Up Close With

Cynthia McMurray

MOLECULAR BIOLOGIST

McMurray fell in love with science in high school.

She realized that chemistry could help her understand the world.

When she's not at the lab, you may find her:

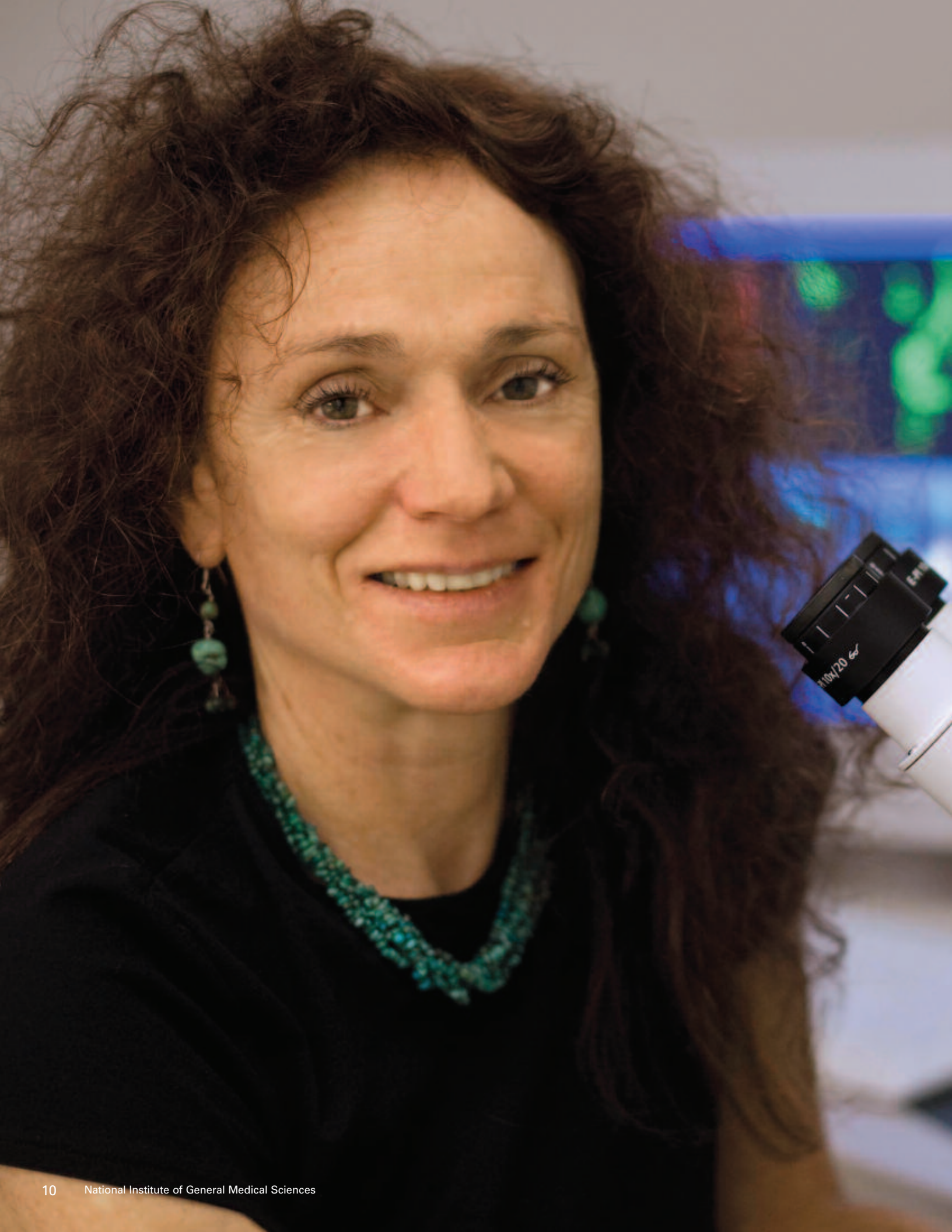
…Listening to music at local jazz clubs

…Playing the piano at scientific meetings

…Sketching in charcoal

…Running on the treadmill

MATT C. MEYER



MATT C. MEYER

Living With Huntington's

BY EMILY CARLSON

Tom makes a quick dinner for his wife and sons and then heads out the door. It's the last Thursday of the month—his day to spend a few hours with friends.

They don't bowl or play cards, or even munch on snacks. They sit in a circle and talk.

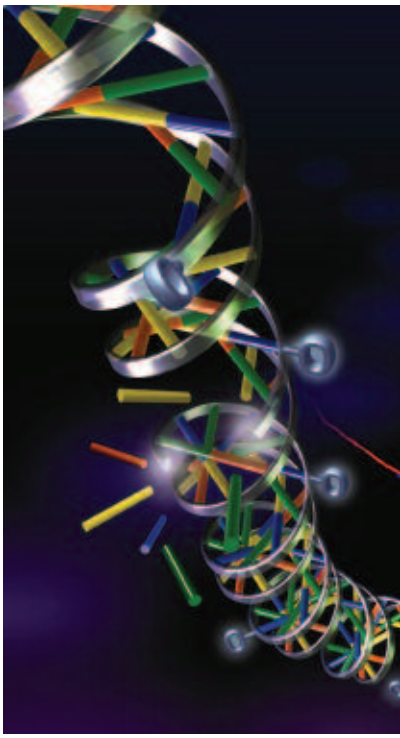
What brings them together is Huntington's, a disease that's ravaging the bodies and minds of their parents and partners.

An NCAA baseball cap hides Tom's graying hair. His shadow of a beard and haggard face show that the last few weeks have been rough. Tom is the sole caretaker of his wife, Beth, who started showing symptoms a few years ago.

An incurable disorder passed from parent to child, Huntington's targets the brain, triggering the death of cells vital to movement, speech, mood, and memory.

The disease has already stalled Beth's mental and physical abilities. She can spend 2 hours signing her name on a greeting card or 20 minutes going down the stairs.

"She doesn't get frustrated," says Tom, who admits that he's not always quite as patient.



CYNTHIA McMURRAY

Huntington's disease damages DNA in brain cells.

Huntress of Huntington's

Cynthia McMurray, 50, is also living with Huntington's. For her, though, the connection is very different.

She doesn't have the disease, but it's a big part of her daily life. For the last 15 years, she has been doing research to learn how Huntington's dismantles and destroys brain cells.

Huntington's has been around for centuries, but we're only beginning to know its secrets.

Records dating as far back as the Middle Ages have described people overtaken by a constant, uncontrollable, dancelike motion that makes them writhe, twist, and turn. People with this condition were said to have chorea—the Greek word for dance.

But this behavior brought on by Huntington's hasn't always been linked to the disease.

Huntington's has been around for centuries, but we're

In fact, experts suspect that some of the women persecuted as witches in Massachusetts during the late 1600s actually had Huntington's, which caused their so-called "possessed" behaviors.

Many people with the disorder have been misdiagnosed. Doctors mistook the erratic moods and movements of folksinger Woody Guthrie, famous for his song "This Land Is Your Land," for alcoholism and schizophrenia.

In 1952 and at the age of 40, Guthrie was properly diagnosed with Huntington's. His mother and two children also had the disease.

Even though only 1 in 10,000 Americans is living with Huntington's, each of their siblings and children has a strong risk for developing the disease.

Believe it or not, we all carry the gene involved in Huntington's—just one of some 20,000 genes that make up the human genome.

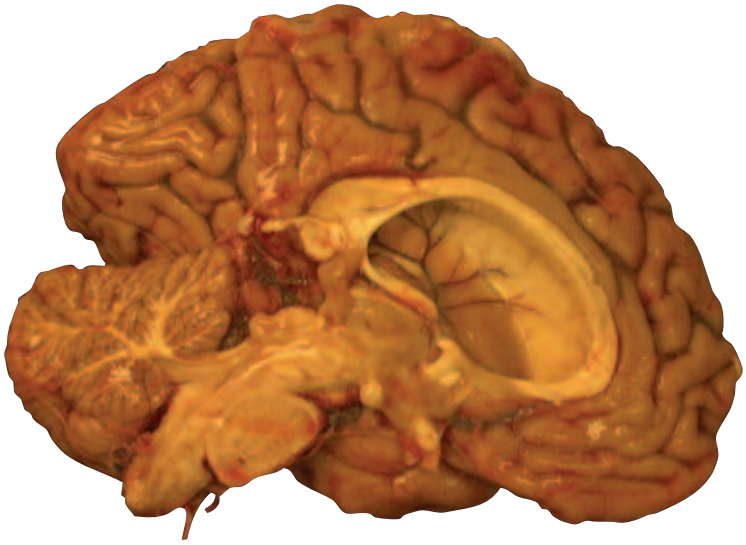
But only those of us with a slight glitch in that gene go on to get Huntington's. The genetic defect is heritable, and children of parents with the disease gene have a 50-50 chance of developing it, too.

And Huntington's doesn't discriminate: It affects men and women equally and crosses all ethnic and racial boundaries.

If you have the Huntington's disease gene, you'd probably start to notice symptoms in your 30s, 40s, or 50s.

It might not be obvious at first. You might seem uncharacteristically irritable, depressed, clumsy, or forgetful. As the disease progresses, so does the severity of symptoms.

Although each person's experience with Huntington's is as unique as a thumbprint, many say that the disease can leave them feeling unbalanced and disoriented. Some report it's like being blindfolded, spun around, and then asked to walk a straight line.



This photo shows that nerve cells have died in the brain of a person with Huntington's disease, creating a large hole or ventricle in the center.

Some lose the ability to follow conversations, perform simple tasks like counting backward from 10, or even swallow food without choking.

They could, as many do, live like this for decades.

To date, there is no cure or treatment to slow the progression of Huntington's. At best, people in the full swing of symptoms rely on an assortment of medicines to help them think more clearly, steady their stride, improve their mood, and, overall, enhance their quality of life.

Missing Pieces

Researchers around the world are tackling different pieces of the Huntington's puzzle. McMurray is looking for the molecular process that causes the Huntington's gene glitch.

That process is called partial gene amplification. It means that certain parts of a gene are repeated over and over (see drawing, page 15).

The DNA in our genes is tightly packaged into organizational structures called chromosomes. As you probably already know, DNA is made of chemical building blocks that form the rungs of the DNA double-helix ladder.

FIND MORE @

Ask Cynthia McMurray about the biology of Huntington's disease at http://www.nigms.nih.gov/findings. Send in your question by October 31, 2008, and in December we'll post McMurray's responses to 5 to 10 reader questions.

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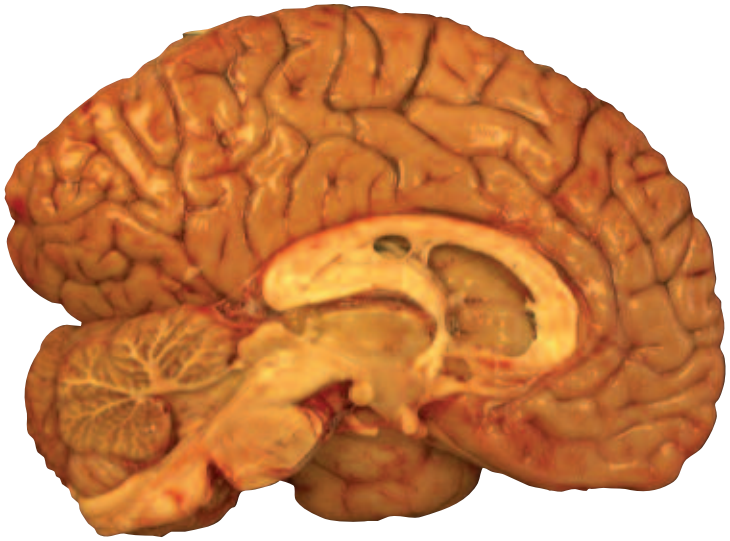

Cells in a healthy brain are intact, leaving a much smaller ventricle.
HARVARD BRAIN TISSUE RESOURCE CENTER AT McLEAN HOSPITAL

These bases are adenine (A), cytosine (C), guanine (G), and thymine (T). The order, or sequence, of the bases codes the specific biological instructions contained in a gene.

So, for example, attached or free earlobes are known to be inherited. Imagine that the sequence ATCG**T**T might say "attached earlobes," while ATCG**C**T might say "hanging earlobes."

In the early 1990s, when McMurray started her molecular biology lab at the Mayo Clinic in Rochester, Minnesota, she planned to study DNA structure. She was particularly fascinated by how gene segments get amplified, especially the repeating trio of bases C, A, and G.

Researchers have known since 1992 that CAG repeats in particular are common to several brain diseases, including Huntington's.

People with Huntington's have between 37 and 80 CAG repeats, while those not at risk have only a few dozen. For those at risk, more repeats typically mean symptoms will appear earlier in life and be more severe.

Looking back on her research, McMurray says, "It seems clear to me now that if we could stop the expansion of CAG in DNA, we could delay the onset of the disease."

McMurray's interest in Huntington's was piqued in 1993 when scientists announced a breakthrough on the disease front: A team had located the Huntington's gene at the tip of chromosome 4. The chromosomes in a single cell pack about 6 feet of DNA, so narrowing down the gene to a short region was a major accomplishment.

Patients and caregivers of loved ones with Huntington's listened with great hope for new treatments and even a cure. McMurray started to think about how the disease could help her understand how genes produce repeats.

"Studying disease is a way to see how things work," explains McMurray. "It's a window that lets

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Some genetic variants of corn are rich in vitamin A.

Corn Gets an A

It's true—eating carrots can actually help you see better! Orange and yellow vegetables are packed with vitamin A that is important for good vision.

Vitamin A deficiency, which causes blindness, affects nearly 200 million children, mostly in sub-Saharan Africa and other developing countries where fruits and vegetables are scarce. Although corn is a dietary staple in these regions, its vitamin A content varies quite a bit.

To combat this, plant breeders have relied on visual cues—such as the "yellowness" of corn, to select and grow corn with more vitamin A. But the method is not always accurate.

Biologist **Eleanore Wurtzel** of the City University of New York and her students teamed up with other researchers to find a more accurate way. They discovered genetic markers—changes in corn DNA sequence—that could identify which varieties contain more of the natural plant molecules that make vitamin A.

Wurtzel hopes that in time, her work will lead to simple genetic tests that farmers in developing countries can use to choose the most nutritious corn seeds. *—A.D.*

Listen to Wurtzel talk about her research at http://publications.nigms.nih.gov/multimedia/wurtzel.mov.

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What's Your Genetic Destiny?

Kind of like gazing into a crystal ball, could gene testing be a way to see your future health?

Today, you can be tested for nearly 1,500 different disorders. Starting with a sample of hair, saliva, or skin, lab researchers can scan your DNA for gene abnormalities linked to certain diseases.

The results may tell you if you are at risk for developing breast cancer, iron overload, or the brain disease called Huntington's (see "Living With Huntington's," page 10).

Would you change your lifestyle? Undergo preventive treatment? Maybe you'd decide to do nothing. Faced with the choice, many people considering genetic testing seek advice from a genetic counselor.

But not everyone wants this information.

Knowing you'll develop a disease—or at least have that chance—could be devastating. If there's no cure or effective treatment for the condition, you may feel helpless in facing the years ahead. With the possibility of passing on an errant gene, you may decide not to have children.

If your boss knew you'd develop a chronic disease in 2010, would she still give you a promotion? Would your insurance company deny you coverage? Many people think a person's genetic information might lead to discrimination.

Looking ahead at these serious issues, legislators introduced a bill in 1995 that would protect genetic information from misuse. In 2008, the Genetic Information Nondiscrimination Act, or GINA, was signed into law.—*E.C.*

"Studying disease is

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you see what cells normally do and why things go wrong."

Just as Huntington's stripped people of stability in their thoughts, moods, and motions, McMurray suspected that it somehow stripped DNA of its stable structure.

Following her hunch, she proved in the lab that the CAG repeats formed abnormal, looplike structures on parts of DNA, enabling them to repeat even more.

Such unusual structures usually don't stick around because our cells know how to seek and destroy them before they cause long-term DNA damage, like the insertion of an incorrect A, C, G, or T, or a deletion of one or several bases.

But what allows the looplike structures to become permanent?

DNA Damage

Picture this: Around 10,000 times a day, the environment and the body itself assault our DNA and we don't even know it. A lot of this damage is a byproduct of the normal energy production taking place in our cells' mitochondria.

The damage is caused by reactive oxygen species, or free radicals. Fortunately, our cells have several DNA repair processes that typically protect us from any permanent harm.

"Almost everybody lives their lives in reasonable health because we have these guardians that check for problems and fix them," says McMurray.

But sometimes, the guardians stop working, McMurray explains, causing the free radicals to pile up. Most experts agree that normal aging results in part from a natural buildup of free radicals.

McMurray's research suggests that this oxidative damage allows CAG looplike structures first to form, and

a way to see how things work."

then to repeat themselves. The body tries to remove the structures, but for some reason fails. So the CAG repeats stay and continue to stretch.

"Our hypothesis is that the oxidative damage initiates the expansion process," says McMurray.

Her recent experiments in mice with the Huntington's disease gene show that normal DNA repair machinery can snip out the extra triplet repeats for a while but loses ground as oxidative damage increases with age. This may explain why symptoms typically appear in mid-life and appear earlier when there are more repeats to remove.

But McMurray suspects there's more to this story.

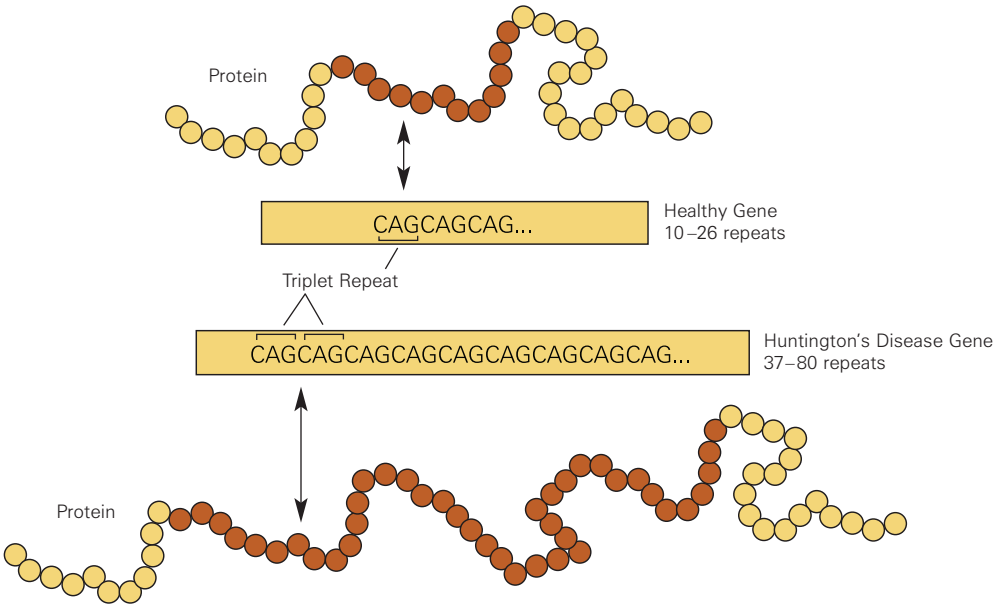
She has also found that cholesterol accumulates in the brains of mice with Huntington's. Cholesterol often gets a bad rap, but this waxy substance is critical for brain cells to work properly and stay structurally intact.

In the case of Huntington's, cholesterol doesn't get delivered to the right locations. McMurray likens the situation to a cholesterol "traffic jam." Clearing the jam, she found, reversed the motor decline typically seen in mice with Huntington's.

McMurray noticed that the cholesterol congestion also appeared to affect the mitochondria, which churn out the free radicals causing DNA damage. She's currently running experiments to see if the cholesterol buildup might contribute to cellular stress and trigger more CAG repeats.

Merging Views

From the perspective of people who are living with Huntington's disease, research has not advanced fast enough, but from the scientific perspective, progress has actually been impressive.



The DNA in brain cells of people with Huntington's has been partially amplified, leading to as many as 80 "triplet repeats" of the bases C, A, and G.

"It's really difficult to find the genesis of a disease," says McMurray. "But I think there's huge hope for the future."

Since scientists identified the Huntington's gene in 1993, researchers worldwide have published more than 5,000 findings related to the disease. Among them is a genetic test to determine if someone at risk carries the disease gene (see "What's Your Genetic Destiny?" page 14).

The scientific advances continue to drive McMurray toward a better understanding of Huntington's and the underlying molecular process that causes it.

"Getting excited about results [of my experiments] and thinking about the implications is what I love the most," says McMurray.

Each morning after a few cups of coffee, a blast of Aretha Franklin, and a quick workout, McMurray hits the lab and stays there for about 12 hours.

You can judge her progress by the papers on her desk. The taller the piles, the busier she is. When she finishes a project, she straightens up to make room for her next big idea.

McMurray also spends a chunk of her workday interacting with people who have Huntington's and their caregivers. As a basic researcher working at the Mayo Clinic, which treats people with a range of complex diseases, McMurray is motivated by both scientific curiosity and a desire to help people.

She routinely answers calls from people with Huntington's or others interested in learning more about the disease. Some even want to donate tissue samples for research. To update the community about research advances, she speaks to local support groups.

"The amount of courage and hope and love that exists in these families," she says, "is just unbelievable."

McMurray says these interactions help the Huntington's disease community

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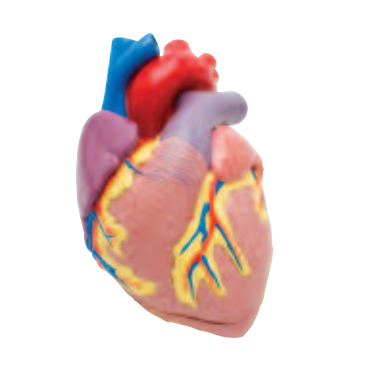

Scientists are one step closer to making a human heart from scratch.

Fix for a Broken Heart?

Embryonic stem cells have the potential to become any of the body's 206 cell types. Scientists are working hard to get these "blank slate" cells to grow into replacement cells for different body organs.

The task has proven to be difficult, but researchers are slowly making progress. In one recent advance, cell biologist **Gordon Keller** of the McEwen Centre for Regenerative Medicine in Toronto, Ontario, Canada, transformed human embryonic stem cells into immature heart cells.

Keller perfected a concoction of nutrients and proteins that, when added to the embryonic stem cells, forced them to become immature heart cells. He then showed that the young heart cells could grow into all three types of cells that make up a functional, beating heart.

With more research, scientists may be able to coax the immature heart cells into forming new heart tissue, a complex blend of the three cell types. The work will also help researchers understand heart disease and test new medicines to treat it. —*A.D.*

There's huge hope for the future.

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understand new findings and, more generally, recognize the challenges of science. The information also helps them appreciate that research can be unpredictable in its pace and outcomes, she adds.

"Each advance is like a puzzle piece," says one Huntington's caregiver at a support group meeting, "but it's like the researchers are starting in the middle of the puzzle and don't know where the edges are."

"The number of pieces seems infinite."

Pandora's Box

But as with any puzzle, a single piece still helps to complete the picture.

For McMurray and other scientists working on Huntington's, advances offer new details that allow them to ask and answer new questions. A research team in Georgia, for example, recently developed a model for studying Huntington's in nonhuman primates, our closest genetic relatives. The finding was posted on numerous Huntington's blogs.

Despite this steady progress, people with Huntington's and their caregivers realize that researchers probably won't find a cure in time to help them. They do hope, though, that a cure—or at least better treatments—will be available to their children who are at risk for developing the same devastating symptoms.

Until then, they must continue to make tough decisions.

On this last Thursday night of the month, Michelle talks about her choice to forgo the Huntington's disease gene test. Her father was recently diagnosed.

If Michelle inherited the gene, there's a chance her teenage daughter did too. She's not ready for that answer.

"You spend a lot of time fretting and dwelling on if you have the gene," she says. "But it's like a Pandora's box—at the bottom is hope."

Meanwhile, Tom talks about his decision to leave his high-paying job to help his wife when she started to need full-time care. As his former colleagues plan for retirement, Tom becomes even more uncertain about his future.

"Her getting sick was one of my worst fears," Tom admits. "Only recently have I realized that something as terrible as Huntington's can make things better."

"I love her more today than ever before," he says.

In a different part of the country, McMurray is still in her lab, deciding the future direction of her Huntington's disease research.

She's working on a plan for a new research project that builds on her earlier findings. The messiness level of her desk: intermediate.

While McMurray can't predict what the new research will tell her, she knows she'll keep hunting for the answers. And that means her desk won't be tidy anytime soon. ●●●

Many people with Huntington's prefer to keep their diagnoses private. For this reason, the names of patients and caregivers mentioned in this article have been changed.

FIND MORE @

Listen to McMurray talk about her research at http://www.nigms.nih.gov/findings.