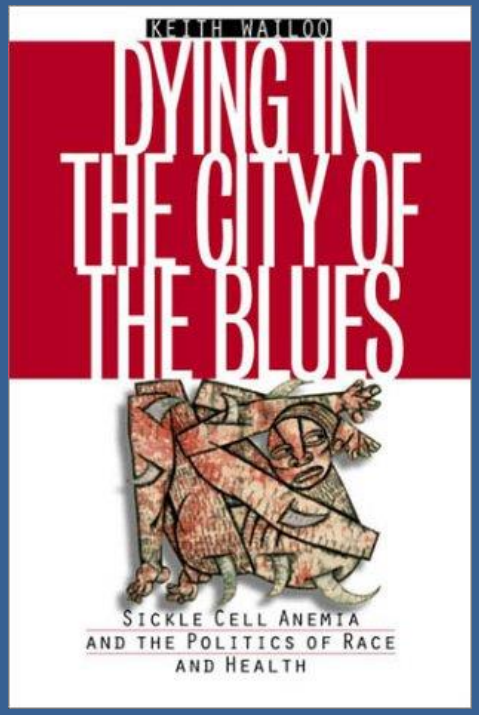
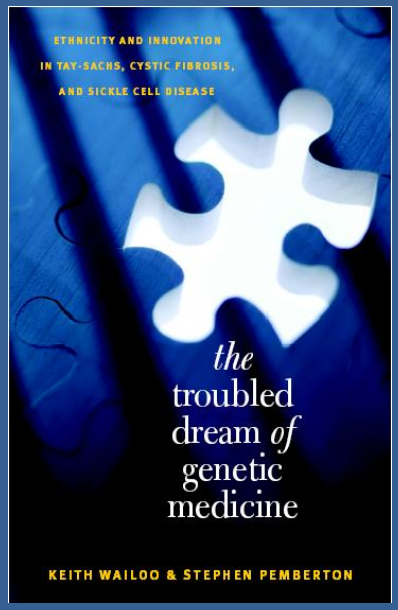
Race and Genetics:

How different cultures mediate issues of testing, prevention, and treatment

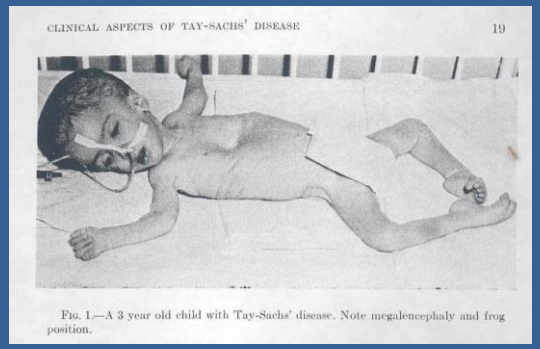
(Committee on Human Gene Editing: Scientific, Medical, and Ethical Considerations)

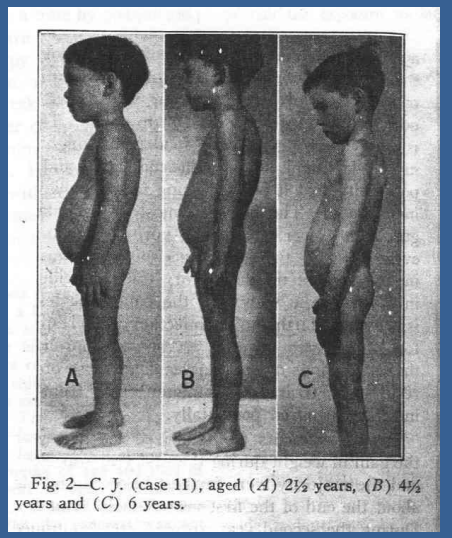
July 12, 2016



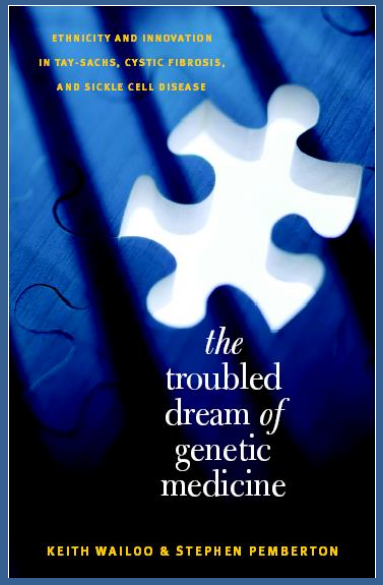


Keith Wailoo, Ph.D.
Townsend Martin Professor of History and Public Affairs
Princeton University
Woodrow Wilson School of Public and International Affairs
Department of History





Sickle Cell Disease, Tay-Sachs Disease, and Cystic Fibrosis



What do the histories of these three diseases tell us about race/ethnicity and genetics?

About vulnerable populations?

About the genetic detection, prevention, testing, and treatment (from era of genetic testing… to era of gene therapy and gene editing)?

TSD, SCD, and CF – common features

Autosomal Recessive (established in 1950s)

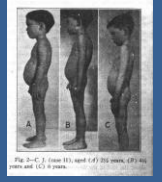
Mechanisms of Inheritance (carriers → disorder)

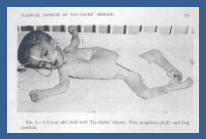
Prevention via Genetic Testing/Counseling (1970s)

Identification of cause/Hope for Treatment:
- Drugs, Surgery: Impact on Life Expectancy, Illness, Experience (1950-present)

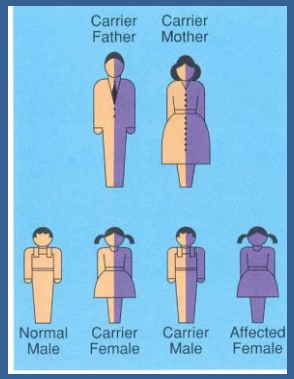
THREE CAUTIONARY TALES
Genetic Progress and Social Complexities

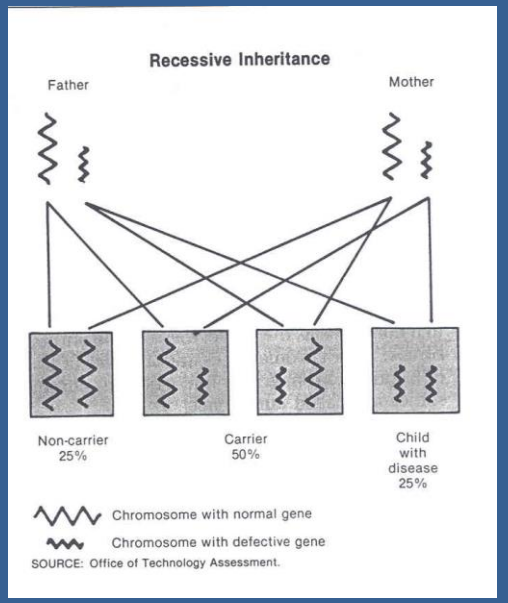
Each genetic disease – travels different pathways because of questions of race and ethnicity

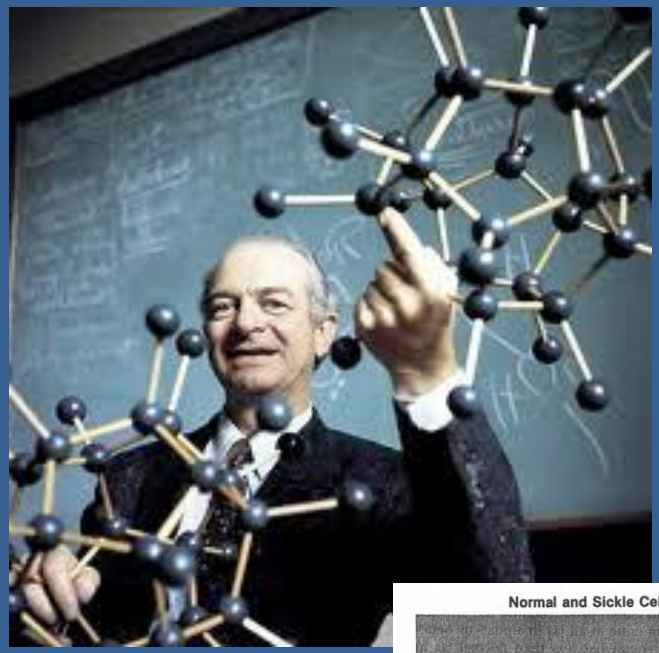




CARRIER PARENTS
25% CHANCE OF HAVING AFFECTED CHILD

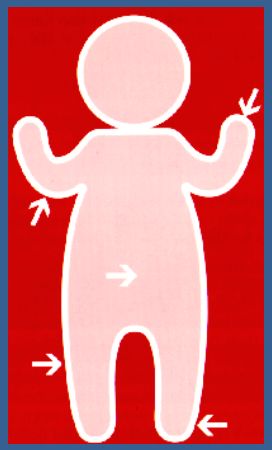


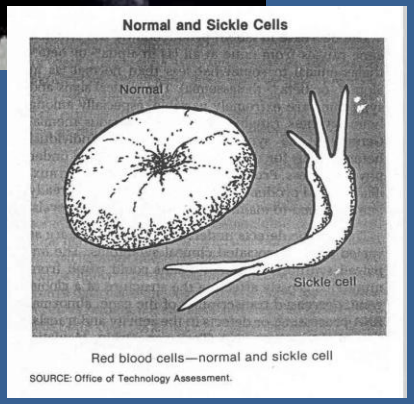




1910 – Sickle Cell clinical description (by James Herrick)

1950 – Linus Pauling discovery that a missubstituted amino acid on the complex hemoglobin molecule caused sickling (turned the disease from an obscure curiosity into the “first molecular disease”)





SEARCH FOR A “DE-SICKLING” AGENT:

One scientist predicts in 1951, medicine “may be able to devise a small innocuous molecule which might lock on to the defective hemoglobin and prevent the abnormal molecule from misbehaving.”

UREA – 1970s promising desickling agent shows “no hematological of clinical benefit,” toxic side effects. 1990s: Hydroxyurea success (reduce painful crises

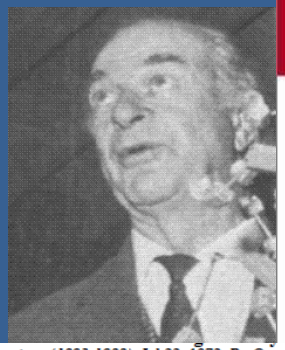
1960s – GENETIC TESTING CONTROVERSIES

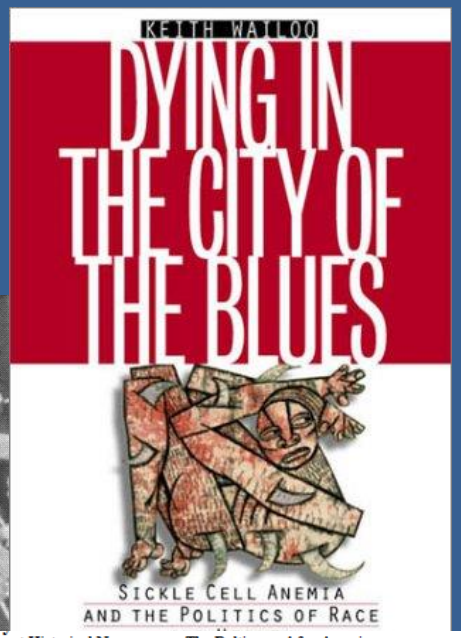
Rising awareness of SCD: “disease of pain and suffering” of African-Americans, too long ignored

Carrier frequency: 1 in 12 African-Americans

TESTING – PROGRESS OR STIGMA?

LINUS PAULING, UCLA Law Review, 1968: “I have suggested that there should be tattooed on the forehead of every young person a symbol showing possession of the sickle cell gene or whatever other similar gene… that he has been found to possess in a single dose… It this were done, two young people carrying the same seriously defective gene in single dose would recognize the situation at first sight, and would refrain from falling in love with one another.”





Afro-American (1893-1988); Jul 22, 1972; ProQuest Historical Newspapers: The Baltimore Afro-American pg. 1

Federal sickle cell clinics facing minority resistance

WASHINGTON (UPI) — Facing state lethargy and the resistance of some blacks, the government is launching a network of hos- disease that primarily afflicts nonwhites.

Although federally-financed centers have been approved for 10 cities and red tape involved in preparing the official announcement.

The centers were ap-

“It should be pointed out that the avoidance of the birth of children with severe disabling diseases is. . . not genocide,” wrote a University of Alabama School of Medicine official under a cover letter from Gov. George C. Wallace.

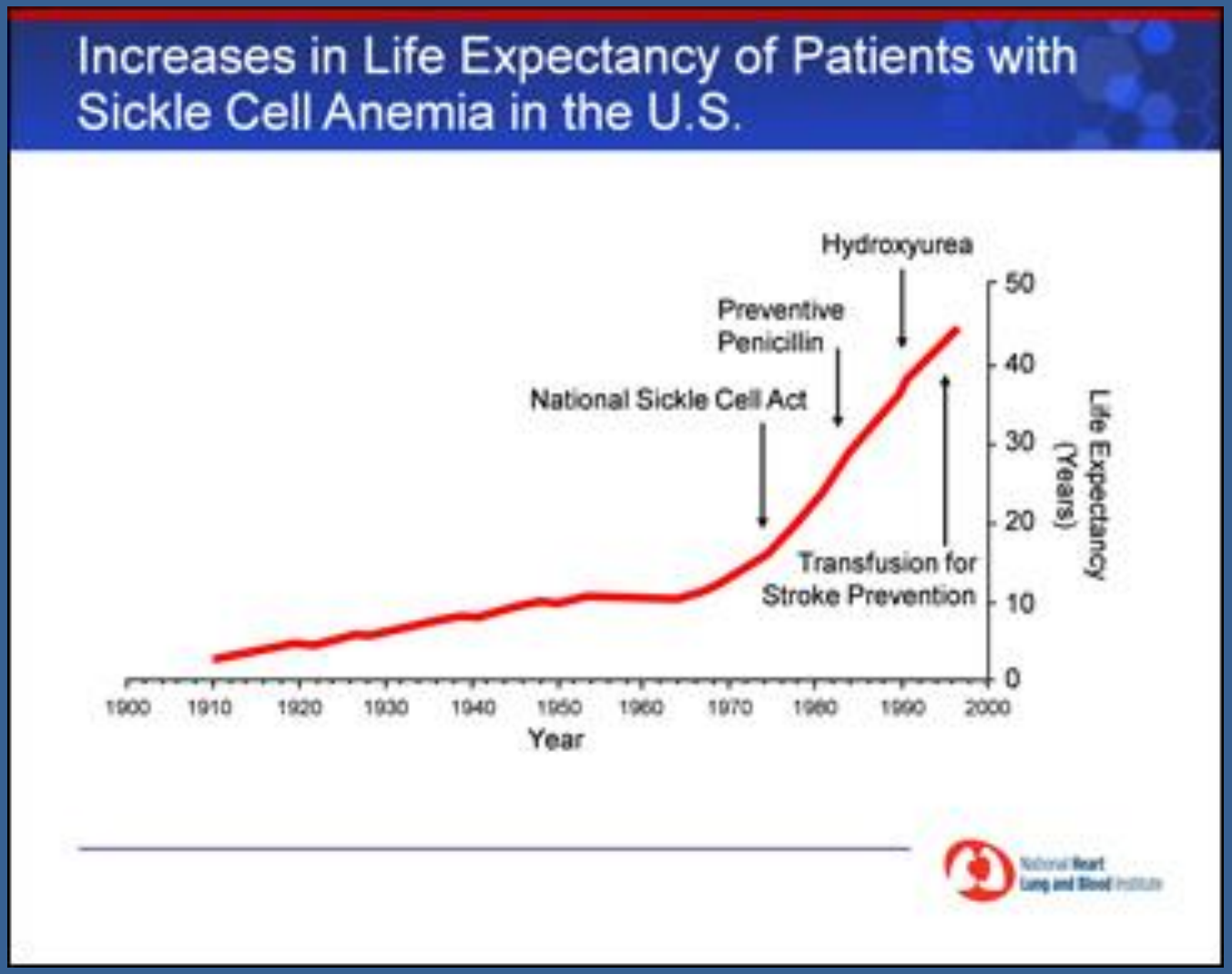
Sickle Cell Disease Therapeutic Progress

- Antibiotics

-Transfusion

- Prophylactic Penicillin

- Hydroxyurea (treatment of crises)



CARRIER TESTING AND DISCRIMINATION – IMPLICATIONS FOR EMPLOYMENT

- **AIR FORCE ban on TRAIT CARRIERS;**
Airlines and carriers as flight attendants (1970s)

THE HEALTH OF SCD CARRIERS (at WORK, at ALTITUDE, under STRESS)?

Clark to s
September

Fitzgerald Cecil
Pittsburgh, PA,
will keep Pittsbu
when the Steele
Sunday.

Clark has sickle
red blood cells
to the player.

Last year, Steel
the Broncos.

In 2007, Clark
ultimately lost h

Blood Doctors Call Foul On NCAA's Screening For Sickle Cell

January 26, 2012 · 6:07 PM ET

SCOTT HENSLEY

If you're a college athlete who's talented enough to play a Division I sport, the NCAA requires that you get a blood test to see if you have sickle cell trait.

People with sickle cell trait carry one copy of a gene that can lead to an abnormal type of hemoglobin, the oxygen-carrying molecule in red blood cells. (Two copies of the gene lead to sickle cell disease.)

ONGOING ETHICAL AND POLICY CONTROVERSY:

Is a ban/restriction on carriers a form of discrimination against or social policy in their best health interest?

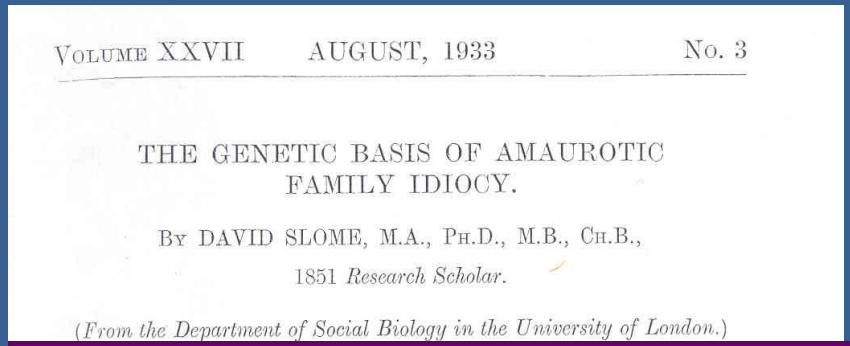
Screening U.S. College Athletes for their Sickle Cell Disease Carrier Status, October 11, 2010 (Secretary's Advisory Committee on Heritable Disorders in Newborn and Children) ---- to advise the Secretary of the U.S. Department of Health and Human Services about the rule of the National Collegiate Athletic Association requiring testing for sickle cell trait in all incoming Division I student athletes.

Tay-Sach's Disease: A Success Story (Warren Tay and Bernard Sachs) 1880s

"The Genetic Basis of Jewish Amaurotic Family Idiocy"

"almost exclusively observed among Hebrews"

neurological and cognitive decline, mental retardation, cerebral seizures, loss of vision and motor control, death by age 2-6.



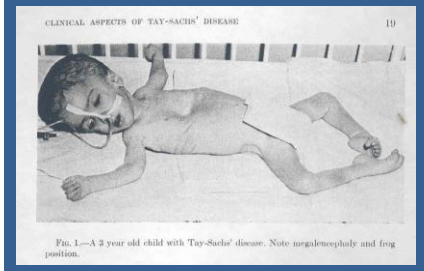
VOLUME XXVII AUGUST, 1933 No. 3

THE GENETIC BASIS OF AMAUROTIC FAMILY IDIOCY.

BY DAVID SLOME, M.A., PH.D., M.B., CH.B.,

1851 *Research Scholar.*

(*From the Department of Social Biology in the University of London.*)



CLINICAL ASPECTS OF TAY-SACHS' DISEASE 19

FIG. 1.—A 3 year old child with Tay-Sachs' disease. Note megalencephaly and frog position.

AT MID- 20th CENTURY

1950s: Rise of clinical genetics, discovery and identification of the heterozygote (carrier) possible; identified as lipid storage disorder, lysosomal storage disease

Carrier frequency: 1 in 25/30 Ashkenazi Jews

1969: O'Brien and Okada – deficiency of hexosaminidase A (hex A) which results in buildup of lysosomes in brain tissue.

Hope for a cure: 1971 -- "with detection and prevention of TSD possible, the question of cure arises…" Friedman

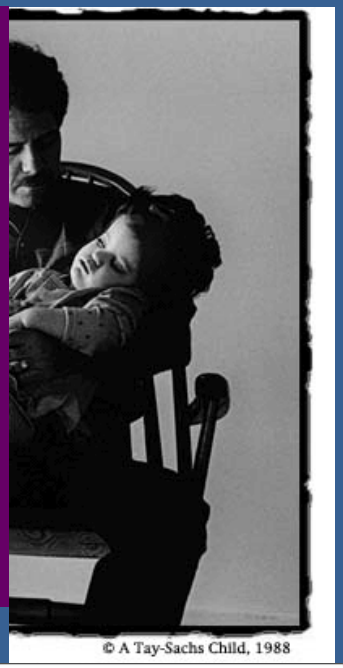
New York Times (1923-Current file); Jul 24, 1981; ProQuest Historical Newspapers: The New York Times
pg. B3

Genetic Disease That Attacks Jews Called Potentially Curable

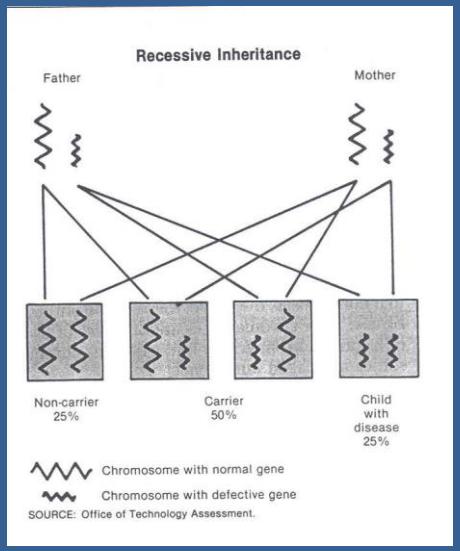
Cure: By 1982 – "Protein Targeting" in TSD

DEEMED A FAILURE

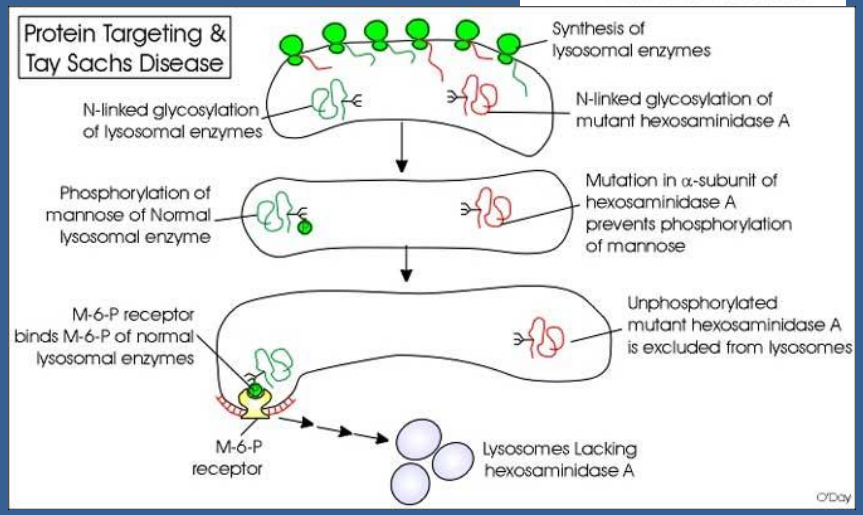
O'BRIEN: "The prospects for the development of therapy in the near future are dismal"



© A Tay-Sachs Child, 1988

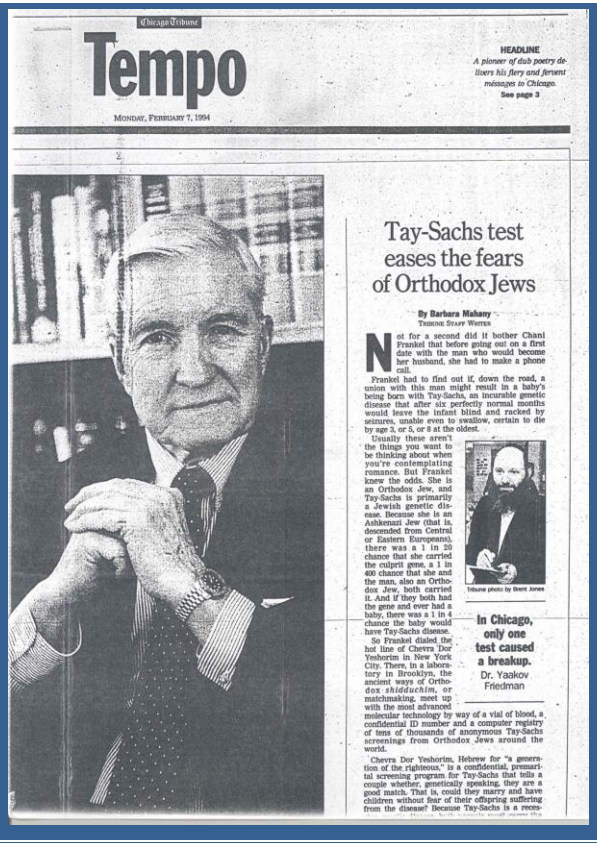


The Question of Prevention: INTERTWINED WITH JEWISH IDENTITY in U.S.



Despite Carrier Frequency (TSD)
1 in 25-30 Ashkenazi Jews
1 in 20 French Canadians/Louisiana Cajuns
1 in 200-300 U.S. population

Modern Matchmaker
Premarital Tests Help Hasidim Avert Genetic Disease
By Alex Shimo-Barry



Chicago Tribune

Tempo

MONDAY, FEBRUARY 7, 1994

HEADLINE
A pioneer of dub poetry delivers his fiery and fervent messages to Chicago.
See page 3

Tay-Sachs test eases the fears of Orthodox Jews

By Barbara Mahany
TRIBUNE STAFF WRITER

Not for a second did it bother Chani Frankel that before going out on a first date with the man who would become her husband, she had to make a phone call.

Frankel had to find out if, down the road, a union with this man might result in a baby's being born with Tay-Sachs, an incurable genetic disease that after six perfectly normal months would leave the infant blind and racked by seizures, unable even to swallow, certain to die by age 3, or 5, or 8 at the oldest.

Usually these aren't the things you want to be thinking about when you're contemplating romance. But Frankel knew the odds. She is an Orthodox Jew, and Tay-Sachs is primarily a Jewish genetic disease. Because she is an Ashkenazi Jew (that is, descended from Central or Eastern Europeans), there was a 1 in 20 chance that she carried the culprit gene, a 1 in 400 chance that she and the man, also an Orthodox Jew, both carried it. And if they both had the gene and ever had a baby, there was a 1 in 4 chance the baby would have Tay-Sachs disease.

So Frankel dialed the hot line of Chevra Dor Yeshorim in New York City. There, in a laboratory in Brooklyn, the ancient ways of Orthodox *shidduchim*, or matchmaking, meet up with the most advanced molecular technology by way of a vial of blood, a confidential ID number and a computer registry of tens of thousands of anonymous Tay-Sachs screenings from Orthodox Jews around the world.

Chevra Dor Yeshorim, Hebrew for "a generation of the righteous," is a confidential, premarital screening program for Tay-Sachs that tells a couple whether, genetically speaking, they are a good match. That is, could they marry and have children without fear of their offspring suffering from the disease? Because Tay-Sachs is a reces-

Tribune photo by Brent Jones

In Chicago, only one test caused a breakup.
Dr. Yaakov Friedman

One notable episode: RACE, ETHNICITY, AND GENETICS

TESTING SERVING THE NEEDS of ethnic/religious community

1983 -- RABBI JOSEF EKSTEIN (had watched four of his own Tay-Sachs children die)

FOR ULTRA-ORTHODOX JEWISH, proscription against abortion limits options

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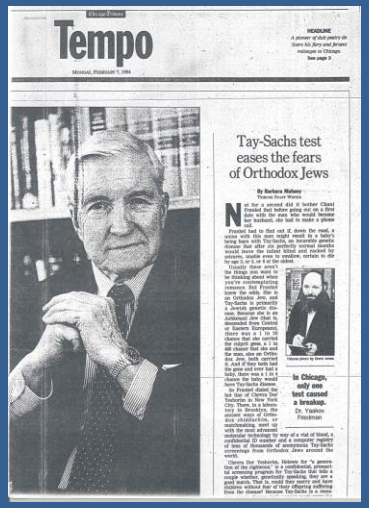
Rabbi Ekstein's Innovation: CHEVRAH DOR YESHORIM "GENERATION OF THE RIGHTEOUS"

Testing Adolescents for Carrier Status – Arranged Marriages to avoid producing TSD

SUCCESS SPREADS: Chicago – "modern matchmaking..helps avert genetic disease"



Tempo

Tay-Sachs test eases the fears of Orthodox Jews

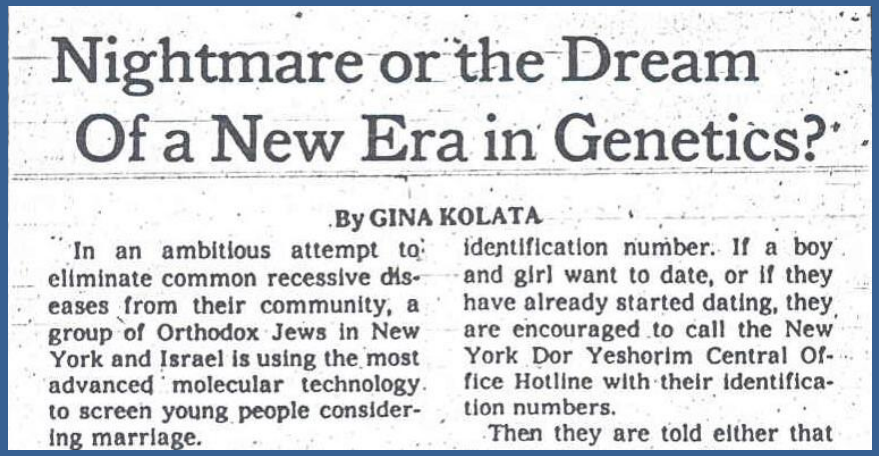
By Barbara Mahany

In Chicago, only one test caused a breakup.

Dr. Yaakov Friedman

1993 -- Why not expanding Dor Yeshorim to test for Cystic Fibrosis and Gaucher's Disease – prevent marriages

Dor Yeshorim: expands testing to other, not invariably fatal, "Jewish genetic diseases" like Gaucher's disease and Cystic Fibrosis



Nightmare or the Dream Of a New Era in Genetics?

By GINA KOLATA

In an ambitious attempt to eliminate common recessive diseases from their community, a group of Orthodox Jews in New York and Israel is using the most advanced molecular technology to screen young people considering marriage.

identification number. If a boy and girl want to date, or if they have already started dating, they are encouraged to call the New York Dor Yeshorim Central Office Hotline with their identification numbers.

Then they are told either that

FROM DREAM TO NIGHTMARE – PREVENTING CF?

"this mentality, unfortunately, has been fostered in some degree by the scientific community… if a test exists, you should use it." Michael Kaback, medical geneticist

"as you move further and further away from an untreatable disease in which no one survives to cystic fibrosis and Gaucher's disease, I find the application much more troubling and much less acceptable." Mark Seigler, Ethicist, U. Chicago

"this is a moderate nightmare… this is a miniature but significant version of Big Brother… " Francis Collins, Director of the Center for Human Genome Research

A CLASH of GENETIC IDEALS

PREVENTION … vs. CURE?

Nightmare or the Dream Of a New Era in Genetics?

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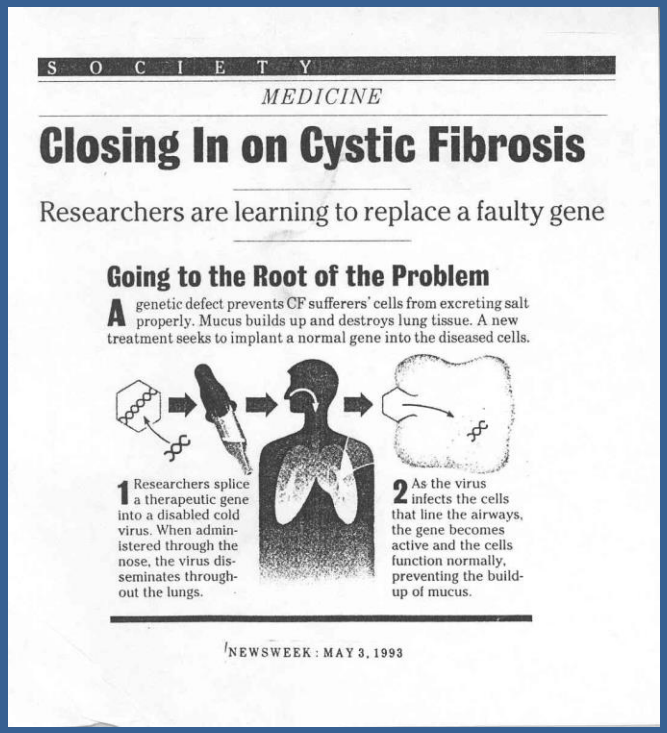
New York Times (1923-Current file); Feb 18, 2003; ProQuest Historical Newspapers: The New York Times pg. F1

Using Genetic Tests, Ashkenazi Jews Vanquish a Disease

By GINA KOLATA

A number of years ago, five families in Brooklyn who had had babies

2003 – Testing for TSD hailed a success



SOCIETY

MEDICINE

Closing In on Cystic Fibrosis

Researchers are learning to replace a faulty gene

Going to the Root of the Problem

A genetic defect prevents CF sufferers' cells from excreting salt properly. Mucus builds up and destroys lung tissue. A new treatment seeks to implant a normal gene into the diseased cells.

1 Researchers splice a therapeutic gene into a disabled cold virus. When administered through the nose, the virus disseminates throughout the lungs.

2 As the virus infects the cells that line the airways, the gene becomes active and the cells function normally, preventing the build-up of mucus.

NEWSWEEK : MAY 3, 1993

STIGMA OF TESTING? EUGENICS? A SUPPORTER OF DOR YESHORIM: "While ethicists agonize over some people's being marginalized as marriage partners, they would do better to focus on the fact that medical conditions not manifesting themselves until middle age [like Gaucher's disease] do not make them benign…. Prevention beats remedy any day."

1993-94: CF – HOPE FOR A CURE:

PREVENTING CF vs. THE DREAM of a CF CURE

Identification of Gene. Envisioning the replacement of faulty genes.

Closing in on CF Gene Therapy

GENE THERAPY – ADENOVIRUS VEHICLE "LEADING THE WAY"

SOCIETY

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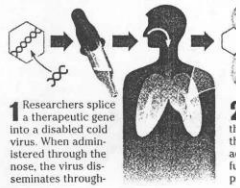


1 Researchers splice a therapeutic gene into a disabled cold virus. When administered through the nose, the virus disseminates through-

Cystic Fibrosis Gene Therapy Leads the Way

patients' lungs to test the therapy, Boucher and his colleagues apply the virus to nasal passages. "The cells in the nose are the same as those lining the lung, and they provide easier access," Boucher explains. As of

Cystic Fibrosis Experiment Hits a Snag

By NATALIE ANGIER

THE first effort to install healthy genes in the lungs of cystic fibrosis patients has hit a few bumpy spots, forcing researchers in the United States to redesign their projects and sharply reduce the dose of the experimental therapy they give to people taking part in the trials.

At the same time, scientists in Britain have begun a human gene therapy trial of their own, using a very different and theoretically gentler method of inserting new genes into

A quest to put healthy genes in diseased lungs.

membranes of cells in the body's airway tissue. Without a working molecular traffic guard, the body's salt and water levels are thrown out of balance and a thick mucus gathers in the lung, serving as a broth for bacterial infections. Many cystic fibrosis patients die of chronic lung infections before the age of 30.

By giving patients working versions of the cystic fibrosis gene, researchers hope to forestall the mucus buildup, prevent lung damage and essentially cure the disease, rather than simply treat the symptoms as is now done. Ideally, the therapy would

woman seemed to be faring just fine, and that his group planned to treat 19 more patients over the next several months.

Nobody knows yet whether any dose of the therapy will correct the defect in the lungs or cure the disease. The early stages of the trial are simply designed to explore questions of safety, to determine whether the gene switches on once the adenovirus has infected lung cells and to learn how long the effect lasts.

Different Approach in Britain

In Britain, researchers at the Roy-

CARRIER FREQUENCY
1 in 25-30 Caucasians and Ashkenazi Jews

The Washington Post (1974-Current file); Apr 20, 1986;
ProQuest Historical Newspapers: The Washington Post
pg. TW5

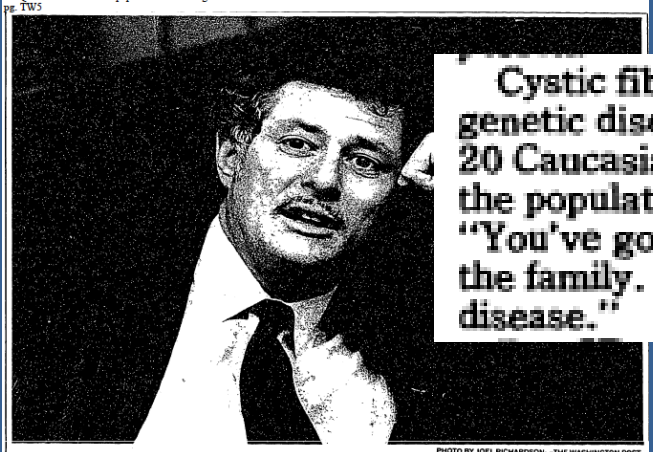


PHOTO BY JOEL RICHARDSON—THE WASHINGTON POST

Frank Deford: "I've learned a lot . . . Death means they're going somewhere all by themselves, and children hate to be alone."

His Daughter's Legacy: 'Alex: The Life of a Child'

Cystic fibrosis is "the largest fatal genetic disease in the world. One out of 20 Caucasians carry it—equivalent to the population of Illinois," he said. "You've got to have it on both sides of the family. Basically, it's a white disease."

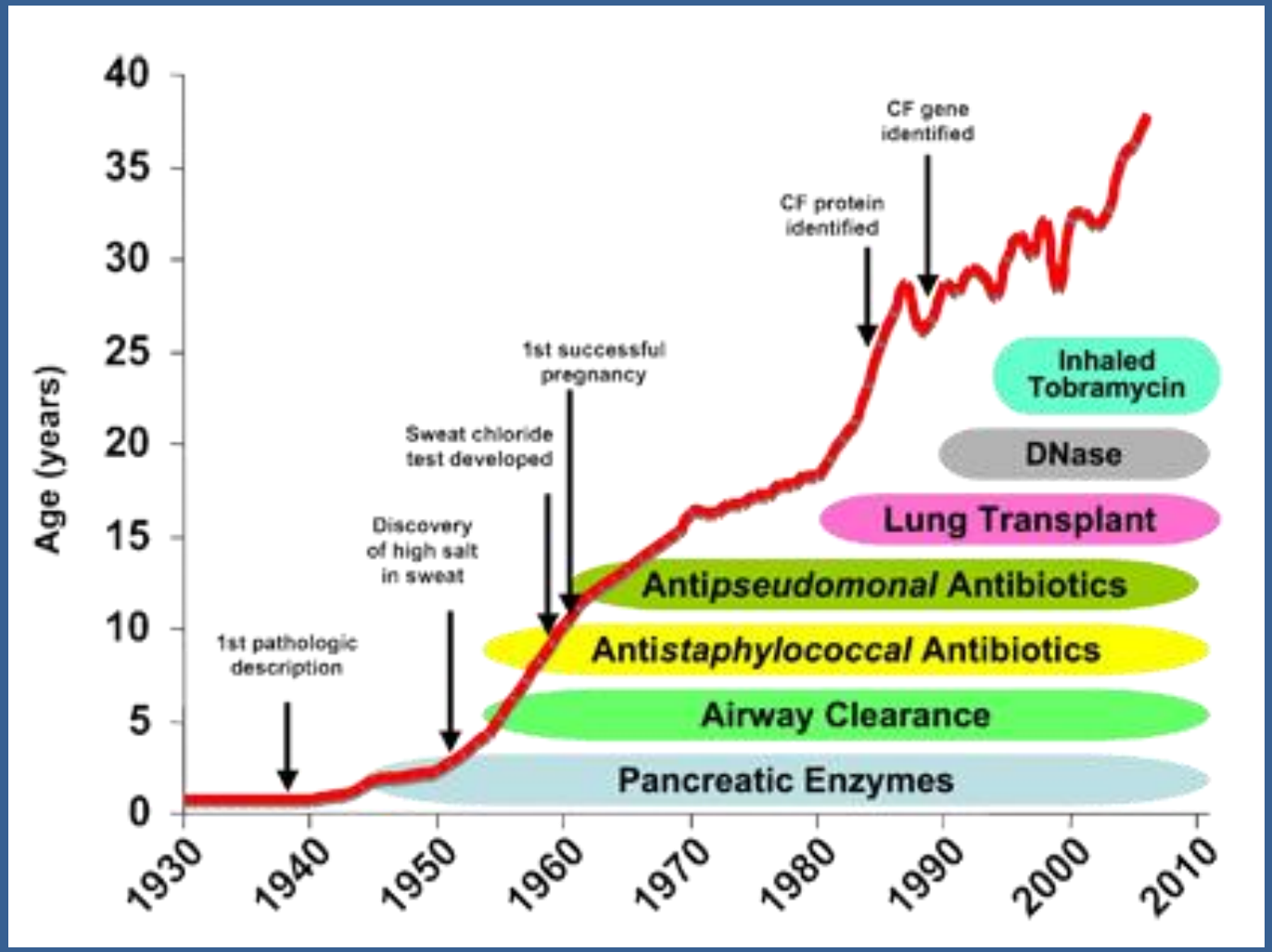
CF Therapeutic Progress

-Sweat chloride test

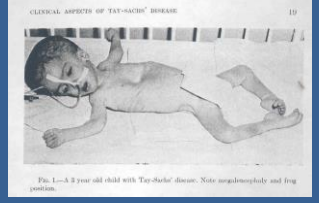
- antibiotics

- lung transplant

- DNase (reduce respiratory infections, improve breathing)



Race and Genetics – how different cultures mediate issues of testing, prevention, treatment



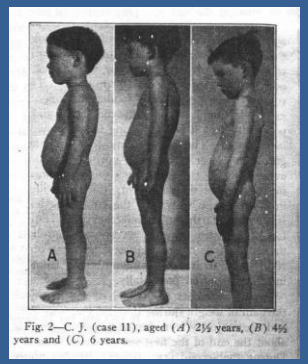


Fig. 2—C. J. (case 11), aged (*A*) 2½ years, (*B*) 4½ years and (*C*) 6 years.

1. RACE and Genetics – these controversies in the U.S. come in many varieties, and shifting forms – no single one-size-fits-all approach to avoiding controversy.
   - Testing, Prevention, Gene Therapy
   - Varies by group and within group, and by social context
   - Defined by progress, and ongoing controversies

2. CLINICAL DIFFERENCES IN DISEASE: shape how genetic innovations have been applied, and how they interact with ethnicity and social values (TSD 100% mortality, Gaucher's disease, SCD)

3. WHO CONTROLS GENETIC TECHNOLOGY – shapes debate over race and genetics
   - Rabbis, Trusted Experts, Community, NCAA, federal government, outside experts to the community?

4. EXPERT and POPULAR DISCUSSION OVER RACE, CARRY MANY DIFFERENT MESSAGES:
   - the era of "personalized genomics" will transcend race
   - but some genetic differences are group specific (Caucasian disease, Jewish disease, black disease)