The Columbus Dispatch

April 26, 2005

Redefining Old Age

By Mike Lafferty

Fruit flies have long been studied to understand genetics and, through the decades, researchers have bred some special varieties. For example, a colony at the University of California, Irvine lived three times longer than normal fruit flies.

Scientists also are trying to figure out why microscopic roundworms bred with certain mutated genes live six times longer than normal worms.

The hope is that uncovering these secrets will help people live longer -- a lot longer.

UC geneticist Michael Rose bred the Methuselah-like flies.

"I started working on aging in 1976. Nobody believed you could substantially change the life span of any organism," Rose said.

The payoff could be enormous.

Understanding the millions of chemical reactions in cells; developing the ability to grow tissue to replace an ailing liver, a failing heart valve or a hip joint; and continuing progress in beating cancer and other diseases is expected to boost the average life span in this century by several decades.

Even doubling the average life span in the United States -- now 77 years -- may not seem far-fetched.

"What if you could control the aging process?" said David Demko, a gerontologist who runs a Web site for aging issues. "You're talking about several hundred of years (of life) or continuing renewal."

Extending lifelines

Scientists think humans have the plumbing, wiring and scaffolding to live to about 125. A century ago, doctors thought humans couldn't live much longer than about 100. But we've added 30 years to our longevity in the past century alone.

At 114, Verona Johnston was the second-oldest American when she died Dec. 1 in Worthington. The 125-year limit was set after Jeanne Calment, a French woman, died in 1997 at 122.

Good genes are important. Calment smoked nearly all her life and reportedly only quit a couple of years before her death because she got tired of asking people to light her cigarettes.

But why some people live so long or why otherwise healthy people seem to die at 80 is still mostly a mystery.

"We have people living longer because of medicine, nutrition and healthier living, but we still don't know enough

about the human body to make significant increases" in life span, said Ohio State University researcher Dr. William Malarkey.

Demko said genetic breakthroughs such as those achieved with the fruit flies could significantly extend our lives.

"If we could eradicate the diseases associated with aging, then everyone would routinely have a life span (of) 120," he said. "We could move on from there.

"We have in this century, achieved the death of death by isolating the gene that controls death."

Every cell has a gene that eventually triggers its death. If that gene can be disabled, the cell would continue living and, in theory, so could we.

Once scientists figure this out, Demko thinks we could live to see 300.

Oxidation, genetics, diet, and enzyme and hormone activity all play a role in how we live and when we die. But what exactly causes the heart, kidney or liver of an otherwise-healthy human to fail? Although these death genes are being isolated, scientists know little about them.

Trying on genes

Rose's fruit flies are the product of natural selection, which normally works against longevity. Ten thousand years ago, people died long before they needed genes to give them an advantage in aging.

Traits that alter diseases that humans get later in life, such as Parkinson's and Alzheimer's, are less likely to be passed on because younger people do most of the reproducing.

To breed his age-defying flies, Rose allowed aging to take its toll by delaying breeding in generation after generation of flies. This allowed cancer and other diseases to weed out individuals before they reproduced.

This meant that flies with genes that helped fight off aging were more likely to be around to pass along those genes to their offspring. With each generation, more of the population had the anti-aging genes.

This technique, of course, could not morally be used with humans. Neither is it practical, since human reproduction is much slower than in fruit flies. A genetically produced change would have to be massive and would take hundreds of years.

Genetics, however, allows researchers to get around Mother Nature.

Scientists investigating hundreds of thousands of human genes identified in the Human Genome Project are looking for those genes most common in centenarians.

Finding those genes, Rose said, would allow researchers to learn how to turn the genes on and off or to make drugs that mimic the proteins regulated by the genes.

Simple changes

Increased longevity would produce huge changes in family life, the workplace and society. People living 150 years might have several careers, and married

couples might want to re-examine the traditional vow of "until death do us part."

"It's one thing to have another 10 years with your wife or husband -- but another 50 of his not cleaning up the sink?" said Robert Binstock, a medical ethicist at Case Western Reserve University in Cleveland.

More fundamental is whether longevity would be available to everyone and not just to the rich or well-connected.

Treatments are not expected to be cheap, and insurance companies may not cover life-extension techniques if they do not treat a specific illness. The oldest among us, Binstock said, may be only those wealthy enough to afford it.

University of California physiologist Bruce Ames said society will have to make some changes if we start seeing a lot of 120-year-olds by midcentury.

"People have to behave. They can't get obese and smoke, and they have to get enough exercise," Ames said.

Slimming down helps lab animals live 25 percent longer. That equates to about 19 years for an American without a single breakthrough in the lab. And although rats are not humans, we do share about 95 percent of the same genes.

More-fundamental changes, such as tinkering with the hormone system, could help.

So would unraveling the complexities of the estimated 1 million chemical reactions that occur in each cell where DNA is transcribed, proteins are made and destroyed, nervous impulses are generated and hundreds of body-regulating enzymes are produced.

Researchers think the key to understanding cell function lies in the mitochondria, microscopic powerhouses that are one of the most complicated systems in the human body. Mitochondria convert food sugars, fatty acids and other food molecules to a form of chemical energy used by the cells.

Ames has studied decaying mitochondria and said he thinks that they lower energy levels in older people and result in loss of brain function, as well as leading to Parkinson's, Alzheimer's and other degenerative illnesses.

Mitochondria function is linked to diet, Ames said, adding that we can "tune up" our mitochondria by paying attention to micronutrients such as iron, manganese and folic acid. These stimulate key proteins such as cardiolipin, which helps maintain the mitochondrial membranes where the energy conversion occurs.

Growing new organs

Ohio State scientists are learning how to use stem cells to grow body parts. Using microscopic, 3-D scaffolding, they have transformed mouse stem cells into fat cells. The technique could be used to entice stem cells to form new kidneys, livers and other tissues.

"There is a serious shortage of transplantable organs available for thousands of patients nationally," said OSU researcher Dr. Douglas Kniss, a professor of obstetrics and gynecology.

"One goal of this work might be creating new tissue that could serve either as a

temporary substitute while waiting for a donor organ or provide a replacement organ."

While organ-replacement research could lead to longer lives, Kniss said it is more likely to improve the quality of life as a person ages.

In part, this is because most of us seem to die of something. Humans are a bit like automobiles in that regard, said Marvin Boluyt, a heart specialist at the University of Michigan.

"When they build a car, they don't build the tires to last 800,000 miles," Boluyt said. "It is not cost-effective to have one component last a lot longer."

Replace a liver and something else eventually goes wrong, he said, pointing out that dieting rats may live longer but still eventually die from organ failure.

For the most part, human cells don't reproduce that much, and those that do can only divide so many times.

And as cells age, muscles weaken, wrinkles form, and eyesight and hearing begin to fail.

Hormones and other regulators also can change function with age.

William Sonntag, a researcher at Wake Forest University's Baptist Medical Center in Winston-Salem, N.C., discovered that deficiencies of certain growth hormones extend the lives of rodents and reduce cancer and kidney disease late in life.

But these same growth hormones also may lead to cartilage degeneration and memory problems.

"Proteins that benefit you when you're young become deleterious as you get older," Sonntag said.

Everything is connected in the human body, said Malarkey, who also studies endocrine hormones, which he thinks age as well.

"Endocrine-immune interactions help determine inflammation, and inflammation leads to accelerated aging, cardiovascular problems, arthritis and probably cancer," he said.

Ames and Rose view such problems as bumps in the road rather than roadblocks, especially as an aging population offers more bodies to study.

Malarkey said he is more interested in increasing the quality of life by pushing back disease, not life spans.

Theoretical life span, however, has proved to be just that. The finish line is constantly changing. Although scientists set the projected maximum life span at 125, that could change.

"Twenty years from now they'll be eating those words," Rose said.