery and have:

1. Post-operative endocarditis, mediastinitis or sternal osteomyelitis, any of which required reopening of the median sternotomy for treatment?

   ☐ Yes ☐ No

2. A post-operative serious infection defined as HIV or Hepatitis C within six months of surgery as a result of blood transfusion associated with the surgery?

   ☐ Yes ☐ No

**Did the above-named Diet Drug Recipient have valvular repair or replacement surgery and require a second surgery through the sternum within 18 months of the initial surgery due to prosthetic valve malfunction, poor fit, or complications reasonably related to the initial surgery?**

☐ Yes ☐ No

**Did the above-named Diet Drug Recipient have valvular repair or replacement surgery and have a left ventricular ejection fraction of < 40% six months after the valvular repair or replacement surgery?**

☐ Yes ☐ No

**Did the above-named Diet Drug Recipient have one or more of the following:**

1. A heart transplant?

   ☐ Yes ☐ No

2. Irreversible pulmonary hypertension secondary to valvular heart disease defined as peak-systolic pulmonary artery pressure >50 mm Hg[21] (by cardiac catheterization), at rest, following repair or replacement surgery of the aortic and/or mitral valve(s)?

   ☐ Yes ☐ No

3. A persistent non-cognitive state[22] caused by a complication of valvular heart disease (e.g., cardiac arrest) or valvular repair/replacement surgery?

   ☐ Yes ☐ No

   **If the individual has such a condition, please supply a detailed statement of the attending Board-Certified Cardiologist or Cardiothoracic Surgeon supported by medical records setting forth the basis for your opinion that the persistent non-cognitive state was caused by a complication of valvular heart disease or valvular repair/replacement surgery.**

4. Death resulting from a condition caused by valvular heart disease or valvular repair/replacement surgery?

   ☐ Yes ☐ No

   **Please supply a detailed statement of the attending Board-Certified Cardiologist or Cardiothoracic Surgeon supported by medical records setting forth your opinion that the patient's death resulted from a condition caused by valvular heart disease and/or valvular repair/replacement surgery.**

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[21] Braunwald, *supra* at 596-98.

[22] Adelman, G., *Encyclopedia of Neuroscience*, Birkhauser; Boston, MA, p. 268 (1987).

5. Ventricular fibrillation or sustained ventricular tachycardia which results in hemodynamic compromise?

☐ Yes ☐ No

If su

6. Endocardial Fibrosis (A) diagnosed by (1) endomyocardial biopsy that demonstrates fibrosis and cardiac catheterization that demonstrates restrictive cardiomyopathy or (2) autopsy that demonstrates endocardial fibrosis and (B) other causes including dilated cardiomyopathy, myocardial infarction, amyloid, Loeffler's endocarditis, endomyocardial fibrosis as defined in Braunwald (involving one or both ventricles, located in the inflow tracts of the ventricles, commonly involving the chordae tendineae, with partial obliteration of either ventricle commonly present)[23], focal fibrosis secondary to valvular regurgitation, e.g., "jet lesions", focal fibrosis secondary to catheter instrumentation, and hypertrophic cardiomyopathy with septal fibrosis have been excluded?

1.

2.

☐ Yes ☐ No

**This form is an official court document sanctioned by the Court that presides over the Diet Drug Settlement and submitting it to the Claims Administrators is equivalent to filing it with a Court. I declare under penalty of perjury, that the information provided in this form is correct to the best of my knowledge, information and belief.**

(Date) (Signature of Board-Certified Physician)

## For Use With Written Statements

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[23] Braunwald, *supra* at 1433-34.

## Part III - Claimant's Lawyer Statement

you checked the box marked "Yes" in Question 9, have your lawyer complete this statement and bmit it with your completed GREEN FORM.

Provide the following information about your Diet Drug Settlement Claimant client ("Your Client"):

_____
(Name of your Client)

Provide the following information about yourself:

_____
(Law Firm Name)

_____
(Attorney's Name)

_____
(Street Address)

_____
(City) (State) (Zip Code)

(_____)_____ (_____)_____
(Daytime Phone Number, & Area Code) (Fax Number)

_____
(E-mail Address, if any)

Please attach a copy of the contingent fee agreement between yourself and Your Client.

State the amount of out-of-pocket costs incurred by you in your representation of Your Client for his/her diet drug claim. (Please attach a copy of your cost sheet to this form.) $_____

Has a subrogation lien or claim been asserted with respect to Your Client's right to receive benefits under the Diet Drug Settlement? ☐ Yes ☐ No

If your answer is "Yes," please identify by whom and the amount: $_____

_____
(Name)

_____
(Address)

_____
(City) (State) (Zip Code)

Does the Claimant contest the lien. ☐ Yes ☐ No

If yes, describe:_____

This form is an official document sanctioned by the Court that presides over the Diet Drug Settlement, and submitting it to the Claims Administrators is equivalent to filing it with a court. I declare under penalty of perjury that all of the information provided in this form is true and correct to the best of my knowledge, information and belief.

_____
(Date) (Signature)

_____
(Print Name)

# Settlement Matrix Compensation Benefits Guide for Physicians, Attorneys and Class Members

A. A nationwide Class Action Settlement has been reached with American Home Products Corporation which will resolve the claims of individuals who took the diet drugs Pondimin® and/or Redux™.

B. Under the Settlement, patients who took the diet drugs Pondimin® and/or Redux™ have a right to receive compensation if they have developed serious levels of valvular heart disease.

C. The amounts which individuals are entitled to recover under this Settlement depend on the person's age at diagnosis of valvular heart disease, the person's "Level of Severity" and additional criteria as set forth below. Payments will be made according to these "Matrices":

**Matrix A-1** *Age at diagnosis/event*

| Severity | ≤ 24 | 25-29 | 30-34 | 35-39 | 40-44 | 45-49 | 50-54 | 55-59 | 60-64 | 65-69 | 70 - 79 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| I | $123,750 | $117,563 | $111,685 | $106,10 | $100,795 | $95,755 | $90,967 | $86,419 | $82,098 | $73,888 | $36,944 |
| II | $643,500 | $611,325 | $580,759 | $551,721 | $524,135 | $497,928 | $473,032 | $449,381 | $426,912 | $384,221 | $192,111 |
| III | $940,500 | $893,475 | $848,801 | $806,361 | $766,043 | $727,741 | $691,354 | $656,786 | $623,947 | $561,552 | $280,776 |
| IV | $1,336,500 | $1,269,675 | $1,206,191 | $1,145,881 | $1,088,587 | $1,034,158 | $982,450 | $933,327 | $886,661 | $797,995 | $398,998 |
| V | $1,485,000 | $1,410,750 | $1,340,213 | $1,273,202 | $1,209,542 | $1,149,065 | $1,091,612 | $1,037,031 | $985,180 | $886,662 | $443,331 |

**Matrix B-1** *Age at diagnosis/event*

| Severity | ≤ 24 | 25-29 | 30-34 | 35-39 | 40-44 | 45-49 | 50-54 | 55-59 | 60-64 | 65-69 | 70 - 79 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| I | $24,750 | $23,513 | $22,337 | $21,221 | $20,159 | $19,152 | $18,194 | $17,284 | $16,420 | $14,778 | $7,389 |
| II | $128,700 | $122,265 | $116,152 | $110,344 | $104,827 | $99,586 | $94,606 | $89,876 | $85,383 | $76,844 | $38,422 |
| III | $188,100 | $178,695 | $169,760 | $161,272 | $153,208 | $145,548 | $138,270 | $131,357 | $124,790 | $112,310 | $56,155 |
| IV | $267,300 | $253,935 | $241,238 | $229,176 | $217,717 | $206,831 | $196,489 | $186,665 | $177,332 | $159,599 | $79,800 |
| V | $297,000 | $282,150 | $268,043 | $254,641 | $241,908 | $229,813 | $218,322 | $207,406 | $197,036 | $177,332 | $88,666 |

D. The circumstances which determine whether "Matrix A-1" or "Matrix B-1" is applicable are as follows:

1. For Matrix A-1: Diet Drug Recipients who ingested Pondimin® and/or Redux™ for 61 or more days, who were diagnosed as FDA Positive, whose conditions are eligible for matrix payments but who do not have any condition or circumstance which makes Matrix B-1 applicable, receive payments on Matrix A-1.

2. For Matrix B-1: Diet Drug Recipients who are eligible for matrix payments and to whom one or more of the following conditions apply, receive payments on Matrix B-1:

   - For claims as to the mitral valve, Diet Drug Recipients who were diagnosed as having Mild Mitral Regurgitation (regardless of the duration of ingestion of Pondimin® and/or Redux™).

- Diet Drug Recipients who ingested Pondimin® and/or Redux™ for 60 days or less, who were diagnosed as FDA Positive.
- Diet Drug Recipients who ingested Pondimin® and/or Redux™ for 61 or more days, who were diagnosed as FDA Positive with any of the following conditions:

**With respect to an aortic valve claim:**

- The following congenital aortic valve abnormalities: unicuspid, bicuspid or quadricuspid valves, ventricular septal defect associated with aortic regurgitation;
- Aortic dissection involving the aortic root and/or aortic valve;
- Aortic sclerosis in people who are ≥ 60 years old as of the time they are first diagnosed as FDA Positive;
- Aortic root dilatation >5.0 cm;
- Aortic stenosis with an aortic valve area <1.0 square centimeter by the Continuity Equation.

**With respect to a mitral valve claim:**

- The following congenital mitral valve abnormalities: parachute valve, cleft of the mitral valve associated with atrial septal defect;
- Mitral Valve Prolapse as determined by Echocardiogram. "Mitral Valve Prolapse" refers to a condition where (a) the echoardiogram video tape or disk includes the parasternal long axis view and (b) that echocardiographic view shows displacement of one or both mitral leaflets >2mm above the atrial-ventricular border during systole, and >5mm leaflet thickening during diastole, as determined by a Board-Certified Cardiologist.
- Chordae tendineae rupture or papillary muscle rupture; or acute myocardial infarction associated with acute mitral regurgitation;
- Mitral annular calcification;
- M-Mode and 2-D Echocardiographic evidence of rheumatic mitral valves (doming of the anterior leaflet and/or anterior motion of the posterior leaflet and/or commissural fusion), except where there is no evidence of rheumatic valve disease upon pathological examination of mitral valve tissue.

**With respect to claims for the aortic and/or mitral valve(s):**

- Heart valve surgery prior to Pondimin® and/or Redux™ use on the valve that is the basis of claim;
- Bacterial endocarditis prior to Pondimin® and/or Redux™ use;
- FDA Positive regurgitation (confirmed by Echocardiogram) prior to Pondimin® and/or Redux™ use for the valve that is the basis of claim;
- Systemic Lupus Erythematosus or Rheumatoid Arthritis[1] and valvular regurgitation and/or valvular abnormalities of a type associated with those conditions[2];
- Carcinoid tumor of a type associated with aortic and/or mitral valve lesions;
- History of daily use of methysergide or ergotamines for a continuous period of longer than 120 days.

E. Diet Drug Recipients' spouses, children and "significant others" ("Derivative Claimants") may also be eligible for Matrix Payments under the law, and if so, they will be paid an amount set forth in one of "Derivative Matrices"— Matrix A-2 or Matrix B-2. Derivative Claimants will be paid at the same "Level of Severity" and age at diagnosis as the Diet Drug Recipient. Matrix A-2 will be used where the Diet Drug Recipient was eligible for Matrix A-1 payments and Matrix B-2 will be used where the Diet Drug Recipient was eligible for Matrix B-1 payments.

Matrix A-2 *Age at diagnosis/event*

| Severity | ≤24 | 25-29 | 30-34 | 35-39 | 40-44 | 45-49 | 50-54 | 55-59 | 60-64 | 65-69 | 70 - 79 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| I | $1 250 | $1,187 | $1,128 | $1,072 | $1,018 | $967 | $919 | $873 | $829 | $739 | $560 |
| II | $6,500 | $6,175 | $5 866 | $5,573 | $5,294 | $5,030 | $4,778 | $4 539 | $4,312 | $3 842 | $1 921 |
| III | $9,500 | $9,025 | $8,574 | $8,145 | $7,738 | $7,351 | $6,983 | $6,634 | $6,302 | $5,616 | $2,808 |
| IV | $13 500 | $12 825 | $12,184 | $11,575 | $10,996 | $10,446 | $9,924 | $9 428 | $8,956 | $7 980 | $3 990 |
| V | $15,000 | $14,250 | $13,537 | $12,861 | $12,218 | $11,607 | $11,026 | $10,475 | $9 951 | $8,867 | $4 433 |

Matrix B-2 *Age at diagnosis/event*

| Severity | ≤24 | 25-29 | 30-34 | 35-39 | 40-44 | 45-49 | 50-54 | 55-59 | 60-64 | 65-69 | 70 - 79 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| I | $500 | $500 | $500 | $500 | $500 | $500 | $500 | $500 | $500 | $500 | $500 |
| II | $1,300 | $1,235 | $1,173 | $1,115 | $1,059 | $1,006 | $956 | $908 | $862 | $768 | $500 |
| III | $1,900 | $1,805 | $1,715 | $1,629 | $1,548 | $1 470 | $1,397 | $1,327 | $1,260 | $1,123 | $562 |
| IV | $2,700 | $2,565 | $2,437 | $2,315 | $2,199 | $2,089 | $1,985 | $1 885 | $1,791 | $1 596 | $798 |
| V | $3,000 | $2,850 | $2,707 | $2,572 | $2,444 | $2,321 | $2,205 | $2,095 | $1,990 | $1,773 | $886 |

F. Under the matrices, the "Levels of Severity" which qualify Diet Drug Recipients for recovery on the Settlement matrices are as follows:

(1) **Matrix Level I** is severe left sided valvular heart disease without complicating factors, and is defined as one of the following:

(a) Severe aortic regurgitation (AR) > 50% jet height/left ventricular outflow tract height (JH/LVOTH)[3] and/or severe mitral regurgitation (MR) > 40% regurgitant jet area/left atrial area (RJA/LAA)[4,5] and no complicating factors as defined below;

(b) FDA Positive valvular regurgitation[6] with bacterial endocarditis contracted after commencement of Pondimin® and/or Redux™ use.

(2) **Matrix Level II** is left sided valvular heart disease with complicating factors, and is defined as:

(a) Moderate AR (25% - 49% JH/LVOTH)[7] or Severe AR (> 50% JH/LVOTH)[8] with one or more of the following:

i) Pulmonary hypertension secondary to severe aortic regurgitation with a peak systolic pulmonary artery pressure > 40 mm Hg measured by cardiac catheterization or with a peak systolic pulmonary artery pressure > 45 mm Hg[9] measured by Doppler Echocardiography, at rest, utilizing standard procedures[10,11] assuming a right atrial pressure of 10 mm Hg;

ii) Abnormal left ventricular end-systolic dimension > 50 mm[12] by M-mode or 2-D Echocardiography or abnormal left ventricular end-diastolic dimension > 70 mm[13] as measured by M-mode or 2-D Echocardiography;

iii) Ejection fraction of < 50%[14]; and/or

(b) Moderate MR (20% - 40% RJA/LAA)[15] or Severe MR (> 40% RJA/LAA)[16] with one or more of the following:

i) Pulmonary hypertension secondary to valvular heart disease with peak systolic pulmonary artery pressure > 40 mm Hg measured by cardiac catheterization or with a peak systolic pulmonary artery pressure > 45 mm Hg[17] measured by Doppler Echocardiography, at rest, utilizing the procedures described in Section F.2.(a)(i);

ii) Abnormal left atrial supero-inferior systolic dimension > 5.3 cm[18] (apical four chamber view) or abnormal left atrial antero-posterior systolic dimension > 4.0 cm (parasternal long axis view) measured by 2-D directed M-mode or 2-D echocardiography with normal sinus rhythm using sites of measurement recommended by the American Society of Echocardiography[19];

iii) Abnormal left ventricular end-systolic dimension ≥ 45 mm[20] by M-mode or 2-D Echocardiogram;

iv) Ejection fraction of ≤ 60%[21].

v) Arrhythmias, defined as chronic atrial fibrillation/flutter that cannot be converted to normal sinus rhythm, or atrial fibrillation/flutter requiring ongoing medical therapy, either of which are associated with left atrial enlargement; as defined in Section F.2.(b)(ii).

(3) **Matrix Level III** is left sided valvular heart disease requiring surgery or conditions of equal severity, and is defined as:

(a) Surgery to repair or replace the aortic and/or mitral valve(s) following the use of Pondimin® and/or Redux™; or

(b) Severe regurgitation and the presence of ACC/AHA Class I indications for surgery to repair or replace the aortic[22] and/or mitral[23] valve(s) and a statement from the attending Board Certified Cardiothoracic Surgeon or Board Certified Cardiologist supported by medical records regarding the recommendations made to the patient concerning valvular surgery, with the reason why the surgery is not being performed; or

(c) Qualification for payment at Matrix Level I(b) (as described in Section F.1.b. above) or Matrix Level II and, in addition, a stroke due to bacterial endocarditis contracted after use of Pondimin® and/or Redux™ or as a consequence of chronic atrial fibrillation with left atrial enlargement as defined in Section F.2.(b)(ii) which results in a permanent condition which meets the criteria of AHA Stroke Outcome Classification[24] Functional Level II, determined six months after the event.

(4) **Matrix Level IV** is defined as follows:

(a) Qualification for payment at Matrix Level I(b) (as described in Section F.1.b. above), II or III and, in addition, a stroke due to bacterial endocarditis contracted after use of Pondimin® and/or Redux™ or as a consequence of chronic atrial fibrillation with left atrial enlargement as defined in Section F.2.(b)(ii) which results in a permanent condition which meets the criteria of AHA Stroke Outcome Classification[25] Functional Level III, determined six months after the event; or

(b) Qualification for payment at Matrix Level I(b), II, or III and, in addition, a peripheral embolus due to Bacterial Endocarditis contracted after use of Pondimin® and/or Redux™ or as a consequence of atrial fibrillation with left atrial enlargement as defined in Section F.2.(b)(ii) which results in severe permanent impairment to the kidneys, abdominal organs, or extremities, where severe permanent impairment means:

i) for the kidneys, chronic severe renal failure requiring hemodialysis or Continuous Abdominal Peritoneal Dialysis for more than six months;

ii) for the abdominal organs, impairment requiring intra-abdominal surgery;

iii) for the extremities, impairment requiring amputation of a major limb; or

(c) The individual has the following:

i) Qualification for payment at Matrix Level III; and

ii) New York Heart Association Functional Class I or Class II symptoms as documented by the attending Board Certified Cardiothoracic Surgeon or Board Certified Cardiologist; and

iii) Valvular repair and replacement surgery or ineligibility for surgery due to medical reasons as documented by the attending Board Certified Cardiothoracic Surgeon or Board-Certified Cardiologist; and

iv) Significant damage to the heart muscle, defined as: (a) a left ventricular ejection fraction < 30% with aortic regurgitation or a left ventricular ejection fraction < 35% with mitral regurgitation in patients who have not had surgery and meet the criteria of Section F.3.(b) or (b) a left ventricular ejection fraction < 40% six months after valvular repair or replacement surgery in patients who have had such surgery; or

(d) The individual has had valvular repair or replacement surgery and has one or more of the following complications which occur either during surgery, within 30 days after surgery, or during the same hospital stay as the surgery:

i) Renal failure, defined as chronic, severe renal failure requiring regular hemodialysis or Continuous Abdominal Peritoneal Dialysis for greater than six months following aortic and/or mitral valve replacement surgery;

ii) Peripheral embolus following surgery resulting in severe permanent impairment to the kidneys, abdominal organs, or extremities;

iii) Quadriplegia or paraplegia resulting from cervical spine injury during valvular heart surgery; or

(e) A stroke caused by aortic and/or mitral valve surgery and the stroke has produced a permanent condition which meets the criteria of the AHA Stroke Outcome Functional Levels II or III determined six months after the event.[26]

(f) The individual has had valvular repair or replacement surgery and suffers from post operative endocarditis, mediastinitis or sternal osteomyelitis, either of which requires reopening the median sternotomy for treatment, or a post-operative serious infection defined as HIV or Hepatitis C within six months of surgery as a result of blood transfusion associated with the heart valve surgery.

(g) The individual has had valvular repair or replacement surgery and requires a second surgery through the sternum within 18 months of the initial surgery due to prosthetic valve malfunction, poor fit, or complications reasonably related to the initial surgery.

(5) **Matrix Level V** is defined as:

(a) Endocardial Fibrosis (A) diagnosed by (1) endomyocardial biopsy that demonstrates fibrosis and cardiac catheterization that demonstrates restrictive cardiomyopathy or (2) autopsy that demonstrates endocardial fibrosis and (B) other causes, including dilated cardiomyopathy, myocardial infarction, amyloid, Loeffler's endocarditis, endomyocardial fibrosis as defined in Braunwald (involving one or both ventricles, located in the inflow tracts of the ventricles, commonly involving the chordae tendineae, with partial obliteration of either ventricle commonly present)[27], focal fibrosis secondary to valvular regurgitation (*e.g.*, "jet lesions"), focal fibrosis secondary to catheter instrumentation, and hypertrophic cardiomyopathy with septal fibrosis, have been excluded; or

(b) Left sided valvular heart disease with severe complications, defined as Matrix Levels I(b) (as described in Section F.1.b. above), III or IV above with one or more of the following:

i) A severe stroke following aortic and/or mitral valve surgery or due to bacterial endocarditis contracted after use of Pondimin® and/or Redux™ or as a consequence of chronic atrial fibrillation with left atrial enlargement as defined in Section F.2.b.(ii) and the severe stroke has resulted in a permanent condition which meets the criteria of AHA Stroke Outcome Classification[28] Functional Levels IV or V, determined six months after the event; or

ii) The individual has the following:

a) Qualification for payment at Matrix Levels III or IV; and

b) New York Heart Association Functional Class III or Class IV symptoms as documented by the attending Board-Certified Cardiothoracic Surgeon or Board-Certified Cardiologist; and

c) Valvular repair or replacement surgery or ineligibility for surgery due to medical reasons as documented by the attending Board-Certified Cardiothoracic Surgeon or Board-Certified Cardiologist; and

d) Significant damage to the heart muscle, defined as: (i) a left ventricular ejection fraction < 30% with aortic regurgitation or a left ventricular ejection fraction < 35% with mitral regurgitation, in patients who have not had surgery and meet the criteria of Section F.3.b.

or (ii) a left ventricular ejection fraction < 40% six months after valvular repair or replacement surgery in patients who have had such surgery; or

iii) Heart transplant;

iv) Irreversible pulmonary hypertension (PH) secondary to valvular heart disease defined as peak-systolic pulmonary artery pressure > 50 mm Hg[29] (by cardiac catheterization) at rest following repair or replacement surgery of the aortic and/or mitral valve(s);

v) Persistent non-cognitive state[30] caused by a complication of valvular heart disease (e.g., cardiac arrest) or valvular repair/replacement surgery supported by a statement from the attending Board Certified Cardiothoracic Surgeon or Board Certified Cardiologist, supported by medical records; or

(c) Death resulting from a condition caused by valvular heart disease or valvular repair/replacement surgery which occurred post-Pondimin® and/or Redux™ use supported by a statement from the attending Board Certified Cardiothoracic Surgeon or Board Certified Cardiologist, supported by medical records; or

(d) The individual otherwise qualifies for payment at Matrix Level II, III, or IV and suffers from ventricular fibrillation or sustained ventricular tachycardia which results in hemodynamic compromise.

In defining the "Levels of Severity" which qualify class members for matrix compensation benefits, the Settlement requires the application of a standardized methodology or protocol. Endnotes have been used in the description of levels of valvular heart disease to indicate reference to a standardized methodology or protocol. The referenced methodologies or protocols, together with the corresponding endnote, are as follows:

## ENDNOTES

*See Harrison's Principles of Internal Medicine,* 1878, 1885 (14th ed. 1998).

*See* C. Otto, *The Practice of Clinical Echocardiography,* 589-91, 592-93 (1997):

Mitral regurgitation can be associated with rheumatoid arthritis. The mitral valve may have the following hocardiographic features: rheumatoid nodules present-usually <0.5 cm in diameter; may occur at any loca-)n on leaflet, homogeneous soft tissue reflectance and irregular body border; usually rounded shape.

The following echocardiographic features of valvular abnormalities associated with Systemic Lupus ·thematosus include: diffuse valvular thickening-aortic and mitral valves, decreased leaflet mobility, and ·sence of Libman-Sacks vegetations, usually <1 cm in diameter.

*See* J.P. Singh, et al., "Prevalence and Clinical Determinants of Mitral, Tricuspid and Aortic Regurgitation The Framingham Heart Study)," *American J. Cardiology,* 83:897-902 (1999):

| GRADES | MR | AR |
|---|---|---|
| Absent | -- | -- |
| Trace | w/in 1 cm of valve | JH/LVOH < 10% |
| Mild | RJA/LAA < 19% | 10%-24% |
| Moderate | 20%-40% | 25%-49% |
| Severe | >41% | >50% |

Valvular regurgitation was assessed qualitatively using these semiquantitative categories as guidelines.
JH= jet height; LAA= left atrial area; LVOH= left ventricular outflow height; RAA= right atrial area; RJA= regurgitant jet area; w/in= within.

Conventional pulsed Doppler echocardiography was performed routinely in apical 4- and 5-chamber views by selective placement of the sample volume on the color Doppler echocardiographic regurgitation signals when present. Valvular regurgitation was diagnosed using color-coded Doppler imaging proximal to the valve plane during its closure and extended into the chamber proximal to the valve. For color Doppler studies, gain settings were adjusted to eliminate background speckling and to maximize the extent of intracavity velocity coding. MR was sought from the parasternal long-axis, apical 4- and 2-chamber, apical long-axis, and subcostal views. AR was sought using the parasternal long-axis, parasternal short-axis, apical 5-chamber, and apical long-axis views.

MR was considered to be present if blue, green, or mosaic signals were seen originating from the mitral valve and spreading into the left atrium during systole. AR was considered to be present if red, yellow, or mosaic signals (blue in the parasternal long axis) were seen originating from the aortic valve and spreading into the left ventricle during diastole. Valvular regurgitation was assessed qualitatively using semiquantitative guidelines and graded none, trace, mild, moderate, or severe (Table I).

4. *Id.*

5. Helmcke, F., Nanda, N.C., Hsiung, M.C., Soto, B., Adey, C.K., Goyal, R.G., Gatewood, R.P., Jr., "Color Doppler Assessment of Mitral Regurgitation with Orthogonal Planes," *Circulation,* 75(1):175-83 (1987):

Three two-dimensional echocardiographic planes (parasternal long and short axis, apical four-chamber view) were used to analyze variables of the mitral regurgitant jet signals in the left atrium. The best correlation with angiography was obtained when the regurgitant jet area (RJA) (maximum or average from three planes) expressed as a percentage of the left atrial area (LAA) obtained in the same plane as the maximum regurgitant area was considered. The maximum RJA/LAA was under 20% in 34 of 36 patients with angiographic grade I mitral regurgitation, between 20% and 40% in 17 of 18 patients with grade II mitral regurgitation, and over 40% in 26 of 28 patients with severe mitral regurgitation.

6. *See* Centers for Disease Control and Prevention, "Cardiac Valvulopathy Associated with Exposure to Fenfluramine or Dexfenfluramine: US Department of Health and Human Services Interim Public Health Recommendations," *MMWR Morb. And Mortal. Wkly Rep.*, 46:1061-66 (1997):

Minimal degrees of regurgitation (i.e., trace or mild mitral regurgitation [MR] or trace aortic regurgitation [AR]) are relatively common in the general population and are not generally considered abnormal. Therefore, in this analysis, a case of fenfluramine- or dexfenfluramine-associated cardiac valvulopathy was defined as documented AR of mild or greater severity and/or MR of moderate or greater severity after exposure to these drugs.

7. *See* Singh, *supra,* note 3.

8. *Id.*

9. E. Braunwald, *Heart Disease. A Textbook of Cardiovascular Medicine* 796-98 (1997):

Although pulmonary hypertension is widely recognized as developing in patients with left atrial hypertension due to mitral stenosis, it can also occur in patients with pure mitral regurgitation. In one series, nearly half of a cohort of 41 patients with severe mitral regurgitation had pulmonary artery systolic pressures in excess of 50 mm Hg (citation omitted).

Left ventricular diastolic failure may result from hypertension; aortic stenosis; ischemic heart disease; hypertrophic restrictive and congestive cardiomyopathies; and constrictive pericarditis. Because chronic increases in mean left ventricular filling pressure exceeding 25mm Hg are uncommon, the resulting pulmonary arterial hypertension is only moderate unless reactive pulmonary hypertension also occurs. In the absence of the latter, a normal pulmonary artery mean pressure of 15 mm Hg may arise to approximately 30 mm Hg as a result of left ventricular diastolic dysfunction. Because cardiac output is usually reduced in such patients, the mean pulmonary artery pressure would be considerably less than 30 mm Hg if pulmonary vascular resistance remains unchanged. However, many patients with left ventricular diastolic dysfunction exhibit increased pulmonary vascular resistance and moderately severe pulmonary hypertension.

H. Feigenbaum, *Echocardiography* 201-03 (5th ed. 1994):

"he principle technique for determining pulmonary artery pressure involves the use of the tricuspid urgitant jet and the Bernoulli equation. By determining the right ventricular systolic pressure and ruling the existence of any obstruction in the right ventricular outflow tract, one can determine the pulmonary ery systolic pressure. This technique is probably the most accurate for quantitating pulmonary artery pres- e (citation omitted).

K.L. Chan, et al., "Comparison of Three Doppler Ultrasound Methods in the Prediction of Pulmonary Artery Pressure," *JACC* 9:549-54 (1987):

'ulmonary artery pressure was noninvasively estimated by three Doppler echocardiographic methods in consecutive patients undergoing cardiac catheterization. First, a systolic transtricuspid gradient was cal- ated from Doppler-detected triscuspid regurgitation; clinical jugular venous pressure or a fixed value of mm Hg was added to yield systolic pulmonary artery pressure. Second, acceleration time from pulmonary v analysis was used in a regression equation to derive mean pulmonary artery pressure. Third, right ven- ular isovolumic relaxation time was calculated from Doppler-determined pulmonary valve closure and uspid valve opening; systolic pulmonary artery pressure was then derived from a nomogram.

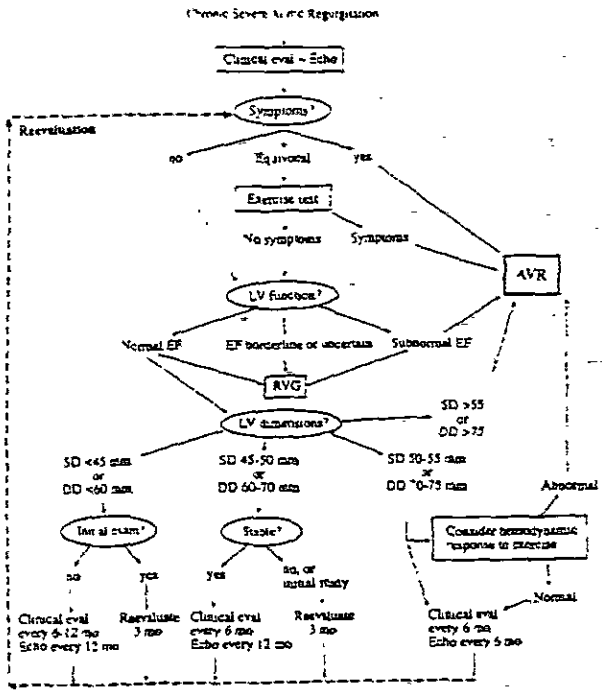
n 48 patients (96%) at least one of the methods could be employed. A tricuspid pressure gradient, ained in 36 patients (72%), provided reliable prediction of systolic pulmonary artery pressure. The pre- tion was superior when 14 mm Hg rather than estimated jugular venous pressure was used to account for rt atrial pressure. In 44 patients (88%), pulmonary artery flow was analyzed. Prediction of mean pul- nary artery pressure was unsatisfactory (r= 0.65) but improved (r= 0.85) when only patients with a heart e between 60 and 100 beats/min were considered. The effect of correcting pulmonary flow indexes for rt rate was examined by correlating different flow indexes before and after correction for heart rate. There s a good correlation between corrected acceleration time and either systolic (r= -0.85) or mean (r= -0.83) monary artery pressure. Because of a high incidence of arrhythmia, right ventricular relaxation time uld be determined in only 11 patients (22%).

Noninvasive prediction of pulmonary artery pressure is feasible in most patients. Among the three meth- s, tricuspid gradient measurement seems to be the most useful and practical. Heart rate correction may prove the accuracy of using acceleration time in predicting pulmonary artery pressure; Doppler-deter- ned right ventricular relaxation time seems to be of limited usefulness.

Doppler recordings were obtained from apical, parasternal and subcostal positions. The tricuspid regurgi- on signal moved away from the transducer and consisted of a relatively dense high velocity spectral rep- ntation. Systematic search for the Doppler signal of tricuspid regurgitation was performed to achieve mal recording, which consisted of highest maximal velocity with a distinct envelope on the spectral dis- . No correction was used to compensate for any presumed angle between the ultrasound beam and the ction of maximal velocity flow. The modified Bernoulli equation was employed to derive a systolic stricuspid gradient that equals 4 $v^2$, in which v is the maximal regurgitant velocity in meters per second.

There is no systematic difference in systolic pulmonary artery pressure between the Doppler-derived and nometric measurements. In individual patients, considerable difference may occur. This may be related the variability of the angle between the ultrasound beam and the blood flow. The SEE was similar to that orted in other series (citations omitted). With an estimated pressure of 50 mm Hg, the 95% limits were and 66 mm Hg. Such an estimate is probably within the bounds of clinical usefulness, because pulmonary ery pressure is a dynamic measurement and can vary by more than 30% within a 24 hour period (citation itted).

. *See* R.O. Bonow, et al., "Guidelines for the Management of Patients with Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines" (Committee on Management of Patients with Valvular Heart Disease), *JACC* 32:1510-14 (1998):




**Description of Figure.** Management strategy for *patients with chronic severe aortic regurgitation.* Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is discordance between clinical findings and echocardiography. In some centers, serial follow-up may be performed with RVG or MRI rather than echocardiography to assess LV volume and systolic function.
Abbreviations:
DD= end-diastolic dimension,
RVG= radionuclide ventriculography,
SD= end-systolic dimension.

Asymptomatic patients with normal systolic function but severe AR and significant LV dilatation (end-diastolic dimension > 60mm) require more frequent and careful reevaluation, with a history and physical examination every 6 months and echocardiography every 6 to 12 months, depending on the severity of dilatation and stability of measurements. If stable, echocardiographic measurements are not required more frequently than every 12 months. In patients with more advanced LV dilatation (end-diastolic dimension >70 mm or end-systolic dimension >50 mm), for whom the risk of developing symptoms or LV dysfunction ranges between 10% and 20% per year (citations omitted), it is reasonable to perform serial echocardiograms as frequently as every 4 to 6 months. Serial chest x-rays and ECGs have less value but are helpful in selected patients.

Repeat echocardiograms are also recommended when the patient has onset of symptoms, there is an equivocal history of changing symptoms or exercise tolerance, or there are clinical findings suggesting worsening regurgitation or progressive LV dilatation. Patients with echocardiographic evidence of progressive ventricular dilatation or declining systolic function have a greater likelihood of developing symptoms or LV dysfunction (citation omitted) and should have more frequent follow-up examinations (every 6 months) than those with stable LV function.

*Indications for Aortic Valve Replacement.* In patients with pure, chronic AR, AVR should be considered only if AR is severe. Patients with only mild AR are not candidates for valve replacement, and if such patients have symptoms or LV dysfunction, other etiologies should be considered, such as CAD, hypertension, or cardiomyopathic processes. If the severity of AR is uncertain after a review of clinical and echocardiographic data, additional information may be needed, such as invasive hemodynamic and angiographic data. The following discussion applies only to those patients with pure, severe AR.

(1) SYMPTOMATIC PATIENTS WITH NORMAL LV SYSTOLIC FUNCTION. AVR is indicated in patients with normal systolic function (defined as ejection fraction ≥0.50 at rest) who have NYHA functional Class III or IV symptoms.

New onset of mild dyspnea has different implications in severe AR, especially in patients with increasing LV chamber size or evidence of declining LV systolic function into the low normal range.

(2) SYMPTOMATIC PATIENTS WITH LV DYSFUNCTION. Patients with NYHA-functional Class II, III, or IV symptoms and with mild to moderate LV systolic dysfunction (ejection fraction 0.25 to 0.49) should undergo AVR. Patients with functional Class IV symptoms have worse postoperative survival rates and lower likelihood of recovery of systolic function compared with patients with less severe symptoms, but AVR will improve ventricular loading conditions and expedite subsequent management of LV dysfunction. Symptomatic patients with advanced LV dysfunction (ejection fraction <0.25 and/or end-systolic dimension >60mm) present difficult management issues. Some patients will manifest meaningful recovery of LV function after operation, but many will have developed irreversible myocardial changes. The mortality associated with valve replacement approaches 10%, and postoperative mortality over the subsequent few years is high. Valve replacement should be considered more strongly in patients with NYHA functional Class II and III symptoms, especially if (1) symptoms and evidence of LV dysfunction are of recent onset and (2) intensive short-term therapy with vasodilators, diuretics, and/or intravenous positive inotropic agents results in substantial improvement in hemodynamics or systolic function. However, even in patients with NYHA functional Class IV symptoms and ejection fraction <0.25, the high risks associated with AVR and subsequent medical management of LV dysfunction are usually a better alternative than the higher risks of long-term medical management alone (citations omitted).

(3) ASYMPTOMATIC PATIENTS. AVR in asymptomatic patients remains a controversial topic, but it is generally agreed that valve replacement is indicated in patients with LV systolic dysfunction LV systolic dysfunction is defined as an ejection fraction below normal at rest. The lower limit of normal will be assumed to be 0.50, realizing that this lower limit is technique dependent and may vary among institutions (citation omitted).

It is recommended that 2 consecutive measurements be obtained before proceeding with a decision to recommend surgery in the asymptomatic patient. These consecutive measurements could be obtained with the same test repeated in a short time period (for example, a second echocardiogram after an initial echocardiogram) or with a separate independent test (for example, a radionuclide ventriculogram or a contrast left ventriculogram after an initial echocardiogram).Valve replacement is also recommended in patients with severe LV dilatation (end-diastolic dimension >75mm or end-systolic dimension >55mm), even if ejection fraction is normal.

Patients with severe AR in whom the degree of dilatation has not reached but is approaching these threshold values (for example, LV end-diastolic dimension of 70 to 75 mm or end-systolic dimension of 50 to 55 mm) should be followed carefully with frequent echocardiograms every 4 to 6 months. In addition, it is reasonable to recommend AVR in such patients if there is evidence of declining exercise tolerance or abnormal hemodynamic responses to exercise, for example, an increase in pulmonary artery wedge pressure ≥ 25 mm Hg with exercise.

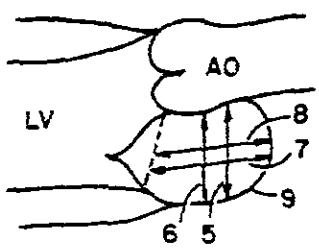
A decrease in ejection fraction during exercise should not be used as an indication for AVR in asymptomatic patients with normal systolic function at rest, because the exercise ejection fraction response is multifactorial and the strength of the evidence is limited. The ejection fraction response to exercise has not proved to have independent prognostic value in patients undergoing surgery (citation omitted).

Valve replacement should also not be recommended in asymptomatic patients with normal systolic function merely because of evidence of LV dilation as long as the dilation is not severe (end-diastolic dimension <75 mm or end-systolic dimension <55 mm). Patients who demonstrate progression of LV dilatation or progressive decline in ejection fraction on serial studies represent a higher-risk group

who require careful monitoring (citation omitted), but such patients often reach a new steady state and may do well for extended periods of time. Hence, valve replacement is not recommended until the threshold values noted above are reached or symptoms or LV systolic dysfunction develop.

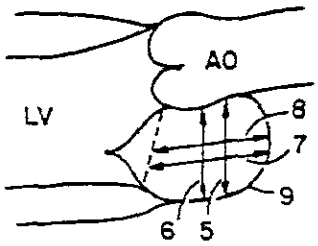
| INDICATION | CLASS |
|---|---|
| 1. Patients with NYHA functional Class III or IV symptoms and preserved LV systolic function, defined as normal ejection fraction at rest (ejection fraction ≥ 0.50). | I |
| 2. Patients with NYHA functional class II symptoms and preserved LV systolic function (ejection fraction ≥ 0.50 at rest) but with progressive LV dilatation or declining ejection fraction at rest on serial studies or declining effort tolerance on exercise testing. | I |
| 3. Patients with Canadian Heart Association functional Class II or greater angina with or without CAD. | I |
| 4. Asymptomatic or symptomatic patients with mild to moderate LV dysfunction at rest (ejection fraction 0.25 to 0.49). | I |
| 5. Patients undergoing coronary artery bypass surgery or surgery on the aorta or other heart valves. | I |

13. *See Id.*
14. *See Id.*
15. *See* Singh, *supra* note 3.
16. *See Id.*
17. *See* Braunwald, *supra* note 9.
18. *See* A.E. Weyman, *Principles and Practice of Echocardiography* 1290-92 (1994).




| PARASTERNAL LONG AXIS VIEW | N | MEAN ± SD* | RANGE |
|---|---|---|---|
| Left Atrium (end-systole): | | | |
| Antero-posterior dimension† | | | |
| 5. Maximal | 62 | 3.0 ± 0.3 | 2.3-3.8 |
| 6. Mid-cavity | 62 | 3.0 ± 0.3 | 2.3-3.8 |

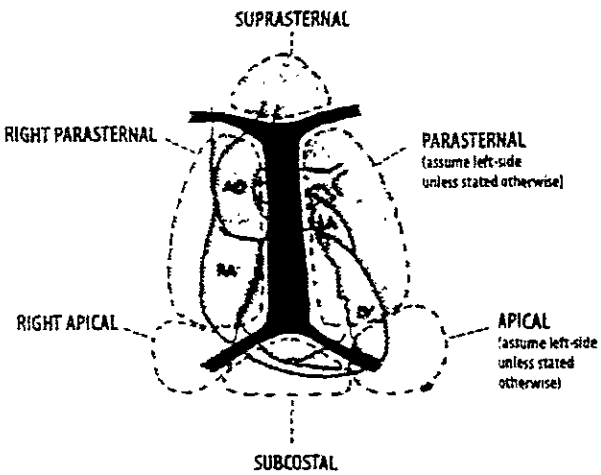
* All linear dimensions are in cm, and areas are in $cm^2$
† Indicates the preferable view for obtaining a particular measurement.




| Apical Four Chamber View | N | Mean ± SD* | Range |
|---|---|---|---|
| Left Atrium (end-systole): | | | |
| Supero-inferior dimension† | | | |
| 44 Maximal | 68 | 4.1 ± 0.6 | 2.9-5.3 |
| 45 Mid-cavity | 68 | 4.0 ± 0.6 | 2.9-5.3 |

* All linear dimensions are in cm, and areas are in cm2
† Indicates the preferable view for obtaining a particular measurement

. *See* W.L. Henry et al., "Report of the American Society of Echocardiography Committee on Nomenclature and Standards in Two-dimensional Echocardiography," *Circulation*, 62:212-17 (1980):

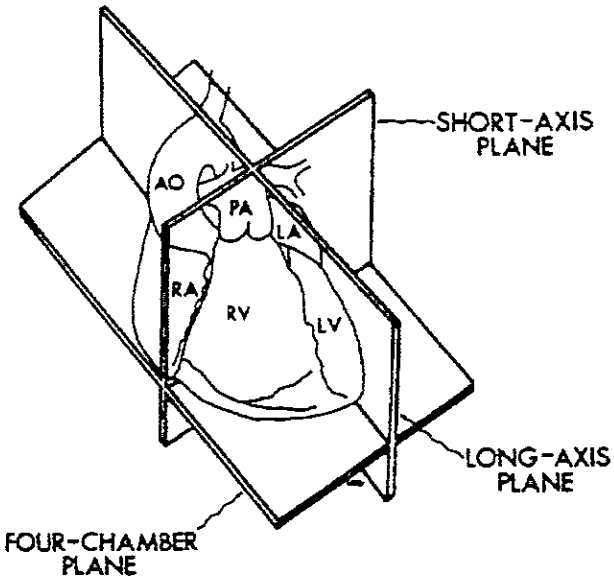



**Discription of figure.** Diagram indicating the nomenclature to describe the locations on the *body from which echocardiographic studies* can be obtained.
AO = aorta;
RA = right atrium;
PA = pulmonary artery;
RV = right ventricule;
LA = left atrium;
LV = left ventricle.

The Committee recommends that when the transducer is placed in the suprasternal notch that it be referred to as in the *suprasternal* location. When the transducer is located near the midline of the body and beneath the lowest ribs, the transducer should be referred to as in the *subcostal* location. When the transducer is located over the apex impulse, the Committee recommends that this be referred to as the *apical* location. If the term *apical* is used alone, it will be assumed that this refers to a *left-sided apical* position. The area bounded superiorly by the left clavicle, medially by the sternum and inferiorly by the apical region will be referred to as the *parasternal* location. If the term *parasternal* is used alone, it will be assumed to be the left parasternal location. In those unusual situations in which the apex impulse is palpated on the right chest, a transducer placed over the right-sided apex impulse will be referred to as in the *right apical* location. The region bounded superiorly by the right clavicle, medially by the sternum and inferiorly by the right apical region will be referred to as the *right parasternal* location.

## Imaging Planes

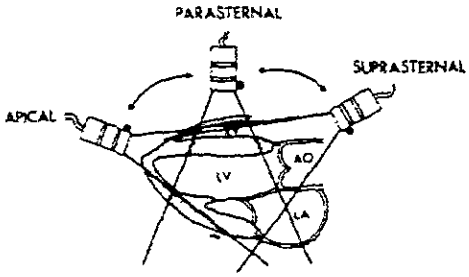
Three orthogonal planes will be used to describe the imaging planes used to visualize the heart with two-dimensional echocardiography. The imaging plane that transects the heart perpendicular to the dorsal and ventral surfaces or the body and parallel to the long axis of the heart will be referred to as the *long-axis* plane. The plane that transects the heart approximately parallel to the dorsal and ventral surfaces of the body will be referred to as the *four-chamber* plane.

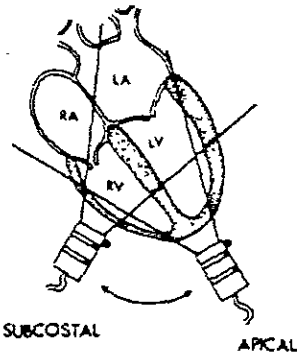


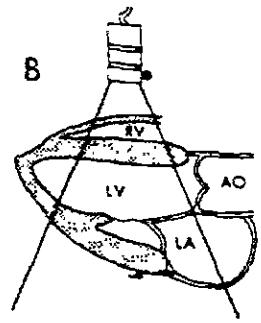

Description of figure. Diagram indicating the nomenclature to describe the locations on the body from which echocardiographic studies can be obtained.
AO = aorta;
RA = Right atrium;
PA = pulmonary artery;
RV = right ventricle;
LA = left atrium
LV = left ventricle.

## Identification of Two-dimensional Images

The Committee recommends that two-dimensional images be identified by referring to the transducer location and the imaging plane. For example, if the transducer is placed in the parasternal location and oriented so that the imaging plane transects the heart parallel to the long-axis of the heart, the Committee recommends that the resulting image be referred to as a *parasternal long-axis* view. As another example, if the transducer is placed in the apical location and oriented so that the four-chamber imaging plane is used, the Committee recommends that the resultant image be referred to as an *apical four-chamber* view.




### Long-Axis View

**Description of figure.** Diagram of the transducer orientation used to obtain the long axis view of the heart. Note that the transducer index mark is always pointed either in the direction of the patient's head or the patient's left side.

### Four-Chamber View

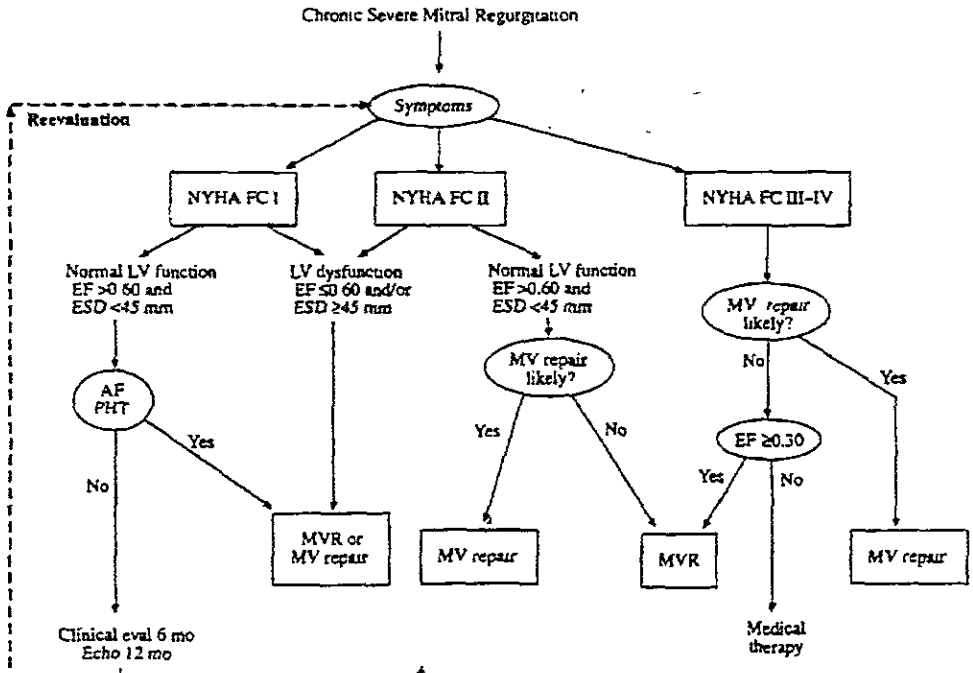
**Description of figure.** Diagram of the transducer orientation used to obtain the four-chamber view of the heart.

### Parasternal Long-Axis

**Description of figure.** Illustration of the long-axis, two-dimensional images that result when the transducer is used to visualize the parasternal long-axis view.

20. *See* R.O. Bonow, *supra* note 12 at 1533-35.

[redacted]




**Description of figure.** Management strategy for patients with chronic severe mitral regurgitation. Abbreviations: AF= atrial fibrillation, EF= ejection fraction, ESD= end-systolic diameter, FC= functional class, MV= mitral valve, NYHA= New York Heart Association, PHT= pulmonary hypertension.

*Timing of Surgery for Symptomatic Patients With Normal Left Ventricular Function.* Patients with symptoms of congestive heart failure despite normal LV function on echocardiography (ejection fraction >0.60 and end-systolic dimension <45 mm) require surgery. Surgery should be performed in patients with mild symptoms and severe MR (Figure 6), especially if it appears that mitral valve repair rather than replacement can be performed. The feasibility of repair is dependent on several factors, including valve anatomy and surgical expertise. Successful surgical repair improves symptoms, preserves LV function, and avoids the problems of a prosthetic valve. When repair is not feasible, MVR with chordal preservation should relieve symptoms and maintain LV function.

*Timing of Surgery for Asymptomatic or Symptomatic Patients with Left Ventricular Dysfunction.* Preoperative variables that are predictive of postoperative survival, symptomatic improvement, and postoperative LV function are summarized in Table 20.

The timing of surgery for asymptomatic patients was controversial, but most would now agree that mitral valve surgery is indicated with the appearance of echocardiographic indicators of LV dysfunction. These include LV ejection fraction ≤0.60 and/or LV end-systolic dimension ≥45mm (Figure 6). Surgery performed at this time will likely prevent further deterioration in LV function and improve longevity. This is true whether repair or replacement is performed, although repair is clearly preferred. Although some recommend a slightly lower threshold ejection fraction (0.55), it must be emphasized that, unlike timing of AVR for AR, LV ejection fraction should not be allowed to fall into the lower limit of the normal range in patients with chronic MR (citations omitted).

Mitral valve surgery should also be recommended for symptomatic patients with evidence of LV systolic dysfunction (ejection fraction ≤0.60, end-systolic dimension ≥45 mm). Determining the surgical candidacy of the symptomatic patient with MR and far-advanced LV dysfunction is a common clinical dilemma. The question that often arises is whether the patient with MR has such advanced LV dysfunction that he or she is no longer a candidate for surgery. Often such cases present difficulty in distinguishing primary cardiomyopathy with secondary MR from primary MR with secondary myocardial dysfunction. In the latter case, if mitral valve repair appears likely, surgery should still be contemplated, provided ejection fraction is ≥0.30 (Figure).

*Asymptomatic Patients With Normal Left Ventricular Function.* Repair of a severely regurgitant valve may be contemplated in an asymptomatic patient with normal LV function in order to preserve LV size and function and prevent the sequelae of chronic MR.

This approach is often recommended in hemodynamically stable patients with newly acquired severe MR, such as might occur with ruptured chordae. Surgery is also recommended in an asymptomatic patient with chronic MR with recent onset of episodic or chronic atrial fibrillation in whom there is a likelihood of successful valve repair.

| INDICATION | CLASS |
|---|---|
| 1. Acute symptomatic MR in which repair is likely. | I |
| 2. Patients with NYHA functional Class II, III, or IV symptoms with normal LV function defined as ejection fraction >0.60 and end-systolic dimension <45mm. | I |
| 3. Symptomatic or asymptomatic patients with mild LV dysfunction, ejection fraction 0.50 to 0.60, and end-systolic dimension 45 to 50mm. | I |
| 4. Symptomatic or asymptomatic patients with moderate LV dysfunction, ejection fraction 0.30 to 0.50, and/or end-systolic dimension 50 to 55 mm. | I |

21. *See Id.*

22. *See Id.*

23. *See Id.*

24. *See* The American Heart Association Stroke Outcome Classification, approved by the American Heart Association Science Advisory and Coordinating Committee, Stroke 29: 1274-80 (1998):

*The AHA Stroke Outcome Classification (AHA.SOC) score classifies the severity and extent of neurological impairments that are the basis for disability. The classification also identifies the level of independence of stroke patients according to basic and more complex activities of daily living both at home and in the community. The classification score is meant to describe the limitations resulting from the current stroke. It is not an evaluation of disabilities caused by other neurological events. Furthermore, it is a summary score.*

## Stroke Outcome Classification

AHA.SOC SCORE_____
(Number of Domains ) (Severity) (Function)

**Number of Neurological Domains Impaired**

| *Score* | | |
|---|---|---|
| 0 | 0 domains impaired | *Neurological Domains* |
| | 1 domain impaired | Motor, sensory, vision, |
| 2 | 2 domains impaired | affect, cognition, language |
| 3 | >2 domains impaired | |

**Severity of Impairment**

| *Level* | |
|---|---|
| A | No/minimal neurological deficit due to stroke in any domain |
| B | Mild/moderate deficit due to stroke in ≥1 domain(s) |
| C | Severe deficit due to stroke in ≥1 domain(s) |

**Function**

| *Level* | |
|---|---|
| | Independent in Basic Activities of Daily Living (BADL) and Instrumental Activities of Daily Living (IADL) activities and tasks required of roles patient had before the stroke. Patient is able to live alone, maintain a household, and access the community for leisure and/or productive activities such as shopping, employment, or volunteer work. |
| I | Independent in BADL but partially dependent in routine IADL. Patient is able to live alone but requires assistance/supervision to access the community for shopping and leisure activities. Patient may require occasional assistance with meal preparation, household tasks, and taking medications. |
| II | Partially dependent in BADL (<3 areas) and IADL. Patient is able to live alone with substantial daily help from family or community resources for more difficult BADL tasks such as dressing lower extremities, bathing, or climbing stairs. Patient requires assistance with such IADL tasks as meal preparation, home maintenance, community access, shopping, handling finances, and/or taking medications. |
| V | Partially dependent in BADL ( ≥3 areas). Patient is unable to live alone safely and requires assistance with IADL except for simple tasks such as answering the telephone. |
| | Completely dependent in BADL (≥5 areas) and IADL. Patient is unable to live alone safely and requires full-time care. |

25. *See Id.*

26. *See Id.*

27. E. Braunwald, supra note 9 at 1433-34:

**Endomyocardial Fibrosis.** EMF occurs most commonly in tropical and subtropical Africa, particularly Uganda and Nigeria. It is typified by fibrous endocardial lesions of the inflow portion of the right or left ventricle or both and often involves the AV valves, resulting in regurgitation (citation omitted).

**Pathology.** A pericardial effusion, which may be quite large, may be present. The heart is normal in size or slightly enlarged, but massive cardiomegaly does not occur. The right atrium is often dilated, and in patients with severe right ventricular involvement there may be massive enlargement of this chamber. Indentation of the right border of the heart above the apex as a result of apical scarring may occur (citation omitted). Combined right and left ventricular disease occurs in about half the cases, with pure left ventricular involvement occurring in 40 per cent and pure right ventricular involvement in the remaining 10 per cent of patients who are examined post mortem (citation omitted).

Left ventricular involvement is similar, with fibrosis extending from the apex up the inflow portion of the left ventricle to the posterior mitral valve leaflet. The anterior leaflet of the mitral valve and the outflow portion of the left ventricle are usually spared. Thrombi often overlie the endocardial lesions, and widely distributed endocardial calcific deposits may occur. The coronary arteries are uninvolved, as is the remainder of the body (citation omitted).

**Left Ventricular EMF.** With predominant *left-sided* involvement, the endomyocardial fibrosis invades the apex of the ventricle and usually the chordae tendineae or the posterior mitral valve leaflet as well, leading to mitral valve regurgitation. The murmur may be confined to late systole, as is characteristic of the papillary muscle dysfunction type of murmur, or it may be pansystolic. Findings of pulmonary hypertension may be prominent. A protodiastolic gallop is commonly heard (citation omitted).

28. *See American Heart Association Stroke Outcome Classification, supra* note 24.

29. Braunwald *supra* note 9, at 796-98.

30. *See* G. Adelman, *Encyclopedia of Neuroscience,* 268 (1987):

The vegetative state is the condition wherein arousal (i.e., sleep-wake cycles) returns or remains but appropriate testing measures elicit no evidence of the person's cognitive awareness of self or environment.