antibody syndrome can cause a reduction in cell-surface annexin V on placental villi. This finding was taken to suggest that antiphospholipid antibodies can promote a greater procoagulant potential of these cells by means of a decrease in the anticoagulant activity of annexin V.

I wish to propose an alternative mechanism. The reduction in surface annexin V as detected in vitro by the enzyme-linked immunosorbent assay may only be apparent. The annexin may be bound and thus blocked by specific antibodies; such anti–annexin V autoantibodies have been described in association with thrombotic events in pregnancy failure and systemic lupus erythematosus.[1,2] Since annexin V may be involved in cellular processes such as exocytosis and membrane fusion (e.g., the syncytiotrophoblast),[3] antibodies to annexin V may interfere with its function and result in the expression of anionic phospholipids from the inner layer to the outer layer of the plasma membrane.

In addition to possessing antiphospholipid and lupus-anticoagulant properties, anti–annexin V antibodies have been shown to induce apoptosis in human umbilical-vein endothelial cells.[4] This may be another activating factor for the selective externalization, in apoptotic membranes, of the procoagulant phospholipid, phosphatidylserine.

HWEE-MING CHENG, PH.D.
Universiti Malaya
50603 Kuala Lumpur, Malaysia

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The authors reply:

To the Editor: We are pleased to hear that Dr. Rote and colleagues have reached conclusions similar to ours using monoclonal antiphospholipid antibody and BeWo trophoblasts. Regarding his question about the antibody preparations, we used IgG fractions from clinically affected patients for the culture studies, because the specificities of the antiphospholipid-antibody subtypes, with respect to their relevance to the pathogenesis of the antiphospholipid-antibody syndrome, have not yet been defined. Indeed, as we noted in the Discussion section of our article,[1] there is evidence that the serum glycoprotein β_2-glycoprotein I and other phospholipid-binding proteins may by themselves or in a complex with anionic phospholipids constitute antigenic sites for the antibodies. At this point, one would therefore not know whether findings with any particular antibody specificity (such as the monoclonal antiphosphatidylserine antibody referred to by Dr. Rote and his colleagues in the title of their paper) are relevant to the pathophysiology of the antiphospholipid-antibody syndrome. For this reason, we chose to work with IgG fractions from affected patients.

The design of our study was based on our previous study, which showed the reduction of immunohistochemically detectable annexin V on placental villi from patients with antiphospholipid antibody and duplicated those findings in cultured placental villi with the use of IgG fractions.[2] The results of our work with IgG fractions and placental villi, BeWo trophoblasts, cultured primary trophoblasts, and human umbilical-vein endothelial cells establish a foundation for further studies using defined antibody subgroups in model systems.

Regarding the question of whether the measured annexin V may be released from dying or antibody-injured cells, Trypan-blue exclusion studies showed that the cells were intact, as we reported.[1] We look forward to reading Dr. Rote's evidence that undifferentiated BeWo cells do not express any annexin V, since we were able to quantify this protein on the cells. Also, because BeWo is a choriocarcinoma-derived trophoblast cell line, we performed experiments with cultured primary placental trophoblasts and found the same reduction of annexin V by antiphospholipid-antibody IgG.

In response to Dr. Cheng's suggestion that we may have been observing the effects of anti–annexin V antibodies, none of the IgG fractions had any detectable anti–annexin V activity in immunoblot screening tests. Also, as we stated in our article,[1] the IgG did not interfere with the ability of the polyclonal rabbit IgG used for the immunoassay to detect known quantities of purified annexin V. We therefore think that human antiphospholipid-antibody IgG causes a reduction in the actual quantity of annexin V.

JACOB H. RAND, M.D.
PETER HARPEL, M.D.
Mount Sinai School of Medicine
New York, NY 10029

CHARLES LOCKWOOD, M.D.
New York University School of Medicine
New York, NY 10016

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Plasma Homocysteine Levels and Mortality in Patients with Coronary Artery Disease

To the Editor: Nygård et al. (July 24 issue)[1] nicely demonstrate an association between elevated plasma homocysteine levels and increased mortality in patients with angiographically confirmed coronary artery disease. It is important to mention that fasting plasma homocysteine levels, as used in this study, identify only some of the patients with disturbances in homocysteine metabolism. Approximately twice as many patients are identified with the additional use of a methionine-loading test.[2,3] One could speculate that the effect seen by Nygård et al. would have been even more pronounced if the patients had been further characterized with a methionine-loading test. Homocysteine may be an even stronger risk factor for mortal-

ity in patients with coronary artery disease than was shown in this study.

It is known that plasma homocysteine levels can be decreased and even normalized in a large proportion of patients through treatment with folic acid, vitamin B_6, and betaine,[4,5] even though it is not known whether such lowering slows the rate of progression of arteriosclerotic disease or decreases thromboembolic events.

STEPHAN MOLL, M.D.
Humboldt Universität Charité
13122 Berlin, Germany

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To the Editor: The article by Nygård et al. reports increased mortality in patients with coronary artery disease who have elevated homocysteine levels. The authors also describe no correlation between folate levels and mortality, although folate is known to lower homocysteine levels.[1] Folate levels were measured in serum, where they correlate less with tissue levels than do folate concentrations in red cells. Perhaps a more accurate estimate of total-body folate would have been obtained if folate had been evaluated in red cells. This value could have been used to select the patients whose homocysteine levels would decrease after the start of folate supplementation.

DAVID FARHADI, M.D.
Hospital of the University of Pennsylvania
Philadelphia, PA 19104

1. Ubbink JB, Vermaak WJ, van der Merwe A, Becker PJ. Vitamin B-12, vitamin B-6, and folate nutritional status in men with hyperhomocysteinemia. Am J Clin Nutr 1993;57:47-53.

To the Editor: Nygård and colleagues have reported that the homocysteine concentration is a strong independent predictor of mortality in patients with angiographically confirmed coronary artery disease. The authors referred to the prothrombotic effects of homocysteine but did not include hemostatic variables in their multivariate analyses. In a previous case–control study we found a strong positive correlation between homocysteine and fibrinogen. Therefore, the association between homocysteine and coronary artery disease was not independent.[1] We have extended this study and analyzed the relation between homocysteine, clinical data, hemostatic variables, lipid risk factors, and coronary anatomy in 348 men and 117 women, 32 to 85 years old, who underwent coronary angiography. Homocysteine was significantly correlated with age, the presence and number of stenosed coronary vessels, and concentrations of apolipoprotein A-II, fibrinogen, the fibrin-split product D-dimer, and C-reactive protein. Age and the concentrations of apolipoprotein A-II, fibrinogen, D-dimer, and C-reactive protein also had significant associations with both the presence and the number of stenosed coronary vessels. In a multivariate model, D-dimer concentration ($\beta = 0.192$, $P = 0.028$) but not age or concentrations of homocysteine, apolipoprotein A-II, fibrinogen, and C-reactive protein was independently associated with the presence of coronary artery disease. In an alternative model that did not include the D-dimer concentration, age ($\beta = 0.219$, $P < 0.001$) and the fibrinogen concentration ($\beta = 0.116$, $P = 0.035$) were independently associated with coronary artery disease, but the homocysteine, apolipoprotein A-II, and C-reactive protein levels were not.

Various prospective studies in the population and in patients with manifest coronary artery disease have identified hemostatic and inflammatory markers, including concentrations of fibrinogen and C-reactive protein, as risk factors for future coronary events.[2-4] Therefore, because of the strong correlations between homocysteine concentration and hemostatic variables and because of the prothrombotic properties of homocysteine in vitro, it seems essential that hemostatic risk factors be included in studies evaluating the possible role of homocysteine as an independent risk factor for coronary morbidity and mortality.

ARNOLD VON ECKARDSTEIN, M.D.
GERD ASSMANN, M.D.
Westphalian Wilhelms University of Münster
D-48129 Münster, Germany

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The authors reply:

To the Editor: The methionine-loading test is performed by measuring the concentration of homocysteine after the patient ingests a standard dose of methionine, which is believed to stress the homocysteine degradation pathway dependent on cystathionine beta-synthase. Although there is a strong correlation between fasting and post-loading homocysteine concentrations and both measurements have similarly strong associations with cardiovascular disease, the information obtained from the two tests is not identical.[1,2] We agree with Dr. Moll that the measurement of post-loading total homocysteine could shed further light on the role of total homocysteine in the prediction of cardiovascular disease. However, the methionine-loading test is a cumbersome procedure, and routine testing may be impractical.

The serum folate concentration is responsive to folate intake and is believed to indicate short-term folate status,

whereas the red-cell folate concentration may reflect the average folate status during the lifetime of the erythrocyte. However, the methods of determining folate levels are seriously flawed, causing considerable analytic imprecision.[3,4] Although we are not convinced that the concentration of folate in red cells is superior to that in serum or plasma as a marker of folate status, we agree with Dr. Farhadi that measurement of red-cell folate would have given additional information relevant to our study.

Drs. von Eckardstein and Assmann suggest that the observed association between plasma total homocysteine levels and subsequent mortality may have been confounded by hemostatic factors. The platelet count was included in the multivariate model, and lipoprotein(a) showed no significant association with mortality. We also measured fibrinogen in our patients but found no association with homocysteine ($r=0.06$), and its inclusion in the multivariate model did not affect the homocysteine–mortality relation.

OTTAR NYGÅRD, M.D.
HELGA REFSUM, M.D.
PER MAGNA UELAND, M.D.
MIKAEL FARSTAD, M.D.
STEIN EMIL VOLLSET, M.D., DR.P.H.
University of Bergen

JAN ERIK NORDREHAUG, M.D.
Haukeland University Hospital
5021 Bergen, Norway

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Fungal Sinusitis

To the Editor: In their otherwise excellent review of fungal sinusitis (July 24 issue),[1] deShazo et al. have made two minor errors. First, in the text and in Table 1, they describe *Pseudallescheria boydii* as a dematiaceous (pigmented) mold, whereas in fact it is a hyaline (nonpigmented) mold.[2] Second, the authors use the term "mycetoma" inappropriately as a synonym for fungus ball. Mycetoma refers strictly to invasive, tumefactive, and destructive infections of skin, soft tissue, and bone caused by a wide variety of aerobic actinomycetes and fungi that form compact mycelial aggregates, called grains or granules, within infected tissues.[2] Although the mycelium in a fungus ball may superficially resemble that in a mycetoma granule, the distinction between the two is important. A fungus ball is a noninvasive, colonizing infection of a preformed air space that is usually cured by simple surgical removal and drainage. On the other hand, successful treatment of mycetoma, a truly invasive infection, frequently requires radical surgical débridement or amputation.

JOHN C. WATTS, M.D.
William Beaumont Hospital
Royal Oak, MI 48073

FRANCIS W. CHANDLER, D.V.M., PH.D.
Medical College of Georgia
Augusta, GA 30912

1. deShazo RD, Chapin K, Swain RE. Fungal sinusitis. N Engl J Med 1997;337:254-9.
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To the Editor: In their review of fungal sinusitis, deShazo et al. point out that fulminant invasive sinusitis can be caused by *P. boydii*. They state that when emergency surgery has yielded tissue confirming invasion, treatment should be given with amphotericin B, because azole antifungal agents lack activity against mucorales species. The authors imply that amphotericin B should be given alone, without azole antifungal agents. The problem is that azoles have activity against pseudallescheria but amphotericin B does not. Bennett states that the response of pseudallescheriasis to amphotericin B is minimal and that intravenous miconazole (800 mg every eight hours) is probably the regimen of choice for rapidly progressive infection.[1]

The pathologist must be able to differentiate pseudallescheria from aspergillus and mucorales. Differentiating pseudallescheria from mucorales is easy, because pseudallescheria has regular septate hyphae, which make it look very different from the irregular, ribbonlike, paucisseptate, wide-angle–branching mucorales. Differentiating pseudallescheria from aspergillus is much more difficult. Pseudallescheria has haphazard (random-angle) branching, midhyphal or terminal swellings, an absence of progressive (arboreal) branching, and the occasional presence of ovoid brown spores. Aspergillus sometimes has haphazard branching or hyphal swellings, and progressive branching is not always evident. The characteristic features of pseudallescheria can sometimes allow the pathologist to differentiate it from aspergillus. However, if the histologic features of the invading fungus are not specific enough to rule out pseudallescheria and if no culture result is available, perhaps the wisest treatment of acute, fulminant, invasive fungal sinusitis is a combination of amphotericin B and an azole.

LARRY NICHOLS, M.D.
University of Pittsburgh Medical Center
Pittsburgh, PA 15213-2582

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The authors reply:

To the Editor: Drs. Watts and Chandler raise two issues. First, the term "mycetoma" is strongly associated with the