The elderly are particularly susceptible to disease, yet the biological mechanisms that bring about this susceptibility remain unclear. Using atherosclerosis as a model chronic illness, we review how recent studies of bone marrow-derived vascular repair systems in mice and humans provide new insights into the causes and potential cures for age-related illness. Organisms are born with a finite capacity for stem cell-mediated repair after chronic exposure to tissue injury. Once that capacity is exhausted, a cycle of pathological inflammation ensues and leads to overt disease manifestations. Augmentation of stem cell-mediated repair systems may provide a novel means of treating or preventing many age-related illnesses.

Introduction
Aging is the most critical risk factor for many common diseases that affect the human organism. Little is known, however, about the mechanisms by which aging per se affects the likelihood and the course of chronic illnesses. Understanding this relationship is particularly germane to Western societies as the longevity of their populace increases. Although progress in science, especially in medicine, has extended the length of life, chronic illnesses still steal quality from the later years, increasing frailty and disability (1). Thus, it is crucial that we understand how we might avoid the ravages of chronic illnesses by strengthening our inherent ability to repair and regenerate the human organism.

Atherosclerosis is the archetype of a chronic disease that spoils our retirement years and has age as its dominant risk factor. Atherosclerosis is now thought of as a chronic inflammatory process punctuated by thromboembolic events, such as heart attack and stroke (2). Epidemiological studies have identified traditional risk factors that accelerate atherosclerotic inflammation, such as smoking, hypertension, diabetes, and high cholesterol. Biologists have produced evidence that such risks translate, at least in part, into an oxidative insult, damaging or destroying cells of the arterial wall (3). The impact of a risk factor’s effect on one’s likelihood of thromboembolic complications of atherosclerosis is exquisitely dependent on age. For example, a 70-year-old person who smokes has a more than 20-fold higher risk for a cardiac event than a 30-year-old person who smokes (4). Thus, a constant amount of smoking leads to markedly worse pathological consequences when it occurs in the elderly than when it occurs in the young. Almost always, the duration of smoking history for a 70-year-old person is longer than for a 30-year-old individual. Yet, for such a duration to have an impact on the local disease process, one has to postulate an “intrinsic tissue memory” within the affected arterial wall such that the cumulative impact of smoking, over time, can be registered. Possibly, lesion severity may account for this hypothetical intrinsic tissue memory, although it is known that the most threatening atherosclerotic lesions are not always the most severe (flow-limiting) or complex ones (2, 5). Alternatively, aging in the presence of risk factors for atherosclerosis could have an impact that operates at a distance from the affected artery. This review focuses on the latter mechanism.

Injury by Atherosclerosis
When arterial tissue is exposed to an acute insult, usually in the form of exaggerated production of free radicals (3), a series of complex cellular and molecular reactions is triggered. Such a chain reaction is relatively well conserved among biological tissues and involves several actions: (i) apoptosis of vascular cells (endothelial and smooth muscle cells) and production of cytokines, chemokines, and growth factors by residual cells of the arterial wall; (ii) thrombosis and thrombolysis and, at the site of arterial injury, the formation of a “Velcro” layer by platelets, which are small eculceated cells that are key to the access of larger cells to the arterial wall; and (iii) an accumulation of neutrophils, dendritic cells, and macrophages, inflammatory cells that are attracted to the damaged tissue. If unchecked, these inflammatory cells within the vessel wall lead to continued cellular damage and a chronic atherosclerotic lesion.

Until recently, our understanding of atherosclerosis was limited to the mechanisms of arterial injury. According to the conventional response-to-injury hypothesis of atherosclerosis, endothelial denudation or dysfunction leads to a chronic inflammatory process in large- and medium-sized elastic and muscular arteries. If unabated, this process results in advanced complex lesions of atherosclerosis (see McGor and McGor Review*). Such an inflammatory response is believed to stimulate migration and proliferation of smooth muscle cells, which then intermix with areas of inflammation. The key inflammatory cells involved in the process are macrophages and specific subtypes of T lymphocytes (see “Immunity Challenge†”). These cells emigrate from the blood and, once activated within atherosclerotic lesions, release pro-atherosclerotic cytokines, growth factors, and enzymes, such as matrix metalloproteinase, which produce further damage and, eventually, focal necrosis of arterial wall cells. The thickening of the arterial wall is compensated for by gradual dilation of the vessels in such a way that the lumen of the artery remains unaltered, a phenomenon called remodeling. Cycles of accumulation of mononuclear cells, migration and proliferation of smooth muscle cells, and formation of fibrous tissue lead to further enlargement and restructuring of the lesion. Eventually, the presence of the lesion no longer can be compensated for by dilatation of the vessel, and the lesion may intrude into the lumen of the artery, altering the flow of blood through it (5).

Science has begun to uncover additional important mecha-
nisms by which the body protects and repairs itself after atherosclerotic injury. In response to signals of cellular damage, repair cells produced in the bone marrow (endothelial and other vascular progenitor cells) migrate to these affected areas (6, 7). After engraftment, it can be assumed that these cells stimulate tissue remodeling, with synthesis and hydrolysis of extracellular matrix proteins and consequent structural repair of the arterial wall. When successful, these reparative processes halt the inflammatory process and further damage. However, the effectiveness of this bone marrow-derived repair system is quite age-dependent. Although robust in youth, older endothelial progenitor cells have a limited capacity for proliferation.

The Role of Age
Traditional thinking about the effect of aging on atherosclerosis implicates successive injuries that progressively disrupt the integrity of arterial walls. However, such a process emphasizes only the forces of damage and fails to account for the opposing forces of repair. When a lesion occurs, homeostatic systems respond to repair it and restore the integrity of the tissue. In situations of profound injury, damage to the tissue might be irreversible because of fibrosis and contraction. Yet it is unclear why a young individual exposed to a constant level of injury might make a full recovery, whereas a similar insult in an older individual can lead to marked inflammation and irreversible damage. There is no simple explanation for the fact that the arterial tissue can “remember” the chronicity of the injurious process.

Memory by Exhaustion
The first clue to this “memory” came from the discovery of circulating progenitor cells that are produced by the bone marrow and can proliferate and differentiate into endothelial and other vascular cells (8). These progenitors are not true stem cells, because they do not display the required characteristics of stem cells. They appear to have already advanced within the pathway of differentiation toward vascular cells, and they have been demonstrated to home in on areas of vascular injury or tissue ischemia (6, 7). Furthermore, they appear to play an important homeostatic role in maintaining the normal healthy vasculature, replacing a high percentage of endothelial cells over time (6-8).

The capacity of bone marrow-derived progenitor cells is finite. Hill and colleagues made the seminal observation that fewer endothelial progenitor cells circulate in patients who are exposed to traditional atherosclerotic risk factors, such as diabetes mellitus and high cholesterol, than in unexposed patients (9). Concurrent with the reduction in the number of circulating endothelial progenitors, normal function of the arterial endothelium diminishes progressively (9). The data support the hypothesis that aging in the presence of risk factors leads to the exhaustion of circulating progenitor cells that are capable of repairing the injured arterial tree. It is not clear, however, whether such exhaustion results from the consumption of repair cells at the level of the peripheral tissue, from the lack of production of these cells by the bone marrow, or both.

Repair Cells: Overconsumption Versus Underproduction
We studied the question of peripheral consumption of repair cells versus loss of production of such cells in a mouse model of atherosclerosis. Apolipoprotein E-deficient (knock-out) mice (ApoE−/−) fed a high-fat diet develop very high total cholesterol levels as well as rapid progression of atherosclerotic inflammation that is similar to that found in patients with elevated blood lipids. Knowing that exogenously delivered marrow cells could engraft onto the arteries of ApoE−/− mice (10, 11), we studied the possibility that exogenous progenitor cells (bone marrow cells) would be able to rejuvenate the arterial tissue of ApoE−/− mice and prevent the genesis of atherosclerotic lesions (12). In a series of experiments, we documented the fact that intravenously injected marrow cells had no effect on the cholesterol concentration of recipient ApoE−/− mice. Yet in spite of ongoing toxic exposure to profound hyperlipidemia, the ApoE−/− mice that received donor marrow infusions did not develop severe atherosclerosis (12).
Using tagged marrow cells, we showed that (i) the donor progenitor cells were circulating in the blood of transplanted ApoE–/– mice; and (ii) they engrafted selectively in disease-prone regions of the arterial surface, arteries that otherwise would have developed atherosclerotic inflammation. In contrast, normal (wild-type) mice that received tagged marrow cells were relatively devoid of progenitor cells on the surface of their healthy arteries. Hence, it is likely that the ApoE–/– mice that received competent marrow progenitor infusions had their disease prevented via direct engraftment to, and repair of, the arterial wall.

Telomere length
Telomeres are the small sections of packed DNA that can be found at the two ends of each chromosome. With advancing age, the telomerase activity of cells declines and telomere lengths shorten (see “More Than a Sum of Our Cells”‡). Telomere length was intermediate between these two extremes for similar cells collected from mice transplanted with competent marrow cells (12). Hence the data are consistent with an activity whereby competent marrow progenitor cells contribute to the rejuvenation of arterial walls exposed to major risk factors.

Donor age
The age of the animal donor also was found to affect the success of the treatment. Marrow from young (pre-atherosclerotic, 4 weeks of age) ApoE–/– mice had a significantly greater capacity to prevent atherosclerosis than did marrow cells originating from older, already atherosclerotic mice. Close study of the marrow of older ApoE–/– mice demonstrated a selective loss of marrow cells that display endothelial progenitor characteristics. These data are consistent with a model in which the marrow of older mice that are chronically exposed to a major risk factor, hypercholesterolemia, become unable to produce the repair progenitor cells required to prevent the development of atherosclerotic lesions.

Marrow progenitors could accomplish repair through at least two putative mechanisms: (i) engraftment/plasticity and (ii) cell fusion. According to the engraftment/plasticity theory, precursor cells engraft to a tissue and proliferate and differentiate to resemble the adult cells of the host tissue. According to the fusion theory, precursor cells fuse with cells of the host tissue and, after cell division, repair and rejuvenate the host tissue. It may be that cells with phagocytic potential, which have built-in fusion expertise (for example, macrophages or Kupffer cells, both of which can engulf bacteria), perform fusion as a way of rejuvenating damaged tissues. Other cells, including endothelial and epithelial cells, might be more prone to repair via an engraftment/plasticity mechanism (13-15).

Inflammatory markers
Inflammatory marker studies performed in our mouse model produced further insights. Markers of inflammation such as C-reactive protein and interleukin-6 (IL-6) are highly correlated with thromboembolic events in patients at risk for atherosclerosis (16). IL-6 is elevated in ApoE–/– mice with advanced atherosclerosis. We found that successful infusion of marrow progenitors into the cholesterol-fed ApoE–/– mice was associated with a marked reduction in the animals’ circulating IL-6 concentrations (12). Furthermore, the ability of marrow cells to normalize IL-6 concentration in a sustained manner was consistent with the ability of such cells to prevent atherosclerosis (12). Donor cell infusions from wild-type mice worked best to lower IL-6 levels, whereas cells from old ApoE–/– mice on a high-fat diet were worst in reducing IL-6. Thus, elevation of inflammatory markers such as IL-6 may be predictive of adverse events, because it indicates that an incomplete repair process is ongoing in the patient’s arteries.

‡ http://sageke.sciencemag.org/cgi/content/full/2001/1/oa4
Progenitor Cells in the Repair of Vascular Injury

These series of experimental findings are consistent with the model of atherosclerosis displayed in Fig. 1. In youth, exposure to circulating toxins such as high cholesterol and metabolic products of smoking leads to cellular injury. Arterial damage causes the release of cytokines, which in turn stimulate both the release and homing of endothelial progenitor cells to the area of injury. Repair of the damaged endothelium by the progenitor cells completes the process, preventing further invasion of inflammatory cells and returning circulating inflammatory markers (IL-6, among others) to basal levels.

With continued exposure and age, progenitor cell stores can be exhausted. Without repair, inflammatory cells continue to invade the site of injury and cause ongoing release of large amounts of inflammatory markers. The continuous elevation of inflammatory cytokines, chemokines, and growth factors can promote the atherothrombotic process directly (17) or indirectly through the recruitment of cells, such as activated macrophages, that can add to the arterial insult (2). Such cells could be recruited from marrow exposed to large amounts of inflammatory cytokines as part of a default pathway after the repair progenitors have been depleted.

Bone marrow stem cells apparently differ with age. For example, hematopoietic stem cells from the bone marrow of old mice are markedly less efficient at homing to and engraving the bone marrow of irradiated recipients than are stem cells from young and middle-aged mice (18) (see Fuller Perspective 3). Furthermore, Edelberg and colleagues have shown that bone marrow-derived stem cells can restore the impaired cardiac angiogenesis observed in older organisms (see Edelberg Perspective 4). Thus, young bone marrow-derived endothelial progenitor cells can restore cardiac angiogenesis, whereas similar cells obtained from old mice fail to do so (19). Together with our data, these results indicate an age-related senescence of the bone marrow, its stem cells, and derived progenitor cells (12, 18, 19). It is tempting to predict that the detailed molecular characterization of this senescence process will be invaluable for the prevention and treatment of chronic illness.

The disease state in an individual is dependent on the duration of exposure to environmental toxins and the person’s capacity for regeneration. Genetic variation in bone marrow-derived repair abilities can further help explain certain phenotypic paradoxes. Early-onset atherosclerosis in those with few or no risk factors may be related to abnormally low stores of endogenous progenitor cells. At the other extreme, patients with abnormally large progenitor cell capacities might be protected from disease into advanced age despite an unhealthy lifestyle. Other aging-related factors could contribute to acceleration of the atherosclerotic process. One likely contributor is the selective loss of marrow progenitors that give rise to immune-competent cells that protect the arterial vessel from developing atherosclerosis. Alternatively, excess production of progenitor cells that mature into immune-competent cells that promote atherosclerotic inflammation, in the presence of risk factors, could account for some of the effects of aging on the disease process. One should also consider the possibility that chronic direct exposure of the arterial wall to noxious stimuli, such as the reactive oxygen species that result from various environmental toxins, could contribute to the effect of aging on atherosclerosis independent of the effect of aging on the loss of marrow-derived repair cells.

It is also tempting to speculate, on the basis of the data reviewed here, that individuals exposed to a variety of global environmental insults may develop disease first in the organ whose repair capacity is most limited, such as the heart. A central (marrow-derived) theoretical model might be more suitable than the traditional peripheral (target tissue-derived) model for tissue repair to account for the interaction that exists among chronic inflammatory diseases, such as rheumatoid arthritis and atherosclerosis. Patients with a history of rheumatoid arthritis are at heightened risk for developing atherosclerosis and its thromboembolic complications, such as heart attacks (20). It may be that experiencing one chronic illness identifies individuals with a generally deficient capacity for tissue repair. Alternatively, one chronic disease might consume some of the repair cells that originate from the marrow and are required to prevent disease in another organ (Fig. 2).

Further understanding of the memory mechanism that operates in chronic illnesses is likely to create novel opportunities to curb many health-threatening problems. Although the mechanisms responsible for age-related damage to marrow pathways that contribute to the production of vascular progenitor cells have not yet been identified, they likely will involve disturbances in the organization of chromatin in cells that participate in progenitor production. One might hope that strategies involving the injection of selected exogenous progenitor cells or retraining of the endogenous marrow of patients, with the aim of recovering lost capacity to produce cellular repair tools, will have a favorable impact on human welfare.

References

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