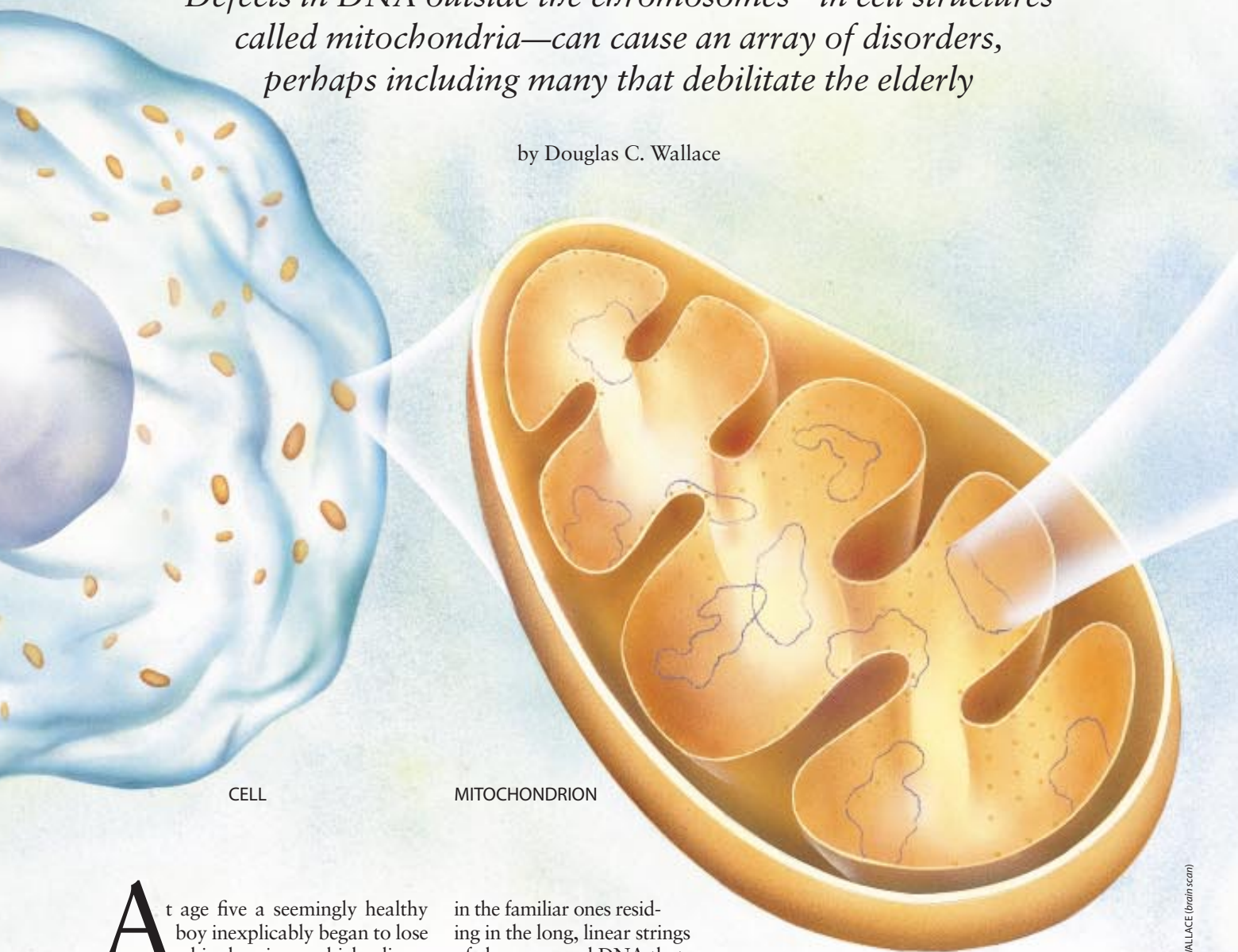# Mitochondrial DNA in Aging and Disease

*Defects in DNA outside the chromosomes—in cell structures
called mitochondria—can cause an array of disorders,
perhaps including many that debilitate the elderly*

by Douglas C. Wallace

CELL   MITOCHONDRION

A t age five a seemingly healthy boy inexplicably began to lose his hearing, which disappeared entirely before he turned 18. In the interim, he was diagnosed as hyperactive and suffered occasional seizures. By the time he was 23, his vision had declined; he had cataracts, glaucoma and progressive deterioration of the retina. Within five years he had experienced severe seizures, and his kidneys had failed. He died at 28 from his kidney disorder and a systemic infection.

At the root of his problems was a minute imperfection in his genes—but not in the familiar ones residing in the long, linear strings of chromosomal DNA that populate every cell nucleus. Instead he was killed by an abnormality in tiny circles of lesser known DNA located in his mitochondria, the power plants of cells. Each such circle contains the genetic blueprints for 37 of the molecules mitochondria need to generate energy.

Scientists have known since 1963 that mitochondria in animals harbor their own genes, but errors in those genes were not linked to human ailments until 1988. In that year, my laboratory at Emory University traced the origin of a form of young-adult blindness (Leber's hereditary optic neuropathy) in several families to a small inherited mutation in a mitochondrial gene. At about the same time, Ian J. Holt, Anita E. Harding and John A. Morgan-Hughes of the Institute of Neurology in London connected deletion of relatively large segments of the mitochondrial DNA molecule to progressive muscle disorders.

       Mitochondrial DNA in Aging and Disease

EVERY CELL IN THE BODY contains hundreds of mitochondria, the power plants of cells. A single mitochondrion contains several loops of DNA, each of which includes 37 genes involved in energy generation. Mutations in mitochondrial genes are inherited solely from mothers. They have been linked to sometimes devastating, often degenerative disorders, especially of the brain and muscles. The brain scan (*right*) shows a pattern common in many people with mitochondrial DNA diseases—degeneration of the basal ganglia (*boxed*), areas that are important to coordinated motion.

MITOCHONDRIAL
DNA
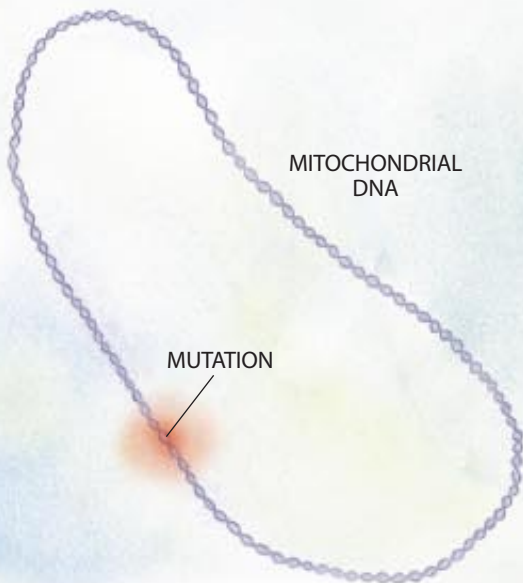
MUTATION

Investigators at Emory and elsewhere have now learned that flaws in mitochondrial DNA cause or contribute to a wide range of disorders, some of which are obscure but potentially catastrophic. Of perhaps more general interest, mutation of this DNA has a hand in at least some, and perhaps many, cases of diabetes and heart failure. Further, a growing body of evidence suggests that injury to genes in mitochondria may play a role in the aging process and in chronic, degenerative illnesses that become common late in life—such as Alzheimer's disease and various motor disturbances.

Mitochondrial DNA has been attracting attention lately on other grounds, too. By comparing the sequences of base pairs (the variable "rungs," or coding units, on the familiar DNA "ladder") in the mitochondrial DNA of different populations across the globe, scientists have gained exciting clues to the evolution and global migrations of anatomically modern humans [*see box on pages 46 and 47*]. And forensic investigators have found smaller-scale comparisons useful for identifying the remains of soldiers missing in action (and for others long dead) and for determining wheth-

er accused criminals are responsible for misdeeds attributed to them [*see box on page 44*].

Although most biologists paid little attention to mitochondrial DNA until quite recently, mutation of the genetic material in mitochondria might have been predicted to have consequences for human disease. Mitochondria provide about 90 percent of the energy that cells—and thus tissues, organs and the body as a whole—need to function.

They generate energy through a complicated process that involves the relay of electrons along a series of protein complexes (collectively known as the respiratory chain). This relay indirectly enables another complex (ATP synthase) to synthesize ATP (adenosine triphosphate), the energy-carrying molecule of cells.

Early on, logic suggested that anything able to compromise ATP production severely in mitochondria could harm or even kill cells and so cause tissues to malfunction and symptoms to develop. Indeed, in 1962 Rolf Luft and his co-workers at the Karolinska Institute and the University of Stockholm reported that an impairment in mitochondrial energy production caused a debilitating disorder. Eventually it became clear that the tissues and organs most readily affected by cellular energy declines are the central nervous system, followed, in descending order of sensitivity, by heart and skeletal muscle, the kidneys and hormone-producing tissues.

Scientists initially sought the explanation for mitochondrial disorders in mutations of nuclear genes, some of which give rise to mitochondrial components. But by the early 1980s, researchers understood that mitochondrial DNA codes for a number of important molecules. It specifies the structure of 13 proteins
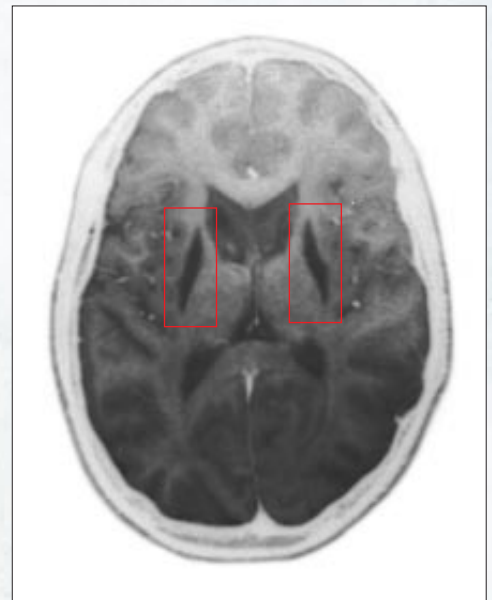
(chains of amino acids) that become subunits of ATP synthase and the respiratory chain complexes, and it specifies 24 RNA molecules that help to manufacture those subunits in mitochondria. These findings implied that mitochondrial DNA mutations able to disrupt mitochondrial proteins or RNAs could potentially disturb the energy-producing capacity of mitochondria and produce disease—a suspicion that was borne out by the 1988 reports.

Odd Rules of Inheritance

Since 1988, investigators have uncovered several remarkable features of the syndromes that spring from defects in mitochondrial DNA. For instance, these conditions are often inherited, though not in the same way as disorders issuing from mutations in nuclear genes. And the resulting symptoms are more unpredictable than those caused by nuclear genetic mutations.

The well-known processes governing inheritance of nuclear genetic diseases begin, of course, with fertilization of an egg by a sperm. The single-cell embryo emerging from this union ends up with a solitary nucleus containing matching sets of gene-laden chromosomes—one set of approximately 100,000 genes (spread along about three billion base pairs) from the mother and an equivalent set from the father. This cell and its descendants replicate repeatedly to form the fully developed child. Before the cells divide, they duplicate their chromosomes, so that they can bequeath a complete complement of maternal and

Why Mitochondrial DNA Is Needed

Mitochondria produce energy by relaying electrons from food (*orange arrows in left diagram*) down the respiratory chain—a series of protein complexes (I–IV) in the mitochondrial inner membrane. At complex IV, the electrons interact with oxygen and protons (H^+) to form water. Mitochondria use the energy released from the oxidation of hydrogen to pump protons (*gray arrows*) across the inner membrane. The resulting charge and chemical differential enables another complex, ATP synthase, to synthesize the energy-carrying molecule ATP (adenosine triphosphate). Thirteen proteins in the complexes are specified by genes in mitochondrial DNA; regions incorporating those proteins are colored brightly. The DNA, shown schematically at the right, also gives rise to 24 RNA molecules used to synthesize those proteins. Each building block (base pair) of mitochondrial DNA is numbered counterclockwise from the position labeled O_H. Some sites of disease-causing mutations are indicated; see the table on the opposite page for full names of acronyms. —*D.C.W.*
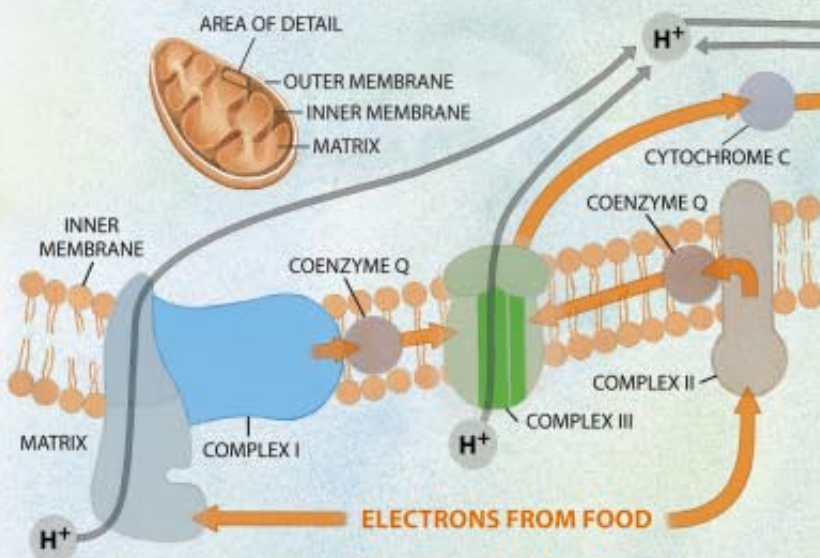
paternal chromosomes to each daughter cell. In this way, every cell of the body comes to carry identical genes—and identical mutations.

In contrast, the genes spread along the 16,569 base pairs in each circle of mitochondrial DNA are inherited solely from the mother, through the mitochondria in her egg; sperm make no lasting contribution. Further, each egg and all other cells of the body carry not one but hundreds of mitochondria, and every mitochondrion can contain several mitochondrial DNA molecules. Although a cell will approximately double its number of mitochondria and mitochondrial DNA molecules before dividing and will provide roughly equal amounts to its daughter cells, the original cell does not regulate which specific mitochondria go to each daughter.

Consequently, if a fertilized egg carries a mutation in some fraction of its mitochondrial DNA (a condition known as heteroplasmy), one daughter cell may inherit a larger proportion of mitochondria bearing mutant DNAs, and the other cell may inherit a larger percentage of mitochondria bearing normal DNAs. The laws of probability dictate that as the cells continue to reproduce, the mitochondrial DNA populations in the emerging daughter cells will move toward uniformity (homoplasmy), tending to consist of predominantly normal or predominantly mutant molecules.

A child born from a heteroplasmic egg can therefore have some tissues enriched for normal mitochondrial DNAs and others enriched for mutant DNAs.

Moreover, the eggs of a woman with heteroplasmic cells can differ in their percentages of mutant mitochondrial DNA; her children can therefore differ markedly in the extent and distribution of mutant molecules in their tissues and in the severity, and even in the kind, of symptoms they display. Individuals who become ill from a homoplasmic mutation, however, will all display similar symptoms.

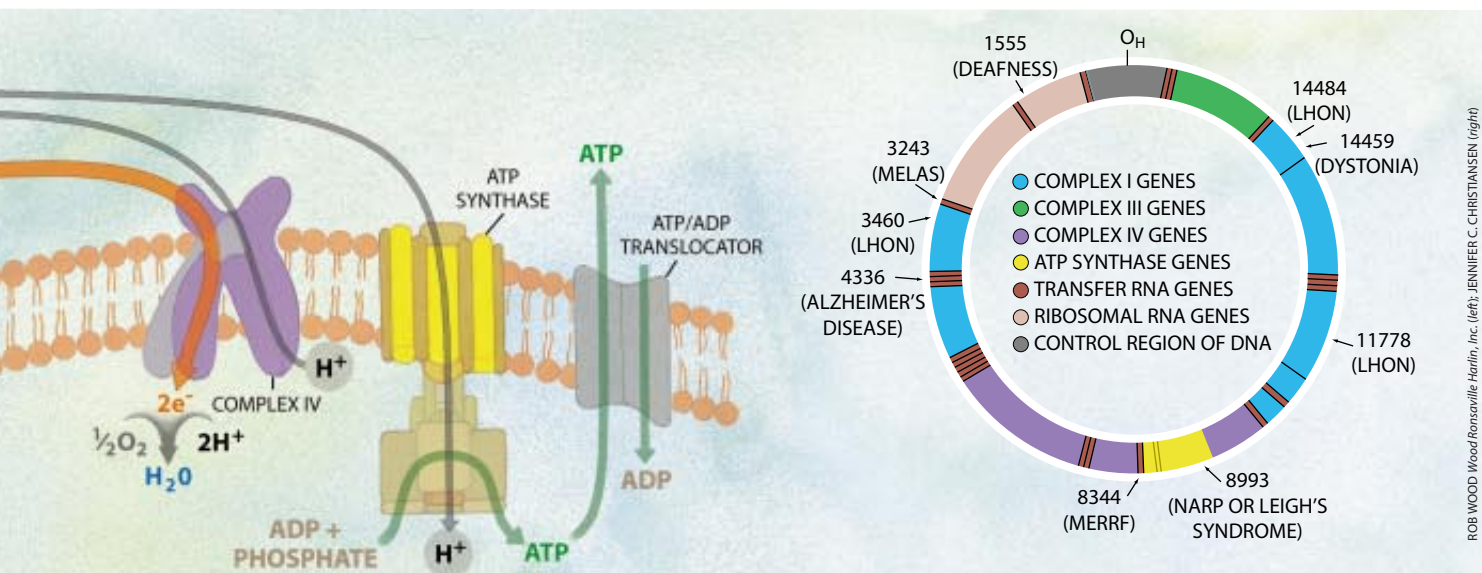### Striking Features of the Diseases

Disease-causing mitochondrial DNA defects are frequently inherited, but they do occasionally arise spontaneously in an egg or early in embryonic development. The latter mutations, like inherited ones, can become widely distributed in the body as the fetus develops, in which case they may produce rather profound effects. Mitochondrial DNA mutations can also form in tissues throughout life, with different mutations potentially occurring in different cells and even in different mitochondrial DNA molecules in a single cell; these changes are called somatic mutations.

The accumulation of somatic mutations might help explain two features frequently observed in inherited mitochondrial DNA diseases. People born with mitochondrial DNA mutations often become ill only after a delay of years or sometimes decades, and their conditions usually worsen over time. My colleagues and I have proposed that many inherited mitochondrial DNA mutations affect mitochondrial function only sub-

tly, allowing tissues throughout the body to produce the energy they need, at least for a time. But the added buildup of random, somatic mutations in the course of a lifetime further depresses energy production, until eventually a given tissue's energy level falls too low to allow normal operations to continue. Then the tissue begins to perform improperly, and symptoms emerge. As somatic mutations accumulate further, energy output continues to decline, and symptoms progress.

Actually, inborn and somatic mutations appear to contribute to disease in ways that go beyond reducing energy production directly. As the respiratory chain participates in energy production, toxic by-products known as oxygen free radicals are given off. These oxygen derivatives, which carry an unpaired electron and so are highly reactive, can attack all components of cells, including respiratory chain proteins and mitochondrial DNA. Anything that impedes the flow of electrons through the respiratory chain can increase their transfer to oxygen molecules and promote the generation of free radicals. A single mutation, then, can presumably initiate a recurring cycle of inhibited electron transport, leading to increased free-radical production and more mitochondrial DNA mutations.

As a rule, a severe mitochondrial DNA mutation—one that suppresses energy production so much that it causes life-threatening disease early on—will turn out to be heteroplasmic; that is, the mutant gene will be found to coexist in the

Diagram labels:
- O$_H$
- 1555 (DEAFNESS)
- 14484 (LHON)
- 14459 (DYSTONIA)
- 3243 (MELAS)
- 3460 (LHON)
- 4336 (ALZHEIMER'S DISEASE)
- 11778 (LHON)
- 8344 (MERRF)
- 8993 (NARP OR LEIGH'S SYNDROME)

Legend:
- COMPLEX I GENES
- COMPLEX III GENES
- COMPLEX IV GENES
- ATP SYNTHASE GENES
- TRANSFER RNA GENES
- RIBOSOMAL RNA GENES
- CONTROL REGION OF DNA

Left diagram labels: ATP, ATP SYNTHASE, ATP/ADP TRANSLOCATOR, H$^+$, 2e$^-$ COMPLEX IV, ½O$_2$ 2H$^+$, H$_2$O, ADP + PHOSPHATE, H$^+$, ATP, ADP

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patient's tissues with the normal version of the gene. The reason for this pattern is that severe homoplasmic mutations (which reside in every copy of a given gene in every tissue) would reduce energy production so profoundly that they would become lethal before birth; they are therefore never seen in patients. In contrast, when a severe mutation is heteroplasmic, the normal copies of the affected gene may provide enough energy to allow a person to survive into childhood or later. Milder diseases can stem from either a heteroplasmic or a homoplasmic mutation that leads to only a weak decline in energy production.

Small Mutations, Powerful Effects

In the text that follows, I will first describe examples of disorders stemming from inherited (or embryonic) mutations in mitochondrial DNA. Few of these ills are household names, but their study has provided important insights into how mitochondrial DNA mutations cause disease. I will then summarize current thinking on the tantalizing possibility that inherited and somatic mitochondrial DNA mutations have a significant role in the aging process and in common late-life diseases.

Various inherited mutations substitute a solitary base pair for another in a protein-coding gene, thereby causing an incorrect amino acid to replace a correct one in the encoded protein. One such "missense" mutation offers a striking illustration of the principle that a heteroplasmic mitochondrial DNA muta-

Mitochondrial DNA Diseases

This table lists only some of the disorders that can be caused by mutations in mitochondrial DNA. Certain of these conditions can also be caused by nuclear mutations or other processes that hinder mitochondrial function.

DISORDER	FEATURES
Alzheimer's disease	Progressive loss of cognitive capacity
CPEO (chronic progressive external ophthalmoplegia)	Paralysis of eye muscles and mitochondrial myopathy [see below]
Diabetes mellitus	High blood glucose levels, leading to various complications
Dystonia	Abnormal movements involving muscular rigidity; frequently accompanied by degeneration of the basal ganglia of the brain
KSS (Kearns-Sayre syndrome)	CPEO combined with such disorders as retinal deterioration, heart disease, hearing loss, diabetes and kidney failure
Leigh's syndrome	Progressive loss of motor and verbal skills and degeneration of the basal ganglia; a potentially lethal childhood disease
LHON (Leber's hereditary optic neuropathy)	Permanent or temporary blindness stemming from damage to the optic nerve
MELAS (mitochondrial encephalomyopathy, lactic acidosis and strokelike episodes)	Dysfunction of brain tissue (often causing seizures, transient regional paralysis and dementia) combined with mitochondrial myopathy [see below] and a toxic buildup of acid in the blood
MERRF (myoclonic epilepsy and ragged red fibers)	Seizures combined with mitochondrial myopathy [see below]; may involve hearing loss and dementia
Mitochondrial myopathy	Deterioration of muscle, manifested by weakness and intolerance for exercise; muscle often displays ragged red fibers, which are filled with abnormal mitochondria that turn red when exposed to a particular stain
NARP (neurogenic muscle weakness, ataxia and retinitis pigmentosa)	Loss of muscle strength and coordination, accompanied by regional brain degeneration and deterioration of the retina
Pearson's syndrome	Childhood bone marrow dysfunction (leading to loss of blood cells) and pancreatic failure; those who survive often progress to KSS

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tion can often express itself in disparate ways in different people. This mutation—the substitution of a base at position 8993—leads to an amino acid substitution in a subunit of ATP synthase (the complex that makes ATP).

For a family in which four generations were available for study, the same mutation caused several individuals to suffer mild retinal degeneration in the periphery of their visual field (retinitis pigmentosa), another person to undergo severe retinal and central nervous system degeneration, and two ill-fated boys to acquire a potentially lethal childhood disease known as Leigh's syndrome. This devastating illness is marked by relatively rapid degeneration of the basal ganglia, a brain region important to coordination of movement. Evidently the differences in symptomatology within this family stemmed to a great extent from differences in the percentages of mutant mitochondrial DNA molecules in the patients' tissues. Those with higher percentages had lower ATP production and more extensive disease.

Certain inherited base substitutions need to reach homoplasmy before they cause problems; these mutations yield more predictable effects. The genetic defects now known to underlie most cases of Leber's hereditary optic neuropathy, otherwise known as LHON, fall into this category. LHON first becomes apparent, usually in young adulthood, when the central region of the optic nerve stops functioning, leading to loss of vision in the center of the visual field. Three mitochondrial DNA mutations,

all of which affect electron transport early in the respiratory chain, account collectively for about 90 percent of cases worldwide. Patients with either of two mutations generally suffer permanent vision loss; those with the third mutation occasionally recover some vision.

A number of pathological base substitution mutations in mitochondrial DNA disrupt RNA molecules that are part of the machinery mitochondria use to construct proteins; these mutations can thus interfere with the synthesis of many different mitochondrial proteins simultaneously and may depress ATP production substantially. For this reason, patients born with such so-called protein synthesis mutations can end up with serious multisystem diseases, often including both central nervous system and muscle abnormalities.

The case I mentioned at the beginning of this article—of the youth who died at age 28 from kidney failure and infection—reflects the potential lethality of protein synthesis mutations. He was felled by a point mutation in which one base in a gene for a transfer RNA molecule was deleted. This RNA molecule normally brings the amino acid leucine to proteins being synthesized in mitochondria. The mutation probably arose in the mother's germ-line cells, because nonreproductive cells (blood cells) of the mother were tested and found to contain only normal mitochondrial DNA.

Ten other mutations in the same gene have been shown to cause a range of serious disorders. For instance, three of the mutations result in mitochondrial

myopathy, a form of progressive muscle weakness characterized by the presence of ragged red fibers—degenerating muscle fibers filled with abnormally shaped, defective mitochondria that turn red when exposed to a specific stain. Two of the genetic defects cause abnormal enlargement and progressive deterioration of the heart muscle (hypertrophic cardiomyopathy). Five mutations affect multiple systems, causing a set of symptoms collectively referred to as MELAS (mitochondrial encephalomyopathy, lactic acidosis and strokelike episodes). One MELAS-inducing mutation also causes approximately 1.5 percent of all diabetes mellitus and can cause diabetes even when the mutation is present in low levels.

Although many inherited protein synthesis mutations in mitochondrial DNA can be fatal at a young age, some are more moderate, making themselves felt quite late in life. One example, a mutation in a gene coding for a transfer RNA molecule that transports the amino acid glutamine, is found in about 5 percent of Europeans with late-onset Alzheimer's disease.

Mitochondrial DNA mutations that affect many genes at once—by deleting or duplicating large chunks of genetic

CORBIS-BETTMANN

Jesse James, 1864

Mitochondrial DNA as a Forensics Tool

On September 3, 1996, in Chattanooga, Tenn., a 27-year-old man was found guilty of murdering a four-year-old girl. He was convicted largely on the strength of an analysis that matched mitochondrial DNA from his saliva to that from hair recovered on his victim. His case was the first in which mitochondrial DNA evidence was allowed into the courtroom.

Mitochondrial DNA tests are also being used increasingly to link names to human remains. For example, the U.S. is sponsoring a program aimed at identifying skeletal fragments of soldiers who died in conflicts dating back to the Korean War in the early 1950s. And less mournful exercises have established that bones unearthed in Russia in 1991 belong to Czar Nicholas II and that the fellow buried as Jesse James in April 1882 was in fact the fabled bandit. (The various other men who had claimed to be James were thus frauds.)

Scientists perform the tests by comparing the sequences of base pairs in mitochondrial DNA molecules, especially in the

control region, which contains no genes. Sequences in this region usually vary from one person to another at several positions. If the DNA from, say, a hair found on a murder or rape victim and DNA from an accused attacker show no differences, chances are good that the hair came from the accused. Similarly, if mitochondrial DNA from bones of a soldier lost in war closely match those of the siblings in a family, investigators can conclude that the remains are those of a member of the tested family.

Nuclear DNA comparisons are still preferred when enough of it can be obtained, because clear similarities and differences are easier to establish. Many times, however, the available tissue (such as a strand of hair, solid bone or teeth) lacks usable nuclear DNA but has abundant mitochondrial DNA. —*D.C.W.*
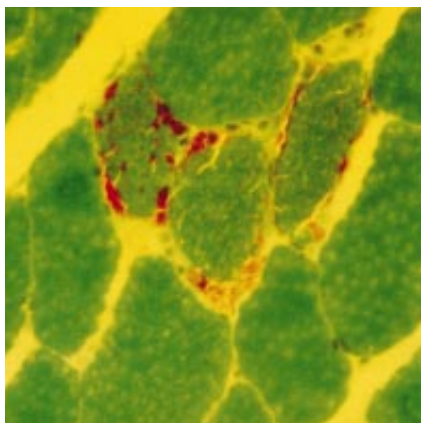
       Mitochondrial DNA in Aging and Disease

RAGGED RED FIBERS are a frequent hallmark of mitochondrial muscle diseases. They are readily identifiable by red staining of the abnormally large and misshapen mitochondria that accumulate in deteriorating muscle fibers.

material—have also been identified. Like base substitutions, these "rearrangement" mutations can cause diseases of varying seriousness.

Wholesale DNA Changes

Among the most studied disorders involving rearrangement mutations are two marked by paralysis of eye muscles and mitochondrial myopathy: chronic progressive external ophthalmoplegia (which generally strikes after age 20) and Kearns-Sayre syndrome (which may become manifest at even younger ages and can include retinal degeneration, heart disturbances, short stature and various other symptoms). Rearrangement mutations also underlie many cases of Pearson's syndrome, a condition in which children fail to make blood cells, become dependent on transfusions from an early age and have impaired pancreatic function. If the children survive, they ultimately suffer the eye paralysis and other problems associated with the Kearns-Sayre syndrome. Sadly, patients afflicted with any of these disorders become ever sicker over time and, in many instances, die of respiratory failure or other systemic dysfunctions.

The cells of a patient with one of these disorders can contain a mixture of mitochondrial DNA molecules, including some DNAs with deletions and some with duplications. But it is the deletions that probably explain why the diseases can be serious from the start. The lost DNA inevitably includes genes for transfer RNA molecules, which means, as will be recalled, that many different proteins needed for energy production are made

improperly, if at all. The characteristic worsening of the diseases over time is thought to occur in part because certain tissues—namely, muscles and others composed of nondividing cells—selectively replicate the incomplete ("deleted") mitochondrial DNAs.

No one knows why deleted mitochondrial DNAs are selectively amplified in nondividing tissues, but two speculations have been put forward. The first is that molecules bearing deletions, being smaller than normal DNA circles, take less time to replicate and so become enriched. The second explanation relates to the internal organization of muscle fibers. Each fiber consists of many merged muscle cells and so contains multiple nuclei. Various findings imply that when a nucleus detects an energetic deficit in its vicinity (such as one caused by mutant mitochondrial genes), the nucleus attempts to compensate for the power shortage by triggering the replication of any mitochondria nearby. Unfortunately, this response promotes replication of the very mitochondria that are causing the local energy deficit, further aggravating the problem.
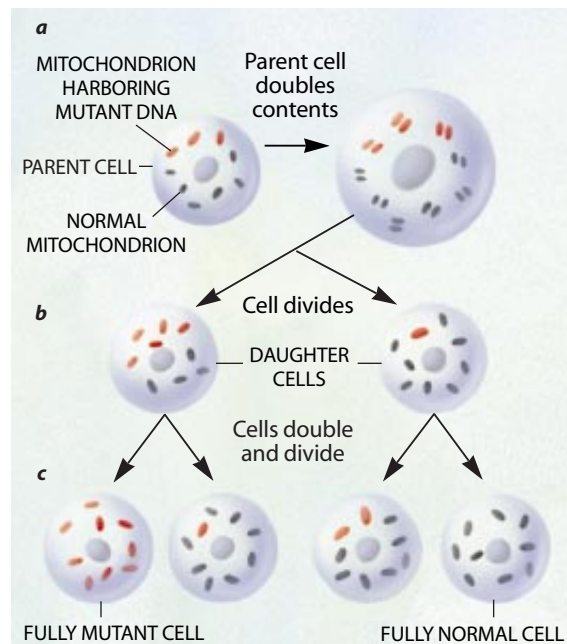
The origin of the deletions that cause mitochondrial diseases has puzzled scientists for some time. Even though these disorders can be passed from generation to generation, deleted mitochondrial DNAs themselves are rarely inherited, probably because a cell or embryo harboring mainly deleted mitochondrial DNAs would die. The solution seems to rest with mitochondrial DNA molecules containing gene duplications. These molecules contain all the genes needed for energy production, and so they may not cause problems directly. Because the molecules have internal duplications, however, they can undergo processes—possibly internal pairing and recombination—that ultimately result in disruptive deletions.

Sometimes inherited mitochondrial DNA defects yield premature versions of disorders that afflict many people in their later years, such as diabetes, deafness, heart disease, muscle weakness, move-

ment problems and dementia. Moreover, certain mitochondrial DNA mutations have been proved to cause some fraction of cases of Alzheimer's disease, dystonia (a progressive movement disorder) and other neurodegenerative diseases. These patterns—combined with the fact that a number of late-life degenerative diseases have been associated with declines in the activity of protein complexes involved in energy production (just as many mitochondrial DNA diseases are)—suggest that progressive reductions in mitochondrial energy (ATP) production in nerve, muscle or other tissues could be an important contributor to aging and to various age-related degenerative diseases.

Aging and Age-Related Diseases

Several factors could cause mitochondrial energy production to decline with age even in people who start off with healthy mitochondrial and nuclear genes. Long-term exposure to certain environmental toxins is one. Many of the most potent toxins work their mis-

CELL containing some mitochondria with mutant DNA and some with fully normal DNA (*a*) will often give rise to "daughter" cells that differ from the "parent" and from one another in the number of mitochondria having flawed DNA (*b*). As daughter cells reproduce, their mitochondrial DNA populations drift toward 100 percent mutant or normal (*c*). This drift toward uniformity occurs in cells during the development of an embryo. It also occurs in the eggs of successive generations of females, causing some children to end up with more mutant DNA, and worse symptoms, than their mother had.

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JENNIFER C. CHRISTIANSEN
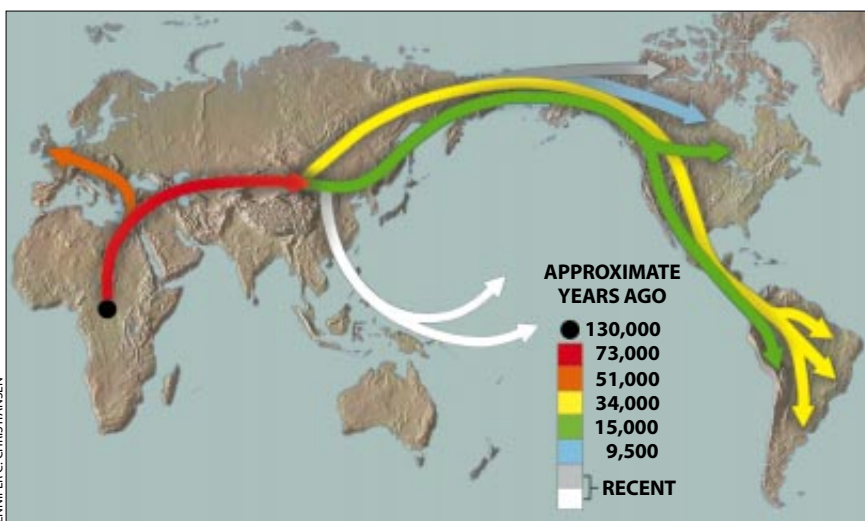
What Mitochondrial DNA Says about Human Migrations

Comparative analyses of mitochondrial DNA molecules obtained from people around the world have enabled geneticists to trace the major migrations of anatomically modern humans. These analyses, carried out by many laboratories, have also put rough dates on the ages of various continental populations, although different groups favor different dates, depending on their methods of calculation.

A scenario based on data from my laboratory suggests that *Homo sapiens* emerged in Africa approximately 130,000 years ago. The initial migration out of Africa took people to Asia (*red arrow on map*) by about 73,000 years ago. Roughly 51,000 years ago another cohort left the Middle East and colonized Europe (*orange arrow*).

Several migratory waves from Asia introduced early modern humans to the New World. About 34,000 years ago some wanderers traveled through Siberia and Alaska and then down through North America and Central America to South America (*yellow arrows*). These were the ancestors of such modern Paleo-Indians as the Pima of Arizona, the Maya of Mexico and the Yanomami of Venezuela. About 15,000 years ago a second wave of immigrants from Asia bypassed the interior of Siberia, possibly hugging the coast before reaching Alaska and dispersing through the Americas (*green arrows*). They mixed with the existing population to create today's Amerind-speaking Paleo-Indians.

About 9,500 years ago an exodus from Siberia brought the founders of the Na-déné, a linguistic group that encompasses northwestern Canadian and Alaskan Athabascan tribes

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chief by inhibiting mitochondria. Another factor could be the lifelong accumulation of somatic mitochondrial DNA mutations.

The mitochondrial theory of aging holds that as we live and produce ATP, our mitochondria generate oxygen free radicals that inexorably attack our mitochondria and mutate our mitochondrial DNA. This random accumulation of somatic mitochondrial DNA mutations in people who began life with healthy mitochondrial genes would ultimately reduce energy output below needed levels in one or more tissues if the individuals lived long enough. In so doing, the somatic mutations and mitochondrial inhibition could contribute to common signs of normal aging, such as loss of memory, hearing, vision and stamina.

In people whose energy output was already compromised (whether by inherited mitochondrial or nuclear mutations or by toxins or other factors), the resulting somatic mitochondrial DNA injury would push energy output below desirable levels more quickly. These individuals would then display symptoms earlier and would progress to full-blown disease more rapidly than would people who initially had no deficits in their energy production capacity.

Is there any evidence that energy production declines and somatic mitochondrial DNA mutation increases as humans grow older? There is. Work by many groups has shown that the activity of at least one respiratory chain complex, and possibly another, falls with age in the brain, skeletal muscle, heart and liver. Further, various rearrangement mutations in mitochondrial DNA have been found to increase with age in many tissues—especially in the brain (most notably in regions controlling memory and

motion). Rearrangement mutations have also been shown to accumulate with age in the mitochondrial DNA of skeletal muscle, heart muscle, skin and other tissues. Certain base-substitution mutations that have been implicated in inherited mitochondrial DNA diseases may accumulate as well.

All these reports agree that few mutations reach detectable levels before age 30 or 40, but they increase exponentially after that. Studies of aging muscle attribute some of this increase to selective amplification of mitochondrial DNAs from which pieces have been deleted.

Supportive Findings

Analyses of tissues from people afflicted late in life with chronic degenerative neurological and muscle diseases also lend support to the hypothesis that some of these conditions may involve the buildup of somatic mutations. For instance, patients with Huntington's disease lose motor control and become demented late in life as a result of having a specific inherited mutation in their nuclear DNA. But they also display higher levels of mitochondrial DNA deletions in their brains than do healthy individuals of equal age—a sign that the somatic mitochondrial mutation rate is

elevated. The nuclear mutation and the somatic mitochondrial mutations may well combine to depress energy production in brain cells and to produce symptoms in adulthood.

As I noted earlier, a certain amount of Alzheimer's disease has also been attributed to inborn mitochondrial DNA mutations. But the failure of these mutations to produce immediate symptoms implies that they may not be sufficient in themselves to cause disease. Acquired mitochondrial mutations that add to the effects of the inherited mutations might again be a missing link. Indeed, brain tissue from Alzheimer's patients appears to have unusually high levels of somatic changes in its mitochondrial DNA.

A particularly intriguing possibility is that a significant fraction of type II (maturity-onset) diabetes mellitus, which afflicts millions of Americans older than 40 years, may be rooted in inherited mitochondria DNA defects still to be discovered. People with this kind of diabetes secrete insulin into the bloodstream, but not enough to meet their body's needs. Diabetes is known to run in families, and the mother is often the affected parent (as would be expected with mitochondrial DNA inheritance). Further, research has already established that known mitochondrial DNA rear-

Mitochondrial DNA in Aging and Disease

(such as the Dogrib) and the southwestern U.S. Apache and Navajo (*blue arrow*). The migrations that brought Eskimos and Aleuts to North America (*gray arrow*) and island peoples to the Pacific (*white arrows*) were more recent but have not been accurately dated on the basis of mitochondrial DNA data.

The global migrations can be reconstructed through mitochondrial DNA analyses because as women migrated from continent to continent, their mitochondrial DNAs gradually accumulated one nonpathogenic mutation after another. Consequently, the sequences of base pairs in mitochondrial DNAs on one continent came to differ in distinctive ways from the sequences on other continents. By grouping related sequences on a continent into "haplogroups" and then comparing the haplogroups from the various continents, investigators can determine the relatedness of the females from different places. Scientists can also determine which lands were colonized first, because greater sequence variation in the mitochondrial DNAs on a continent is a sign of greater longevity. African populations are oldest because they harbor the greatest mitochondrial DNA variation. Asians, Europeans and the Native American populations display progressively less variation.

The actual time at which each continent came to be colonized can only be estimated, however, because the dates depend on the rate at which the mitochondrial DNA molecule accumulates mutations. This rate is relatively constant but is not known precisely. Mutations seem to occur about once in every 2,000 to 3,000 years. The dates presented here assume the mutation rate is roughly in the middle of that range.

Aside from revealing global migration patterns, analysis of mitochondrial DNA suggests that early *H. sapiens* replaced all the more primitive human species (such as Neanderthals) they encountered in their new homes. This conclusion, though, is disputed by a number of anthropologists. Those investigators hold that human predecessors of *H. sapiens* emerged in Africa more than a million years ago. They then fanned out through the Old World and evolved regionally into the major races of *H. sapiens* [see "Debate: Where Did Modern Humans Originate?"; SCIENTIFIC AMERICAN, April 1992]. —*D.C.W.*

rangement and base-substitution mutations can at times cause type II diabetes. It stands to reason that other mutations may have the same effect. One plausible diabetes-producing mechanism could be that, by reducing ATP synthesis, mitochondrial DNA mutations deprive insulin-producing cells of the energy they need to secrete insulin appropriately.

Another interesting proposal is that heart failure in patients with atherosclerosis is accelerated by the development of somatic mitochondrial DNA mutations. As arteries that are partially occluded by an atherosclerotic plaque constrict, they can close off temporarily, blocking blood flow to the heart and starving the heart muscle of oxygen—a state known as ischemia. Without oxygen, the respiratory chain stops working, only to emit a burst of oxygen free radicals when blood flow and oxygen return (reperfusion). Such bursts would be expected to damage mitochondrial DNA in the heart muscle and to limit ATP for contraction. In keeping with this scenario, patients whose hearts have become dilated from chronic ischemia and reperfusion show a high degree of mitochondrial DNA damage.

Studies of rodents bolster the suspicion that an accelerated buildup of mitochondrial DNA mutations can hasten aging. Animals raised on restricted diets remain healthy and survive longer than do their free-feeding counterparts [see

"Caloric Restriction and Aging," by Richard Weindruch; SCIENTIFIC AMERICAN, January 1996]. The long-lived, diet-restricted animals, who produce fewer oxygen free radicals, accumulate less mitochondrial DNA damage than do their well-fed littermates.

What Is to Be Done?

If free-radical damage does indeed drive the accumulation of somatic mitochondrial DNA mutations and thus influences the speed of aging, then treatments that block mitochondrial production of such radicals and thereby protect mitochondrial DNA could potentially slow aging and delay the onset of age-related diseases. Such approaches could perhaps consist of lifelong treatment with antioxidants (for example, coenzyme Q or vitamins C or E). Animal studies are encouraging in this regard.

Another strategy for slowing aging would be to limit the amplification of mutated mitochondrial DNAs in muscle and other tissue. To that end, scientists are attempting to clarify the molecular interactions by which nuclei detect local energy deficits and stimulate the reproduction of aberrant mitochondria in their neighborhood.

Ten years ago few biologists would have imagined that mutations in mitochondrial DNA would be implicated in dozens of mysterious disorders as well as in aging and a variety of chronic degenerative diseases. Today study of this DNA is offering new clues to the development of many ailments and, even better, is suggesting approaches to treating them and preventing their progression. If speculations on the role of mitochondrial DNA mutations in aging and disease prove correct, further studies of mitochondrial biology should have great potential for lessening a good deal of human suffering. **SA**

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Further Reading

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