Biology and Society

Unit Four: Genetics and Medicine

Topic Two: Genetic Screening for Cystic Fibrosis

The first rings in Peter Singer's expanding circle are the ethical issues related to individuals. Nothing is more immediate to the individual than reproduction, and nothing is more devastating to parents than genetic disease in their children.

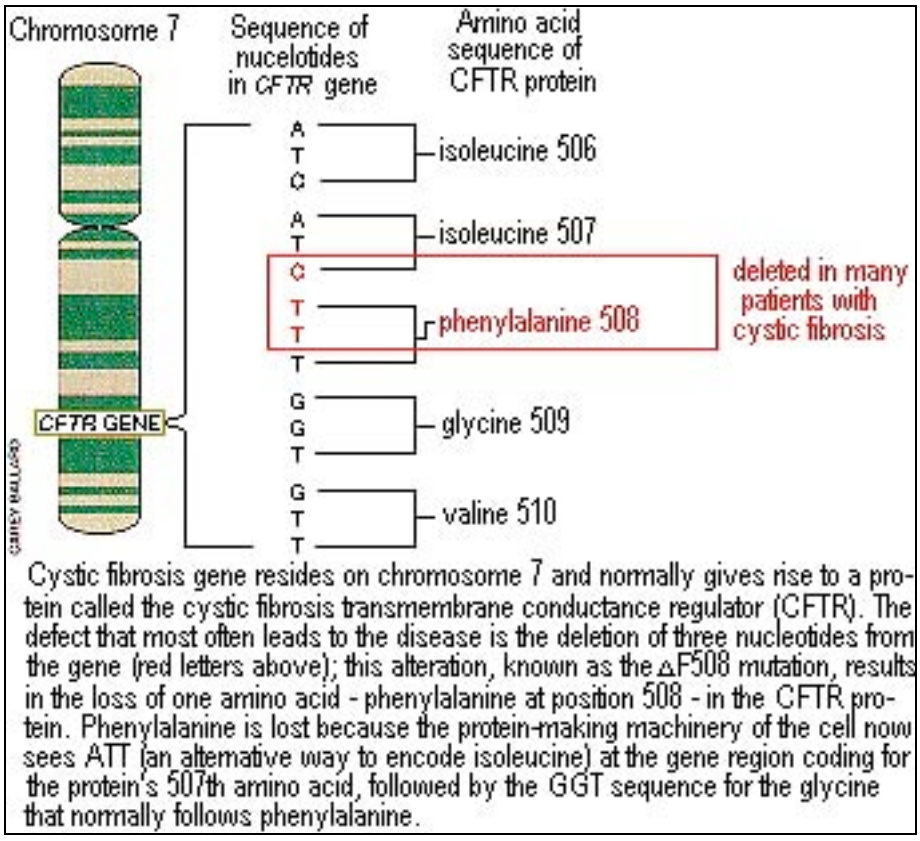
What scientific knowledge do we need to understand these issues?

What are the ethical issues raised by genetic screening for carriers of genetic diseases?

The gene and gene mutation for the most common form of cystic fibrosis was isolated in 1989. The protein produced by the gene involved was named the cystic fibrosis transmembrane conductance regulator (CFTR).

Francis Collins (1950 -)

Francis S. Collins, M.D., Ph.D., is a physician-geneticist and the current Director of the National Human Genome Research Institute. In 1989, together with Lap-Chee Tsui and Jack Riordan of the Hospital for Sick Children in Toronto, Canada, his research team from the University of Michigan identified the gene for cystic fibrosis.



Cystic fibrosis gene resides on chromosome 7 and normally gives rise to a protein called the cystic fibrosis transmembrane conductance regulator (CFTR). The defect that most often leads to the disease is the deletion of three nucleotides from the gene (red letters above); this alteration, known as the ΔF508 mutation, results in the loss of one amino acid - phenylalanine at position 508 - in the CFTR protein. Phenylalanine is lost because the protein-making machinery of the cell now sees ATT (an alternative way to encode isoleucine) at the gene region coding for the protein's 507th amino acid, followed by the GGT sequence for the glycine that normally follows phenylalanine.

Location of the most common CF mutation ΔF508

CFTR protein, mRNA sequence (6121 bases)

ORIGIN

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   1 aattggaagc aaatgacatc acagcaggtc agagaaaaag ggttgagcgg caggcaccca
  61 gagtagtagg tctttggcat taggagcttg agcccagacg gccctagcag ggaccccagc
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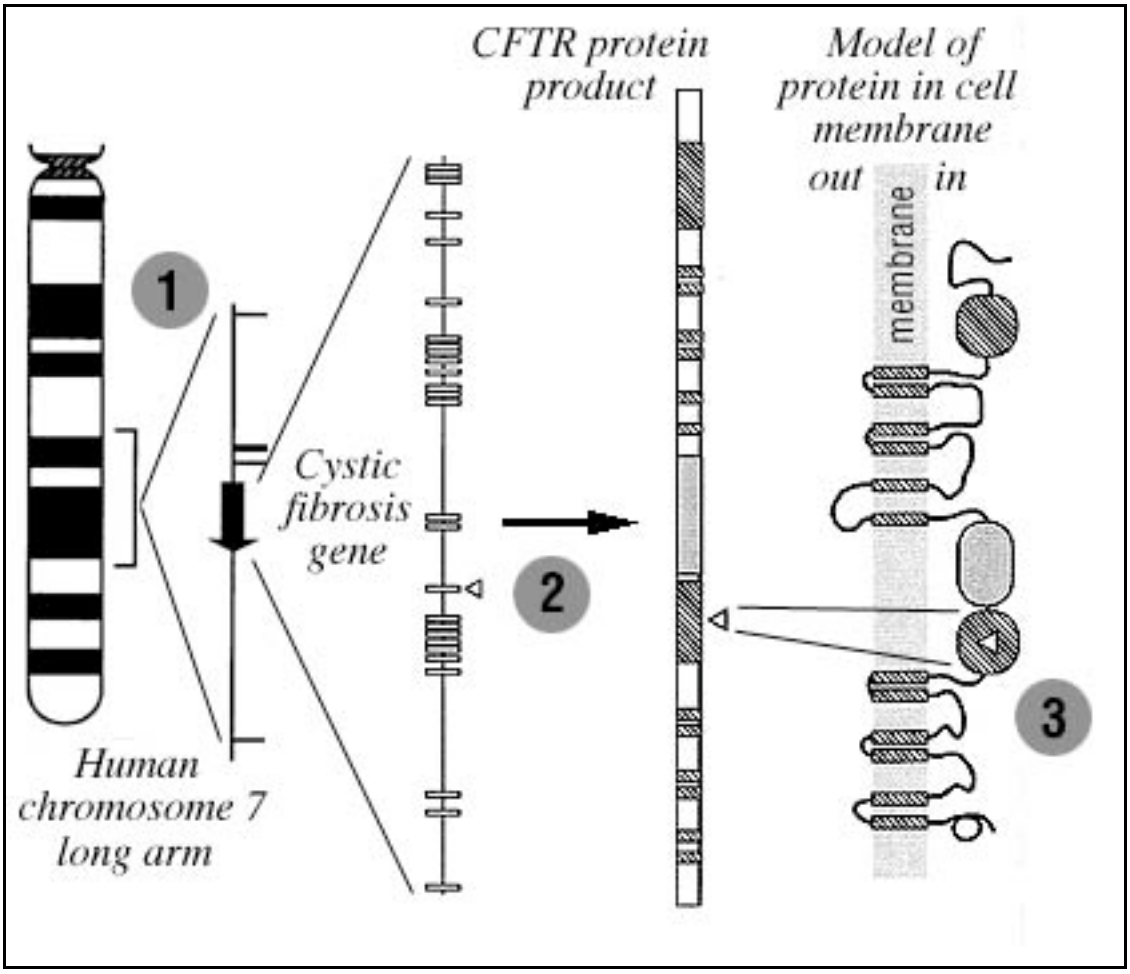

CFTR protein product
Model of protein in cell membrane
out
in
membrane
1
Cystic fibrosis gene
2
3
Human chromosome 7 long arm

1. Human Chromosome 7

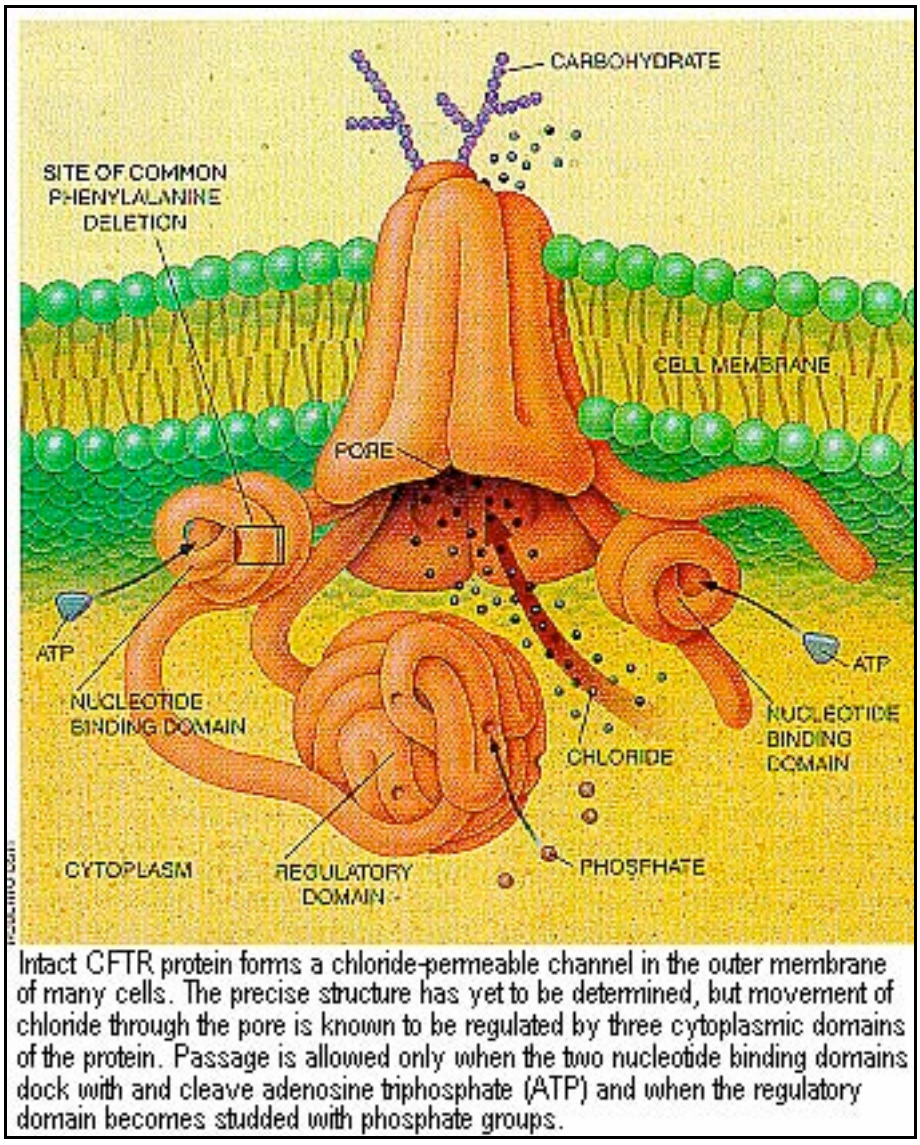
The cystic fibrosis gene sits on the long arm of chromosome 7. One out of every 29 people in the Caucasian population carry the genetic mutation for CF in this gene. Chromosome 7 has 150,000,000 base pairs of DNA.

2. The Cystic Fibrosis Gene

The CF gene region has 230,000 DNA base pairs which spell out a series of 1480 amino acids that curl up to make the Cystic Fibrosis Transmembrane conductance Regulator protein. The little triangle shows the location of the 3-base-pair deletion mutation that was discovered.

3. Model of CFTR protein in cell membrane

A normal gene makes this protein that regulates the passage of chloride ions and hence the secretion of mucous in epithelial (surface) cells lining the gut, lungs, etc. One missing amino acid at this spot (ΔF508) in the protein causes the CF.



Intact CFTR protein forms a chloride-permeable channel in the outer membrane of many cells. The precise structure has yet to be determined, but movement of chloride through the pore is known to be regulated by three cytoplasmic domains of the protein. Passage is allowed only when the two nucleotide binding domains dock with and cleave adenosine triphosphate (ATP) and when the regulatory domain becomes studded with phosphate groups.

CFTR protein imbedded in the cell membrane

Excerpt from **Cystic Fibrosis**

by Michael J. Welsh and Alan E. Smith
Scientific American, **December, 1995**

Testing Dilemmas

Now that many genetic mutations leading to cystic fibrosis have been pinpointed, prospective parents can easily find out whether they are likely to be carriers of the disease, that is, whether their cells silently harbor a defective copy of the CFTR gene. Couples can also learn whether an already developing fetus has inherited two altered copies of the gene (one from each parent) and ill thus be afflicted with cystic fibrosis.

The difficulty for many people is deciding how to proceed once they receive their test results. The trouble arises in part because the laboratories that perform the genetic analyses do not detect every mutation in the CFTR gene. Consequently, a reassuring negative finding may not fully rule out the possibility that someone is a carrier or is affected with cystic fibrosis. (A favorable prenatal test result will be conclusive, however, if the fetus is shown to lack the specific CFTR mutants known to be carried by the parents.) Moreover, it is not yet possible to predict the extent of symptoms in a person who inherits two CFTR mutants; even if the inherited genes are usually associated with highly severe or less severe disease, such associations do not necessarily hold true in every individual. Prospective parents need to understand, therefore, that a child born with cystic fibrosis today will still have to cope with the disease and may not be spared a premature death.

NIH Consensus Statement on Genetic Testing for Cystic Fibrosis, April 16, 1997

Genetic testing for CF should be offered to adults with a positive family history of CF, to partners of people with CF, to couples currently planning a pregnancy, and to couples seeking prenatal care. **The panel does not recommend offering CF genetic testing to the general population or all newborn infants.** The panel advocates active research to develop improved treatments for people with CF and continued investigation into the understanding of the pathophysiology of the disease. Comprehensive educational programs targeted to health care professionals and the public should be developed using input from people living with CF and their families and from people from diverse racial and ethnic groups. Additionally, genetic counseling services must be accurate and provide balanced information to afford individuals the opportunity to make autonomous decisions. Every attempt should be made to protect individual rights, genetic and medical privacy rights, and to prevent discrimination and stigmatization. It is essential that the offering of CF carrier testing be phased in over a period of time to ensure that adequate education and appropriate genetic testing and counseling services are available to all persons being tested.

NIH Consensus Statements are prepared by a nonadvocate, non-Federal panel of experts, based on (1) presentations by investigators working in areas relevant to the consensus questions during a 2-day public session; (2) questions and statements from conference attendees during open discussion periods that are part of the public session; and (3) closed deliberations by the panel during the remainder of the second day and morning of the third. This statement is an independent report of the panel and is not a policy statement of the NIH or the Federal Government.

Doctors offer cystic fibrosis gene test

by Lauran Neergaard (**2001**)

Gene testing is going mainstream: Starting this month, tens of thousands of white Americans will be offered testing to see if they carry a gene mutation that causes cystic fibrosis even if no one in their family has the disease. Obstetricians and gynecologists are supposed to offer the gene test to every Caucasian—or the partner of a Caucasian—who is pregnant or considering having a baby.

It marks the first time gene tests are being offered to the general population. Until now, they have been recommended just for small groups of people who know they're at high risk for a particular inherited disease, such as an illness that runs in the family.

Are we ready for mainstream gene tests? The American College of Obstetrics and Gynecology is betting that with a little education, Americans will be savvy enough medical consumers that the screening will prove a boon.

To help expectant couples decide whether to accept the test, the group has prepared easy-to-understand educational pamphlets—available from your doctor—explaining cystic fibrosis, how gene testing works, and the relevance of parents-to-be discovering they have the gene mutations that cause it. Babies must inherit a bad gene from both parents to have the disease, so if the mother has the gene, the dad must be tested too.

About 30,000 American children and young adults are living with cystic fibrosis. It attacks their lungs, clogging them with a thick mucus, and can harm digestion and vitamin absorption by clogging the pancreas and intestines. Patients typically die in their 30s.

Cystic fibrosis is the most common inherited disease among Caucasians. More than 10 million Americans carry the gene, including one in every 29 whites. But because there are so many unsuspecting carriers, most babies with the disease are born into families that didn't know they were at risk. If both parents harbor the defective gene, they have a one-in-four chance of having a baby with the incurable disease.

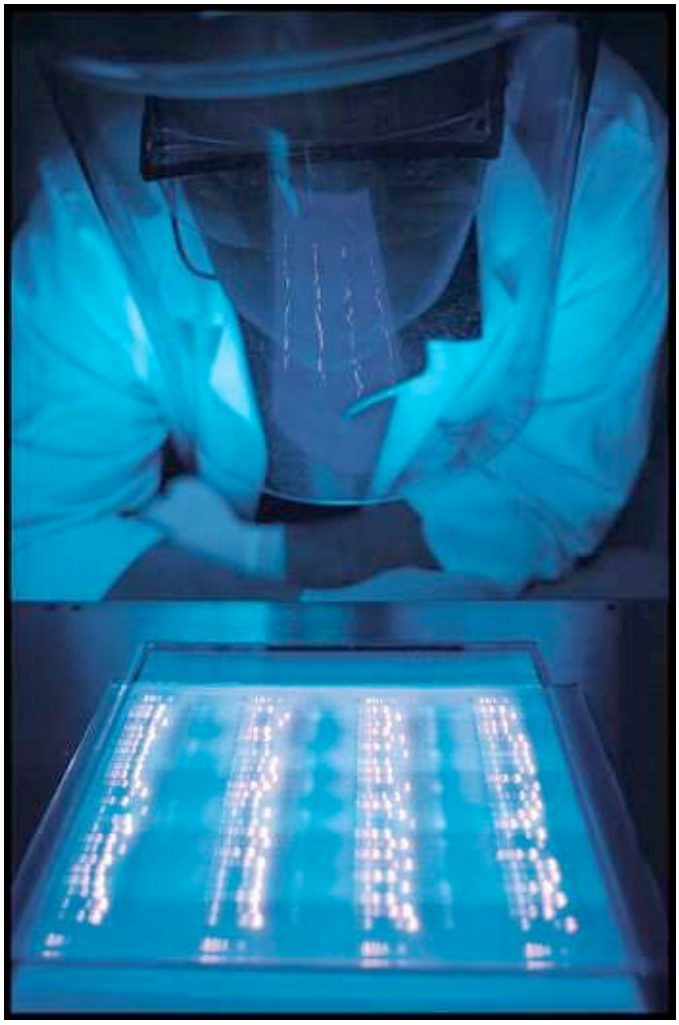
"The vast majority of couples will get reassuring news," that they aren't carriers, notes Dr. Francis Collins of the National Institute of Health, who co-discovered the gene in 1989. Testing is best done before a woman gets pregnant, he says. If both parents are carriers, they might opt for in vitro fertilization, for instance, where the resulting embryos can be tested for the disease and only healthy one are implanted into the mother's uterus.

If parents learn they are carriers early in pregnancy, the fetus can be tested. If the fetus does have it, abortion is one option—but many such parents do as patients of Dr. Debra Baseman recently did: They spent the months of pregnancy learning about top-notch care and lining up specialists for their child. Very early care, especially nutritional care, keeps many patients healthier longer.

A test typically costs about $265; doctors say many insurers do pay for it.

Gene Test Accuracy for Cystic Fibrosis

The test is good but not 100 percent accurate. There are about 1,000 known mutations in the gene that causes it, and the new guidelines advise test laboratories to check for a minimum of the 25 most common. Genzyme Corp., the largest test provider, typically tests for 87 mutations.



Reading stained DNA bands by UV light

Gene Test Accuracy by Ethnic Group

Ethnic Group	% accuracy	chance of being a carrier
Ashkenazi Jewish	97%	one in 29
Non-Jewish Caucasians	80%	one in 29
African-Americans	69%	one in 65
Hispanic-Americans	57%	one in 46
Asian-Americans	(no data)	one in 90

The First Large-Scale Gene Screening

How well this widespread gene testing works will influence how other gene tests are introduced to Americans. “It will be very important to see how this goes,” Collins says. “Certainly it requires the obstetricians to become more familiar with genetics than many of them have previously had occasion to do.”

What are the ethical issues raised by genetic screening for cystic fibrosis?

"Testing is best done before a woman gets pregnant, he says. If both parents are carriers, they might opt for in vitro fertilization, for instance, where the resulting embryos can be tested for the disease and only healthy one are implanted into the mother's uterus."

"If parents learn they are carriers early in pregnancy, the fetus can be tested. If the fetus does have it, abortion is one option—but many such parents do as patients of Dr. Debra Baseman recently did: They spent the months of pregnancy learning about top-notch care and lining up specialists for their child. Very early care, especially nutritional care, keeps many patients healthier longer."

"Every attempt should be made to protect individual rights, genetic and medical privacy rights, and to prevent discrimination and stigmatization."

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Some of the Ethical Issues related to Cystic Fibrosis Screening

• The Status of Fertilized Embryos

• Therapeutic abortion

• Discrimination against Carriers

• Stigmatization of Carriers

• The Right to Medical Privacy

• The "Right" to Genetic Health

What is the legal status of embryos fertilized in vitro?

When, if ever, is therapeutic abortion ethically justified?

When, if ever, is a therapeutic abortion ethically required?

Lawsuits, Smoking, and Fetal Alcohol Syndrome

Are unborn fetuses persons under the law and, therefore, afforded the protection of the courts even against the desires of the mother?

Can a child born with fetal alcohol syndrome receive compensation from the mother (by lawsuit) for the actions of their mother during her pregnancy?

Excerpt from **The Politics of Fetal / Maternal Conflict**

by Ruth Hubbard

It is easy to extrapolate from court-mandated caesarians [which have occurred] to court-mandated Prenatal tests and therapies. This has not happened yet, but it may once prenatal testing or therapy becomes standard medical practice. **And what if courts one day decide that, if no therapy is available and a fetus is predicted to be disabled, the woman must have an abortion?**

This suggestion is not altogether far-fetched. Insurance discrimination against families predicted to have a child with a disability has already occurred. Medical geneticist Paul Billings and his colleagues (1992), in their research into genetic discrimination, have come across an instance that is not very different from this hypothetical scenario. In this case, a woman who had borne one child with cystic fibrosis decided to have her fetus tested for this condition during a subsequent pregnancy. When the result indicated that this baby, too, was going to have cystic fibrosis and the woman decided to continue the pregnancy (which is not unusual for families who have experience caring for a child with cystic fibrosis), the HMO that provided the family's health care announced that it was prepared to pay for an abortion, but not for continued prenatal care or the health care of the future baby because that baby now had what insurers call a pre-existing condition. Only after the family threatened to publicize this decision and, if necessary, take it to court, did the decision get reversed. As prenatal tests proliferate, these kinds of situations are going to become more common, unless we get laws passed to prevent such forms of discrimination and coercion.

Hubbard, Ruth (1994). The Politics of Fetal/Maternal Conflict in *Power and Decision: the Social Control of Reproduction*. Cambridge, MA: Harvard School of Public Health.

Web Reference

http://www.hsph.harvard.edu/Organizations/healthnet/gender/docs/hubbard.html

Is discrimination against carriers of genetic diseases ever justified?

Examples of discrimination could be insurance companies who, based on information that an individual carried the mutation for a genetic disease, deny an individual insurance coverage or dramatically increased the cost of insurance for that individual.

Discrimination could also be an employer who denies an individual a job or a promotion based on that individual being a carrier of a genetic mutation.

Is the stigmatization of carriers of a genetic disease ever justified?

What rights to privacy does a carrier of a genetic disease have in the United States?

The French Uproar

Based on Condorcet's Obligation, does an unborn fetus have a "right" to genetic health?

Who is responsible if the answer is yes to this question?

For the full article on The French Uproar go to:
http://fire.biol.wwu.edu/trent/alles/350Discussion_Essays.pdf

References

Neergaard, L. (2001, 1 Oct.). Cystic Fibrosis Gene Test Offered. *Associated Press*.

Pier, G. B., et al. (1998). Salmonella typhi uses CFTR to enter intestinal epithelial cells. *Nature*, 393(7 May), 79-82.

Welsh, M. J., & Smith, A. E. (1995). Cystic Fibrosis. *Scientific American*, 273 (December), 52-59.

Simons, M. (2001, 19 Oct.). French Uproar Over Right to Death for Unborn. *NYT*, pp. International, A3.

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