

PERSPECTIVES & OPINIONS

Elizabeth Nabel

A WINDOW
ON AGING

STUDYING A RARE DISEASE
PROVIDES UNCOMMON INSIGHT.

Paul Fetters

One of the rarest diseases in the world is progeria. It is known to exist in only 100 children, causing them to age rapidly—looking 60 years of age when they're 10. They eventually die in their early teens. Elizabeth G. Nabel, director of the National Heart, Lung, and Blood Institute, says research on this rare disorder may offer help to these children, provide insights into normal aging, and furnish information about one of our biggest killers, heart disease.

How can studying rare diseases lead to broader discoveries?

By sorting through the molecular and genetic mechanisms involved in rare diseases, we can learn a great deal of biology that has implications for common diseases. For example, by studying progeria, we are learning about the biology of smooth muscle cells, which line the blood vessels. This has important implications for many vascular diseases that affect millions of Americans.

Your research area is atherosclerosis. How did you get involved in studying progeria?

Children with progeria uniformly die of heart attack or stroke in their early teens. But there were few pathology reports on the cardiovascular aspects of progeria. Nothing was really known. When two groups working on progeria asked me to join them, I was really intrigued.

For the past 20 years, I'd been studying smooth muscle cells, the cells that proliferate in atherosclerosis and eventually cause heart attacks and stroke. These smooth muscle cells, we learned, also play a key role in progeria.

At the beginning of the project, did you think you might learn something about normal aging?

Initially, we just wanted to understand this rare disorder. But I quickly realized that understanding progeria would provide a window into understanding atherosclerosis that occurs with aging. The signal feature of blood vessel disease in progeria is a loss of the smooth muscle cells in the arteries. When these cells die, the blood vessels become scarred and inflexible. Eventually, the normal artery is replaced by a stiff, fibrotic tube that can no longer constrict or dilate. The coronary blood vessels can't respond to blood flow demands and a heart attack follows.

This process in progeria is a little different from the atherosclerosis that occurs during aging. In fact, you can think of them as opposite processes with similar results. In progeria, smooth muscle cells die. But in normal atherosclerosis, smooth muscle cells proliferate in a chronic,

inflammatory condition caused by high levels of low-density lipoprotein, nicotine, diabetes, high blood pressure, and other things. But because cell growth and cell death are intimately connected, studying one provides insight into the other.

And what have you learned?

We knew that smooth muscle cells arise from a specific kind of progenitor or stem cell that resides within blood vessels. We thought that these progenitor cells generated new smooth muscle cells throughout life. But by studying progeria, we've learned that the progenitor cells can only divide, or double, a finite number of times and then they die. In children with progeria, these cells double only until the children are in their mid-teens. Our working hypothesis is that this early death of the progenitor cells is due to the genetic defect that causes progeria, which was identified by Francis Collins [former head of the National Human Genome Research Institute]. That defect occurs in the gene that makes the protein lamin A, turning it into a defective protein called progerin. And while we haven't worked out the precise molecular mechanisms involved, we think that progerin causes the progenitor cells to die early.

How is this relevant for normal aging?

A colleague, Tom Misteli at the National Cancer Institute, discovered that as healthy people age, they begin to make progerin. Somehow their normal lamin A gene starts producing this mutant protein. We don't know why this happens, but because we now have the resources from the progeria work—including a mouse model and a tissue bank—we hope we'll be able to puzzle out exactly why older people produce progerin. We think it could be an important clue to understanding many aspects of aging.

INTERVIEW BY BRIAN VASTAG. Elizabeth Nabel, National Heart, Lung, and Blood Institute director since 2005, is a cardiologist whose lab focuses on molecular, cellular, and genetic mechanisms of vascular diseases.