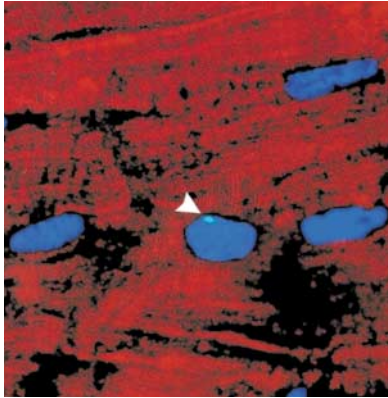




This Week in the Journal

January 3, 2002



Chimerism of the Transplanted Heart

Eight male patients received cardiac transplants from female donors. In samples from these hearts, the investigators were able to detect Y chromosomes in about 10 percent of the myocytes, proving that they came from the male recipients. These results show that cells from the recipient are able to migrate into the donor heart and take up residence. Some of the Y-chromosome–positive cells were primitive and had the capacity to proliferate.

The origin of the cells that migrated from the recipient to the transplanted heart is uncertain, but this study raises the possibility that primitive cells from the recipient may migrate to the donor heart and participate in the remodeling process.

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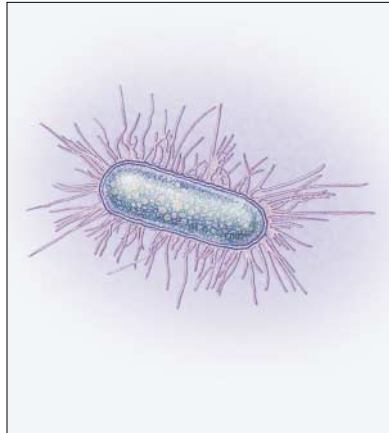
“Outpatients with schizophrenia have a lower risk of relapse if they are treated with risperidone than if they are treated with haloperidol.”

Risperidone versus Haloperidol to Prevent Relapses of Schizophrenia

Preventing relapse is an important goal in treating patients with schizophrenia or schizoaffective disorder. This study compared risperidone, a newer, atypical antipsychotic medication, and haloperidol, an older, conventional neuroleptic drug, for the prevention of relapse in clinically stable adult outpatients. Patients treated with risperidone had a lower risk of relapse.

Patients with schizophrenia typically have a chronic course with frequent relapses and repeated hospitalizations. The findings of this study suggest that risperidone may be beneficial for some patients and should spur research on other new antipsychotic medications.

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E. coli

Prothrombotic Coagulation Abnormalities Preceding the Hemolytic–Uremic Syndrome

This prospective study included 53 children with *E. coli* O157:H7 infections. The hemolytic–uremic syndrome developed in 16 of the children, who had coagulation abnormalities that preceded the onset of azotemia and thrombocytopenia. The abnormalities included increases in the concentrations of prothrombin fragment 1+2, tissue plasminogen activator antigen, and plasmin–antiplasmin complex.

The hemolytic–uremic syndrome is a serious complication that develops in some children with E. coli O157:H7 infection, usually about one week after the onset of diarrhea. This study provides evidence that thrombin generation and inhibition of fibrinolysis precede the renal injury and may be the cause of it.

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PERSPECTIVE

Can the Heart Repair Itself?

Bone marrow, the liver, and intestinal epithelium can regenerate, but the conventional teaching is that the heart cannot, because cardiac myocytes cannot divide. Consequently, it is generally accepted that the basis of cardiac enlargement and remodeling in response to disease or excessive work is an increase in the size of individual heart cells (hypertrophy) but not in their number (hyperplasia).

Hypertrophy is a beneficial response to the demand for increased cardiac work, but it has drawbacks. Since myocytes cannot enlarge indefinitely, the extent to which the heart can adapt through hypertrophy has intrinsic limits. A sustained hemodynamic overload may end in heart failure when the capacity of the hypertrophic response is exceeded. Fur-

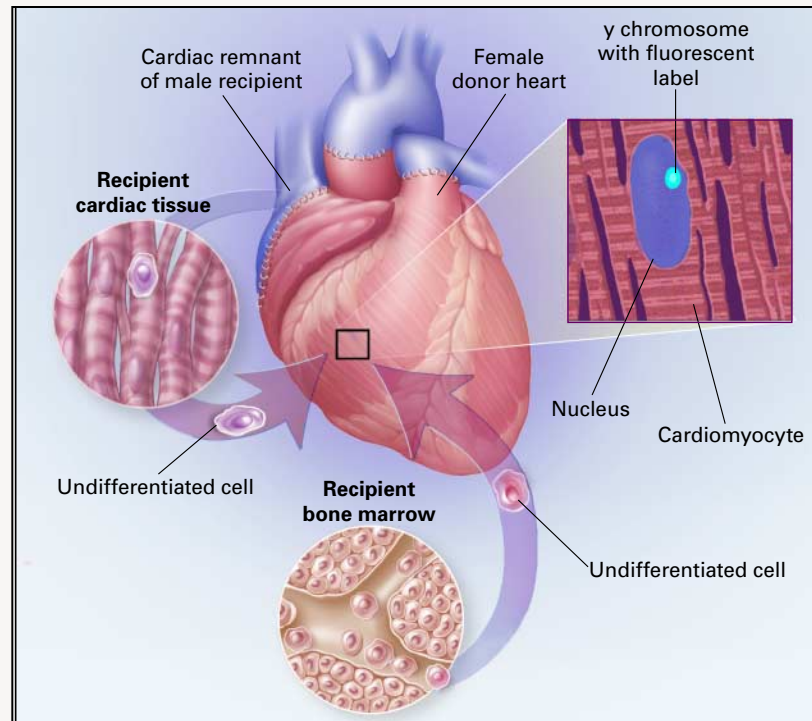
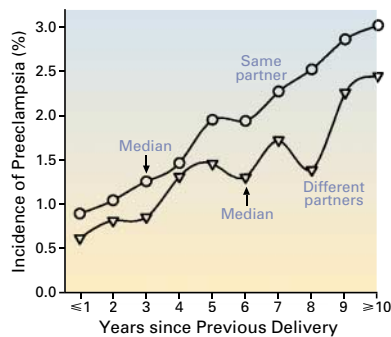


Figure 1. Pathways by Which a Heart from a Female Donor Might Be Populated with Cells from a Male Recipient.

Male cells in the female donor’s heart are identified by the presence of a Y chromosome labeled by fluorescence in situ hybridization. Y-chromosome–positive cells in the transplanted heart may have come through the systemic circulation from undifferentiated cells in the recipient’s bone marrow or may have come from the cardiac remnant. The pathways are not necessarily mutually exclusive.

The Interval between Pregnancies and the Risk of Preeclampsia



The risk of preeclampsia is lower in second than first pregnancies if the woman's partner is the same, but not if the partner is different. This study used data from a large birth registry in Norway to evaluate whether a longer interval between deliveries, rather than a change in partner, might explain this finding. The risk of preeclampsia in a second or third pregnancy correlated directly with the interval between deliveries and approximated the risk during a first pregnancy if 10 years or more had elapsed between pregnancies.

These findings suggest that the reduction in the risk of preeclampsia associated with a previous pregnancy is transient. The increased risk that had previously been observed with a change of partner seems to be explained instead by a longer interval since the previous delivery.

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thermore, hypertrophied myocardium is not physiologically normal and may confer a predisposition to potentially fatal arrhythmias. The imperfections of adaptation by cardiac hypertrophy make it highly desirable to find ways of inducing heart cells to enter the cell cycle and divide.

Cell Division in the Heart

Anversa and others have reopened the possibility that heart cells can undergo division under certain circumstances. This important research was facilitated by confocal microscopy, which allows precise focusing of the microscope on one layer of heart cells, and even single cells, in a tissue section. In a 2001 study using fluorescent labeling in conjunction with confocal microscopy, the Anversa group identified mitotic figures within myocytes early after myocardial infarction; these dividing myocytes were most numerous in regions adjacent to the infarct (N Engl J Med

2001;344:1750-7). This work established that heart cells can divide after damage to the myocardium by infarction, but the source of the replicating cells was unclear. Were they derived from *in situ* myocytes, or did they originate from primitive cells that had migrated from outside the heart and then differentiated into replicating myocytes?

Further work on the question appears in this issue of the *Journal* (see pages 5–15). The Anversa group took advantage of the availability of transplanted hearts from recipients who had died of causes other than graft rejection. In hearts from female donors that had been transplanted into male recipients, approximately 10 percent of the myocytes and coronary arterioles contained a Y chromosome, the definitive marker of a male cell. This is compelling evidence of the migration of cells from the recipient into the transplanted heart. Moreover, some of the cells were

undergoing division, and others had markers of primitive stem cells. These results indicate that cells from the recipient can enter a graft and contribute to remodeling and growth of the transplanted heart. A question that remains unanswered is whether the migrating cells arose from precursors in the remnant of the recipient's heart or traveled from the recipient's bone marrow through the circulation to the transplanted heart (Fig. 1). Another open question is the extent to which replicating myocytes contribute to the repair process. Are such myocytes minor actors in the drama that begins after cardiac damage, or do they hold center stage?

The Role of Stem Cells

Since multipotent bone marrow stem cells have extraordinary versatility, it is possible that they can differentiate into cardiac myocytes. These ancestral precursors give rise to all the lineag-

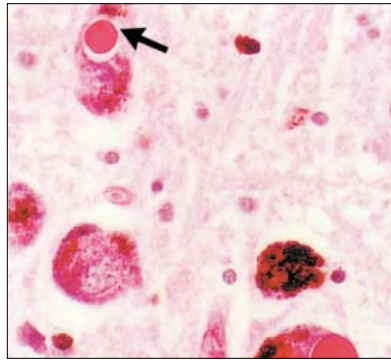


Clinical Practice: **Screening for Colorectal Cancer**

A healthy 50-year-old woman with no risk factors for colorectal cancer other than age comes in for an annual examination. Which screening test for colorectal cancer should be recommended?

This article reviews various screening strategies for colorectal cancer, including three-sample fecal occult-blood testing, sigmoidoscopy, and colonoscopy.

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Mechanisms of Disease: **Alpha₁-Antitrypsin Deficiency — A Model for the Conformational Diseases**

Alpha₁-antitrypsin is a member of a family of protease inhibitors known as the serpins. Mutations in these molecules can lead to disease, not only because the biologic activity of the protease in tissue is increased, but also because the mutations result in misfolded (i.e., conformationally abnormal) protease molecules that accumulate in tissue. This review article summarizes the action of these protease inhibitors and how mutations lead to their accumulation in particular neurodegenerative disorders such as prion encephalopathies and Alzheimer's disease.

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es of the hematopoietic system. Moreover, stem cells that circulate in the blood can completely regenerate damaged marrow. It appears that growth factors in the environment influence the path taken by a differentiating multipotent stem cell. Such local factors may account for the known ability of marrow stem cells to become neurons. There are, furthermore, stem cells in striated muscle and the brain that seem able to differentiate into hematopoietic stem cells under particular circumstances. The ebb and flow

of stem cells in adult tissues may have considerable physiologic importance, but our knowledge of these events is less than scanty.

The new findings of the Anversa group raise the hope that, counter to traditional beliefs, the heart can repair itself. If it can, we will have opportunities to enhance the process that regenerates damaged myocardium. A convincing demonstration that bone marrow stem cells can migrate to the injured heart and there differentiate into cardiac myocytes would be far more than an exer-

cise in cell biology: methods of moving marrow stem cells into the circulation are already in clinical practice. Such approaches to therapy, which were previously only pipe dreams, are now realistic goals that may soon be within reach.

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