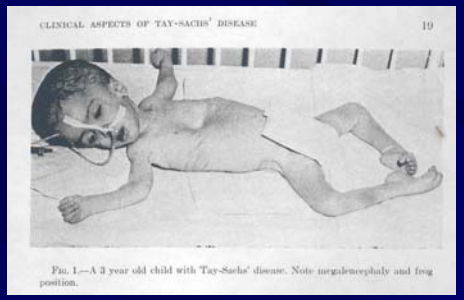
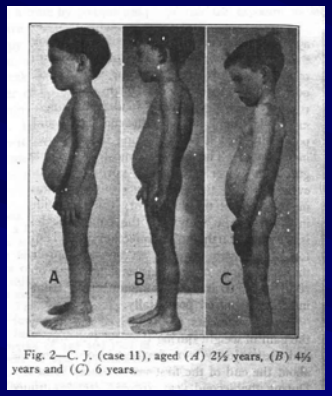


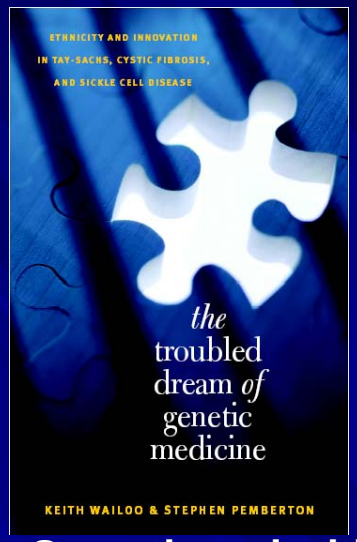





# CARRIER SCREENING:

## POPULATION DIFFERENCES, STIGMA,

## AND THE SPECTER OF EUGENICS




**Co-authored with Stephen Pemberton**

Tay Sachs Disease

Cystic Fibrosis

Sickle Cell Disease


# KEITH WAILOO, PH.D.

**Martin Luther King Jr. Professor**

**RUTGERS UNIVERSITY**

**DEPARTMENT OF HISTORY**

**INSTITUTE FOR HEALTH, HEALTH CARE POLICY, AND AGING RESEARCH**



**RESEARCH SUPPORTED BY: ETHICAL, LEGAL, AND SOCIAL ISSUES (ELSI) PROGRAM, NHGRI; and THE JAMES S. MCDONNELL FOUNDATION**

**Lessons of the Past:**

- **Balancing the screening interests of individuals, communities, and society?** ***The importance of historical sensitivity and cultural competence among health practitioners who engage in screening***

- **How to target screening to distinct populations?** ***The challenge of "hidden" versus obvious subpopulations. One-size does not fit all; how screening relates to group values and concerns***

- **In health care, knowing when screening is not the answer for some populations. Other goals: treatment and extension of life, relief.** ***The importance of competent screening programs among populations whose group identities are invested in the maintenance of values that are distinctively different than that of the majority culture.***

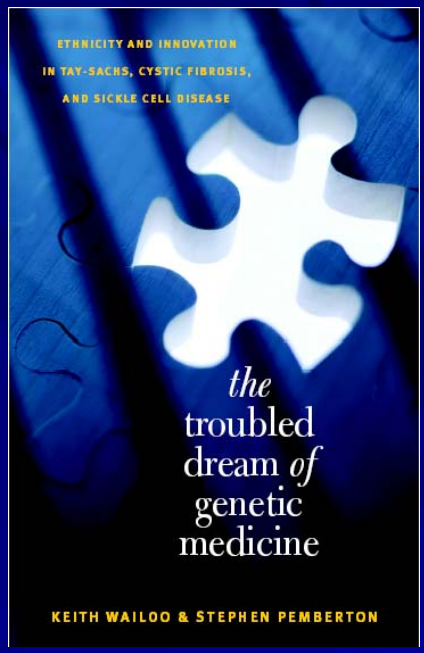
*TODAY: ONE HISTORICAL CASE STUDY (TAY-SACHS DISEASE), WITH SICKLE CELL DISEASE AND CYSTIC FIBROSIS AS BACKDROP*

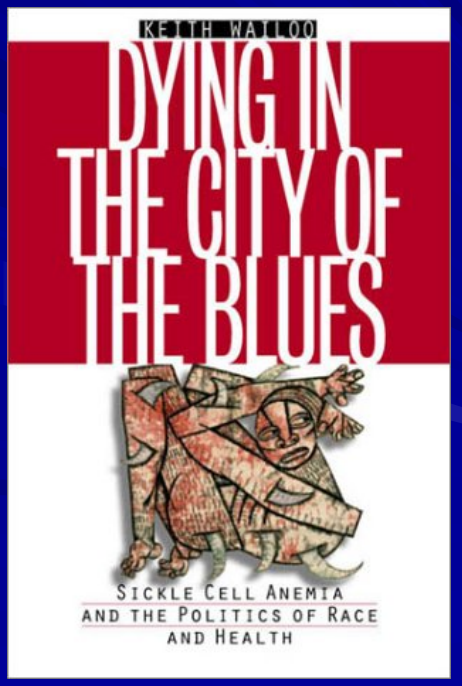
**CONTROVERSIES in CARRIER SCREENING, STIGMATIZATION, AND POPULATION – the case of sickle cell disease**

**• LINUS PAULING 1968: "I have suggested that there should be tatooed 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." UCLA Law Review**

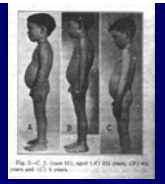
**• AIR FORCE POLICY ON TRAIT CARRIERS (1970s); UREA DEBACLE AND SEARCH FOR DESICKLING AGENTS**

**• Hydroxurea; Pain Management (80s/90s); Prophylactic Penicillin**



## TSD, SCD, and CF: Linked Historically




**Autosomal Recessive (established in 1950s)**

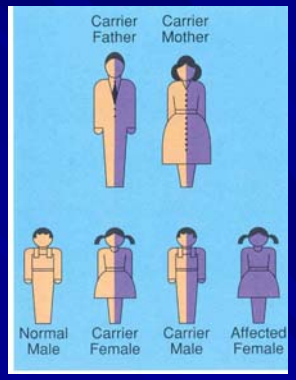
**Molecular Mechanisms and Mechanisms of Inheritance Explained (1960s)**

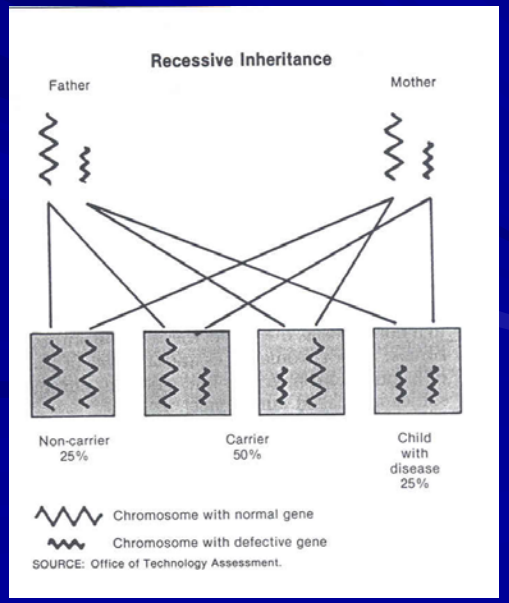
**Possibilities of Prevention via Genetic Testing/Counseling (1970s)**

**New Scientific Insights, Diagnostic Tests, Drugs, Surgery: Impact on Life Expectancy, Illness, Experience (1950-present)**

**> Each disease -- linked to questions of race and ethnicity; the term "genetic disease" does not do full justice to their complexities**

**CARRIER PARENTS 25% CHANCE OF HAVING AFFECTED CHILD**

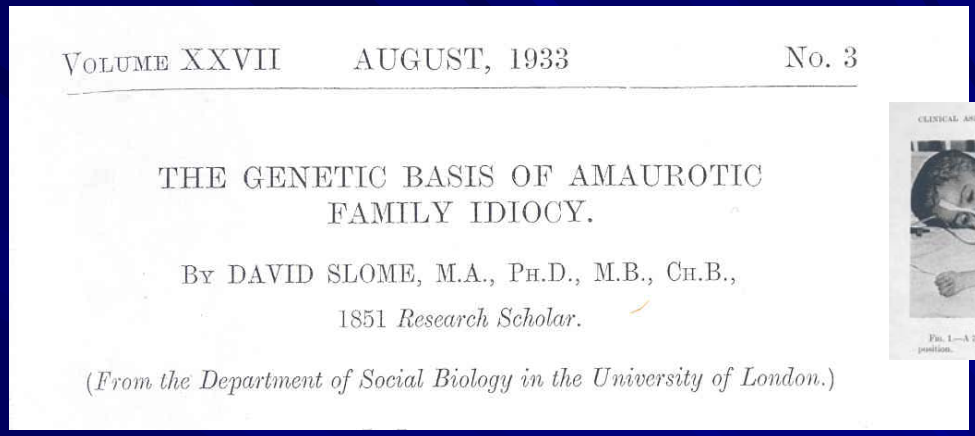


**The Tay-Sach's Historical Trajectory (**Warren Tay and Bernard Sachs)

**1880s -- ORIGINS AS "JEWISH AMAUROTIC 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.



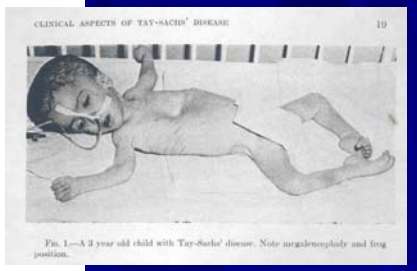
VOLUME XXVII AUGUST, 1933 No. 3

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 2 year old child with Tay-Sachs' disease. Note myoclonicephaly and frog position.

**TECHNOLOGICAL DEVELOPMENTS AT MID-CENTURY – transform screening/prevention possibilities**

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

**1969: O'Brien and Okada – deficiency of hexosaminidase A** (hex A) which results in buildup of lysosomes in brain tissue. 1971 -- "with detection and prevention of TSD possible, the question of cure arises…" Friedman

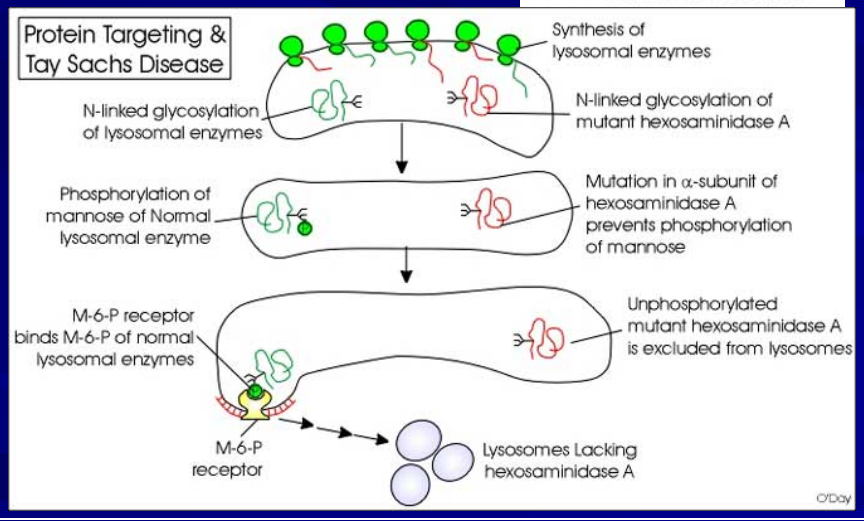
THERAPEUTIC OPTIMISM: 1975 -- **"we are entering a new phase in the treatment of genetic disease -- therapy by replacement of the deficient enzyme"** (Roscoe Brady)

**BY 1982 -- ENZYMATIC REPLACEMENT 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




> Despite its prevalence also among: *French-Canadians*, *Catholic Franco-Canadians in NH*, *Louisiana Cajuns*


CURSE AND BLESSING OF THE GHETTO

Marie and I hated her at first sight, even though she was trying hard to be helpful. As our obstetrician's genetics counselor, she was just doing her job, explaining to us the unpleasant results that might come out of the genetic tests we were about to have performed. As a scientist, though, I already knew all I wanted to know about Tay-Sachs disease, and I didn't need to be reminded that the baby sentenced to death by it could be my own.

Fortunately, the tests would reveal that my wife and I were not carriers of the Tay-Sachs gene, and our preparenthood fears on that matter at least could be put to rest. But at the time I didn't yet know that. As I glared angrily at that poor genetics counselor, so strong was my anxiety that now, four years later, I can still clearly remember what was going through my mind: If I were an evil deity, I thought, trying to devise exquisite tortures for babies and their parents, I would be proud to have designed Tay-Sachs disease.

...his is completely incurable, unpreventable, and present in the genes. A Tay-Sachs infant usually appears ...r the first few months after birth, just long enough ...eems to grow to love him. An exaggerated "startle ...to sounds is the first ominous sign. At about six ...e baby starts to lose control of his head and can't ...or sit without support. Later he begins to drool, ...s into unmotivated bouts of laughter, and suffers ...ns. Then his head grows abnormally large, and he ...blind. Perhaps what's most frightening for the par... at their baby loses all contact with his environment ...nes virtually a vegetable. By the child's third birth... still alive, his skin will turn yellow and his hands ...ost likely he will die before he's four years old.

...e and I were tested for the Tay-Sachs gene because ...e we rated as high-risk candidates, for two reasons. ...ie was carrying twins, so we had double the usual ...bear a Tay-Sachs baby. Second, both she and I are ...n European Jewish ancestry, the population with by ...orld's highest Tay-Sachs frequency.

...ples around the world Tay-Sachs appears once ...400,000 births. But it appears a hundred times ...quently—about once in 3,600 births—among descen... Eastern European Jews, people known as Ashke... ...or descendants of most other groups of Jews— ...Jews, chiefly from the Middle East, or Sephardic ...m Spain and other Mediterranean countries—the ...y of Tay-Sachs disease is no higher than in non-Jews. ...th such a clear correlation, one cannot help but ...What is it about this one group of people that

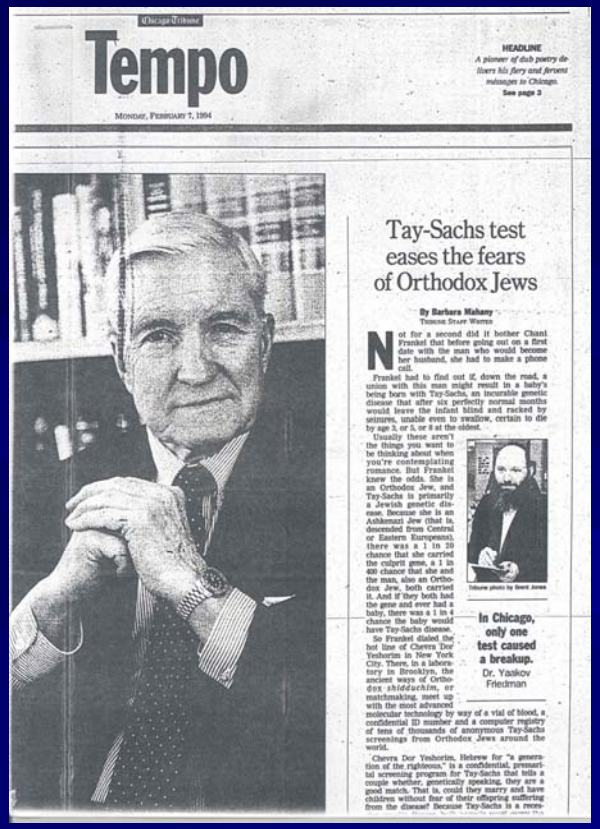

Figure 12.1. Possible geographical origins of some autosomal recessive diseases observed among Ashkenazi Jews. From R. A. Meals, 1971, *J. Chronic. Dis.* 23:547. Reprinted by permission of Pergamon Press, Ltd.

Jewish schoolchildren in Palenica, Poland, 1927

**DEEPLY INTERTWINED WITH JEWISH IDENTITY**

**-- Theories about TSD (balance polymorphism?)**
**-- Evolutionary adaptation to Jewish ghetto and TB??**
**-- Heterozygote resistance??**
**-- Mate selection?? (Rabbis marital choices)**

**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 European), there was a 1 in 30 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 recessive

Tribune photo by Brett Jones

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

**A BREAKTHROUGH IN PREVENTION? A dramatic SUCCESS STORY of modern genetics emerges – TESTING SERVING THE NEEDS of ethnic/religious community**

**Into 1971-75: SCREENING COUPLES, COUNSELING, THERAPEUTIC ABORTION**

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

**FOR ULTRA-ORTHODOX JEWISH, proscription against abortion limits options**

---

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

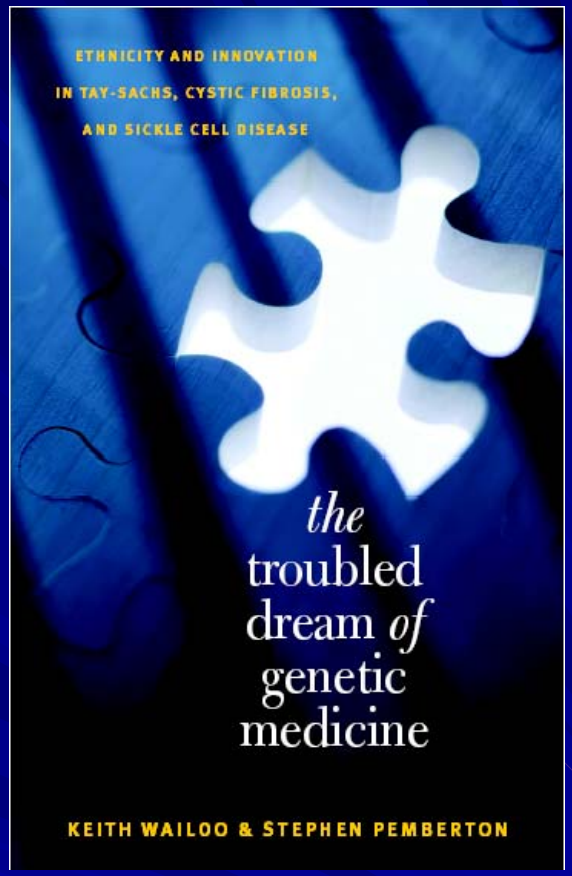
Testing Adolescents for Carrier Status – Arranged Marriages to Avoid Producing TSD

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

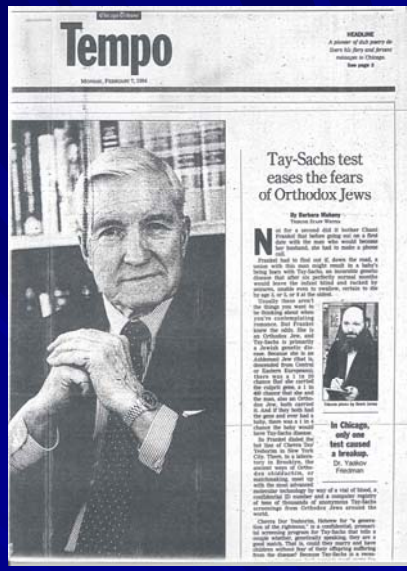
By the early 1970s, a wide range of techniques available for preventing the birth of Tay-Sachs babies. Where prenatal testing available, many Americans chose to abort TSD fetuses. Carriers may choose not to have children. For these and other reasons, the results since the 1970s have been dramatic: a gradual decline of TSD among Jews living in the United States, and in many communities even its total eradication. In a relatively short time, TSD had been transformed into a modern genetic success story.

One of the major factors in the success of prevention has been the role of rabbis, religious leaders, and scientists in developing innovative techniques to spread information about the disease.

"I went knocking on the doors of community leaders, rabbis, anyone who would listen to me and some of those who weren't, telling them that this was a problem and we had to do something about it. The point I made was that this was a problem for the entire community, not just for me…" -- Rabbi Josef Ekstein, founder Dor Yeshorim



## DESCRIPTIONS OF THE DOR YESHORIM


Tempo

Tay-Sachs test eases the fears of Orthodox Jews

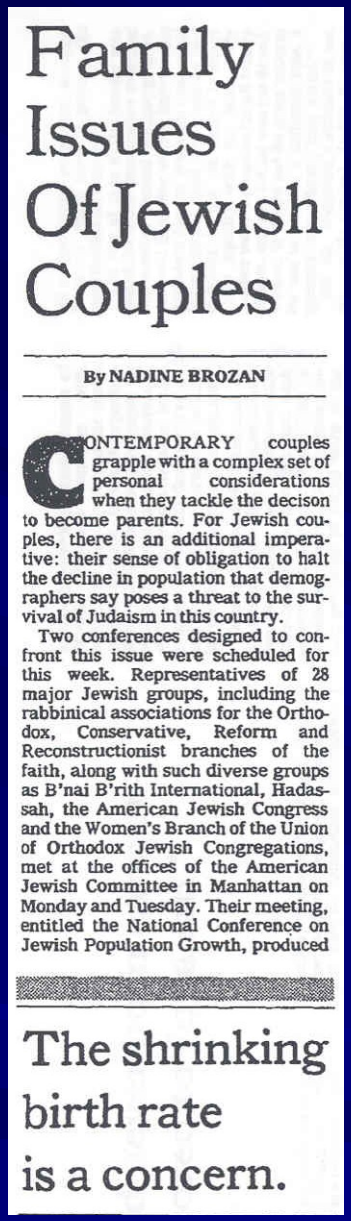
"It is the obligation of every parent, without exception, to turn to the Dor Yeshorim and heed their advice, before finalizing a match for his or her child."

The goal: "to eliminate Tay-Sachs from the Orthodox community, and to do it in accordance with strict Jewish law."

"If a peek into a prospective couple's genetic code shows a bad match, they are discouraged from even dating and certainly from marrying."

"an adolescent rite of passage"

"Every year, Dor Yeshorim representatives go to the private high schools where many Orthodox families send their children… Those tested are given a six digit identification number. If a boy and girl want to date, or if they have already started dating, they are encouraged to all the New York Dor Yeshorim Central Home Office with their identification numbers. Then they are told either that the match is compatible – that they are not at risk of having children with the disease in question – or that they each carry a recessive gene that could result in a child with the diseases."



# Family Issues Of Jewish Couples

By NADINE BROZAN

CONTEMPORARY couples grapple with a complex set of personal considerations when they tackle the decison to become parents. For Jewish couples, there is an additional imperative: their sense of obligation to halt the decline in population that demographers say poses a threat to the survival of Judaism in this country.

Two conferences designed to confront this issue were scheduled for this week. Representatives of 28 major Jewish groups, including the rabbinical associations for the Orthodox, Conservative, Reform and Reconstructionist branches of the faith, along with such diverse groups as B'nai B'rith International, Hadassah, the American Jewish Congress and the Women's Branch of the Union of Orthodox Jewish Congregations, met at the offices of the American Jewish Committee in Manhattan on Monday and Tuesday. Their meeting, entitled the National Conference on Jewish Population Growth, produced

The shrinking birth rate is a concern.

RELIGION

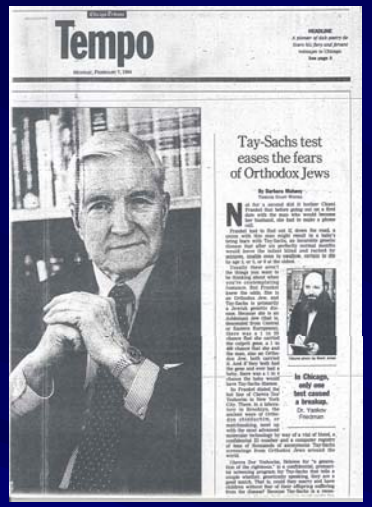
## Intermarriage Threatens American Jewish Community

The spiraling rate of intermarriage between Jews and non-Jews in the U.S. could seriously diminish the American Jewish community, according to a report released by the American Jewish Committee (AJC). The report urged Jewish families and communal groups to combat this trend by developing a variety of new and meaningful outreach programs to intermarried couples. Titled ''Intermarriage and the Jewish Future,'' the report presented the results of a three-year study of the dynamics of intermarriage and of the relationships of intermarried men and women to Jews and Judaism. Respondents included 446 intermarried couples in Cleveland, Dallas, Long Island (N.Y.), Los Angeles, New York City, Philadelphia, San Francisco, and Westchester County (N.Y.).

**"the spiraling rate of intermarriage between Jews and non-Jews… could seriously diminish the American Jewish community, according to a study… by the American Jewish Committee"**

# A SUCCESSFUL EFFORT IN CARRIER SCREENING: The Chevrah Dor Yeshorim in broader context

- **Ultra-Orthodox proscription against abortion**
- **Role of rabbi in family and marital decision-making, prevention of suffering (of parents)**
- **American Jewish concerns about group survival, shrinking birth rate, intermarriage (1970s-1980s)**


Tempo

Tay-Sachs test eases the fears of Orthodox Jews

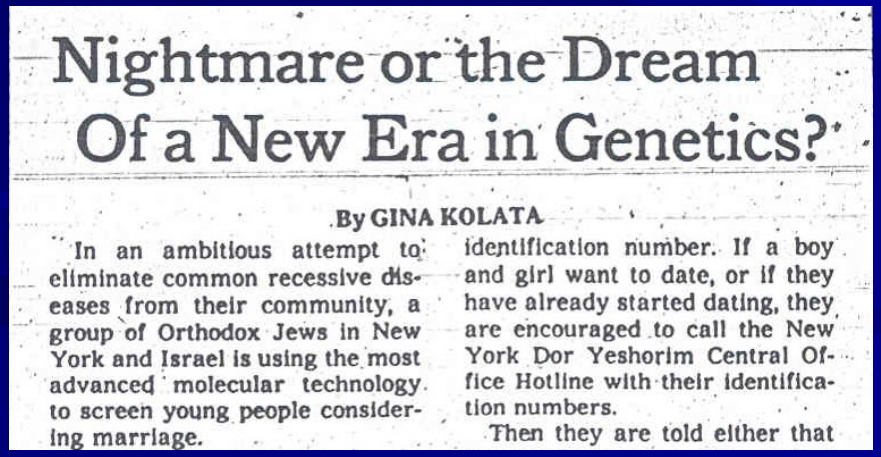
By Barbara Mishkin

In Chicago, only one test cannot a breakup.

Dr. Yaakov Freiman

**1993**
**BUILDING ON SUCCESS**

**Expanding Dor Yeshorim to test for Cystic Fibrosis and Gaucher's Disease**


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

CARRIER SCREENING: FROM DREAM TO NIGHTMARE – PREVENTING CF?

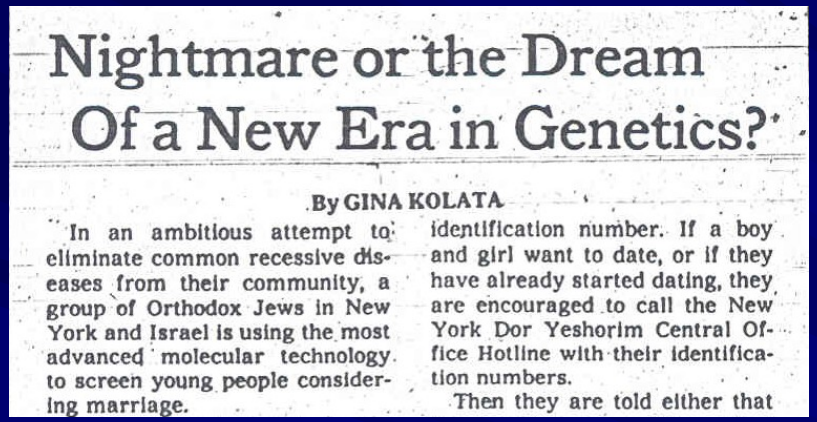
"this mentality, unfortunately, has been fostered in some degree by the scientific community… if a test exists, you should use it." Michael Kaback, medical geneticist

"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

# EARLY 1990s – CONFLICTING GENETIC IDEALS

## PREVENTION OF GENETIC DISEASE … OR CURE?



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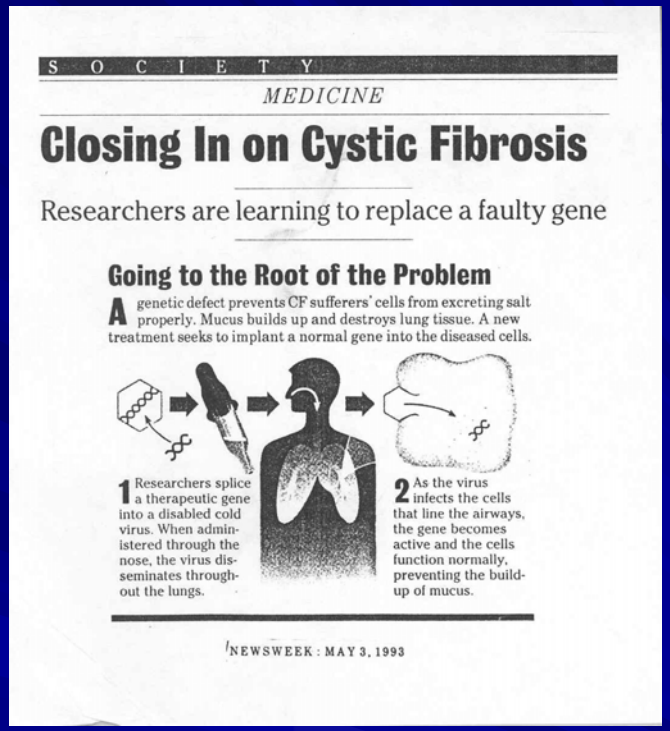
Dor Yeshorim: expands testing to other, not invariably fatal, "Jewish genetic diseases" like Gaucher's disease and Cystic Fibrosis



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 buildup of mucus.

NEWSWEEK : MAY 3, 1993

Weighed against rising life chances and hope of cure… Francis Collins sees Dor Yeshorim for CF as "moderate nightmare"

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."

# THE CYSTIC FIBROSIS POPULATION --

**Traveling a very different path, rising life expectancy, and shifting scientific paradigms**

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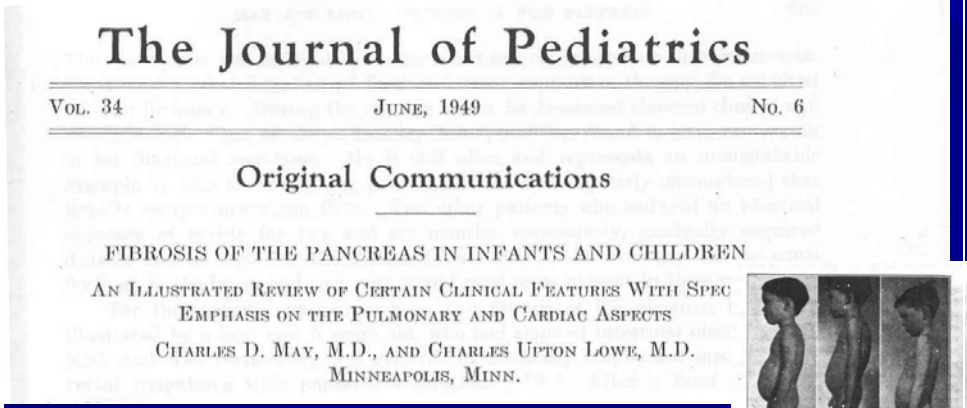
**1930s -- DOROTHY ANDERSON…. Cystic fibrosis of the pancreas: "severe malabsorption potentially treatable by dietary supplements and nutritional management."**



The Journal of Pediatrics

VOL. 34 JUNE, 1949 NO. 6

Original Communications

FIBROSIS OF THE PANCREAS IN INFANTS AND CHILDREN

AN ILLUSTRATED REVIEW OF CERTAIN CLINICAL FEATURES WITH SPEC EMPHASIS ON THE PULMONARY AND CARDIAC ASPECTS

CHARLES D. MAY, M.D., AND CHARLES UPTON LOWE, M.D.
MINNEAPOLIS, MINN.

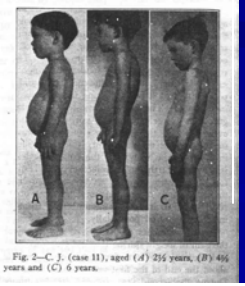



Fig. 2—C. J. (case 11), aged (A) 2½ years, (B) 4½ years and (C) 6 years.

50s and 60s: FROM PANCREATIC INSUFFIENCY to generalized disorder

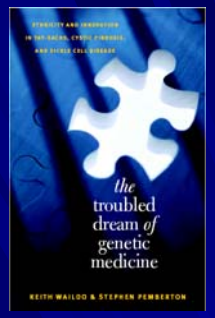
"In light of the 'newness' of the disease, it is understandable that those who are studying it and caring for patients ***should not be in full agreement on all its aspects***." (Kenneth Landauer, Guide to Diagnosis… Management of CF, 1963)

1965 -- Paul di'Sante Agnese notes sweat electrolytes elevated in CF patients… "most eventually die in childhood, adolescence, or young adulthood, of the chronic pulmonary involvement which usually dominates the clinical picture… ***despite its name, so-called cystic fibrosis of the pancreas is in reality a generalized disorder***."

"In patients with CF there is a ready-made experimental model in which to study the interaction of mucopolysaccharides and electrolytes."

# Making CF visible: The impact of the ANTIBACTERIAL REVOLUTION


**Trajectory – 50s/60s**




**"CF is an elusive simulator of other diseases…"**

**Patients dies from …**
**Pulmonary disease**
**Infection**

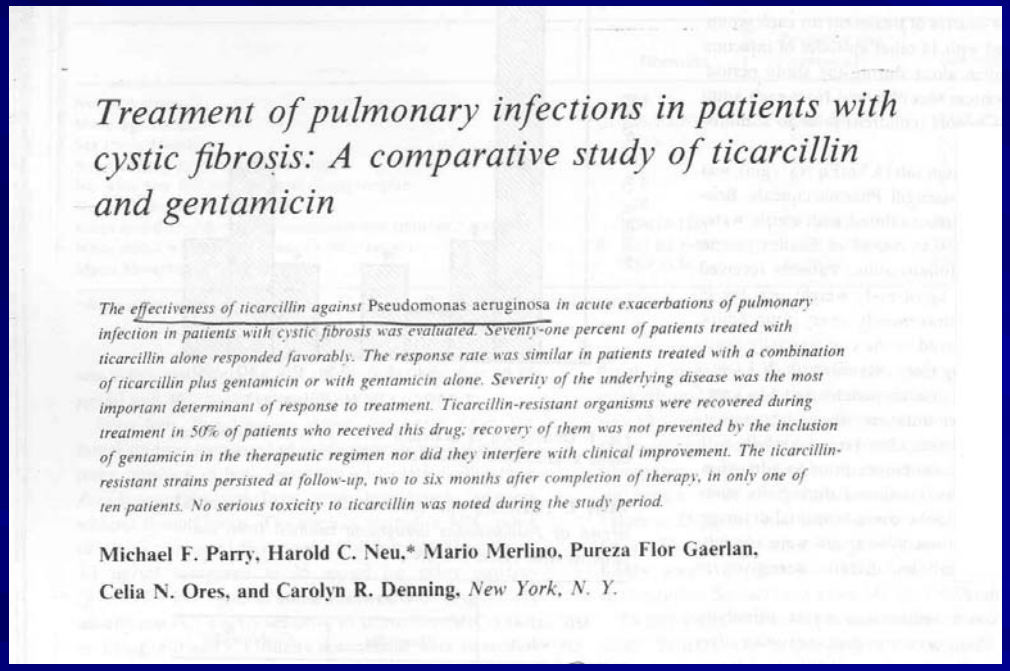
**Antibacterial agents in the 1950s and 1960s -- the leading edge of therapy**

**More patients being diagnosed and treated (parallels SCD story) – a panethnic disease?**

BUT ALSO… advent of the antibacterials transforms nature of the disease…
1951: "the enlarged chemical and antibiotic armamentarium of the physician today has brought increasing clinical importance to the Pseudomonas strain of organisms at all ages." (Garrard, et.al.)

**THE AGE OF ANTIBIOTICS AND THE POPULATION OF CF PATIENTS – research and patient care**

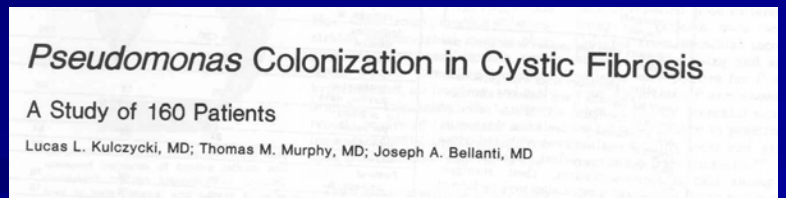
- **UNMASKED "The great masquerader"**
- **TRANSFORMING the clinical reality of disease (acute disease into a chronic one)**



*Treatment of pulmonary infections in patients with cystic fibrosis: A comparative study of ticarcillin and gentamicin*

*The effectiveness of ticarcillin against* Pseudomonas aeruginosa *in acute exacerbations of pulmonary infection in patients with cystic fibrosis was evaluated. Seventy-one percent of patients treated with ticarcillin alone responded favorably. The response rate was similar in patients treated with a combination of ticarcillin plus gentamicin or with gentamicin alone. Severity of the underlying disease was the most important determinant of response to treatment. Ticarcillin-resistant organisms were recovered during treatment in 50% of patients who received this drug; recovery of them was not prevented by the inclusion of gentamicin in the therapeutic regimen nor did they interfere with clinical improvement. The ticarcillin-resistant strains persisted at follow-up, two to six months after completion of therapy, in only one of ten patients. No serious toxicity to ticarcillin was noted during the study period.*

Michael F. Parry, Harold C. Neu,* Mario Merlino, Pureza Flor Gaerlan, Celia N. Ores, and Carolyn R. Denning, *New York, N. Y.*



*Pseudomonas* Colonization in Cystic Fibrosis

A Study of 160 Patients

Lucas L. Kulczycki, MD; Thomas M. Murphy, MD; Joseph A. Bellanti, MD

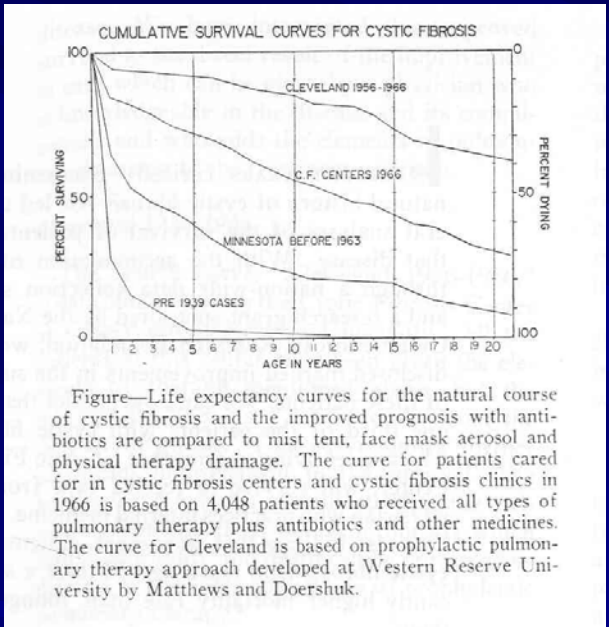
ADVANCES IN THERAPY AND RESEARCH CREATE NEW PROBLEMS… LOOKING INTO THE FUTURE FROM 1951

"Any regimen of long-continued therapy with a single antibacterial agent invites the development of highly resistant organisms which may flourish in an environment rendered more favorable by the absence of susceptible bacteria." (Garrard, et.al)

1968: "There is little doubt that the establishment of this species [Pseudomonas aeruginosa] in the respiratory tract is encouraged by suppression of other bacteria by antibiotics" (Burns and May, 1968)

# BY 1980s... THE IMPACT OF DRUG REVOLUTION ON CF

- **RISING LIFE EXPECTANCY – CF TRAJECTORY**
- **RISING EXPECTATIONS**
- **NEW FRUSTRATIONS**
- **POPULATION – "most common lethal genetic disease among Caucasian Americans"**




Figure—Life expectancy curves for the natural course of cystic fibrosis and the improved prognosis with antibiotics are compared to mist tent, face mask aerosol and physical therapy drainage. The curve for patients cared for in cystic fibrosis centers and cystic fibrosis clinics in 1966 is based on 4,048 patients who received all types of pulmonary therapy plus antibiotics and other medicines. The curve for Cleveland is based on prophylactic pulmonary therapy approach developed at Western Reserve University by Matthews and Doershuk.

PATIENTS GROWING OLDER: "the median survival age in 1989 was 26 years, compared to only 7 years in 1964. The extended survival is due in part to more aggressive treatment of pulmonary disease and malnutrition…" W.H. Frist, 1991 (article on Heart-Lung transplant)

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RESEARCH, SUBJECTS, INNOVATION, 1985: "Historically, patients with CF have been given a variety of prophylactic regimens. It was common at one time to give tetracyline for a few months, then chloramphenicol for a few months, and then other drugs for a few months… Perhaps when the basic defect is understood, the relationship of the host to the microorganism will be better understood." (Nelson)

# 1993/4: EXPANDING THE DOR YESHORIM TO TEST FOR AND PREVENT CF RUNS CONTRARY TO THE DREAM of a CURE

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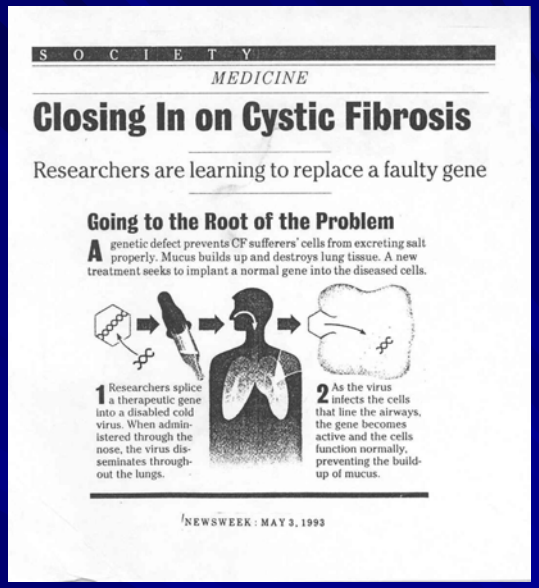
**Identification of Gene. Envisioning the replacement of faulty genes.**

**Closing in on CF Gene Therapy**

**GENE THERAPY – ADENOVIRUS VEHICLE "LEADING THE WAY"**

**A NEW REVOLUTION?**



SOCIETY

MEDICINE

**Closing In on Cystic Fibrosis**

Researchers are learning to replace a faulty gene

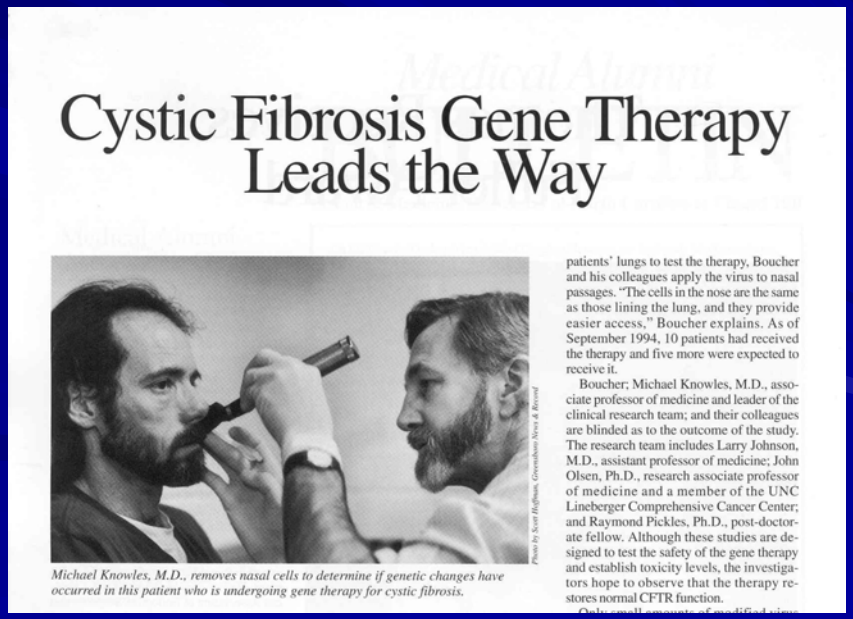
**Going to the Root of the Problem**

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



# Cystic Fibrosis Gene Therapy Leads the Way

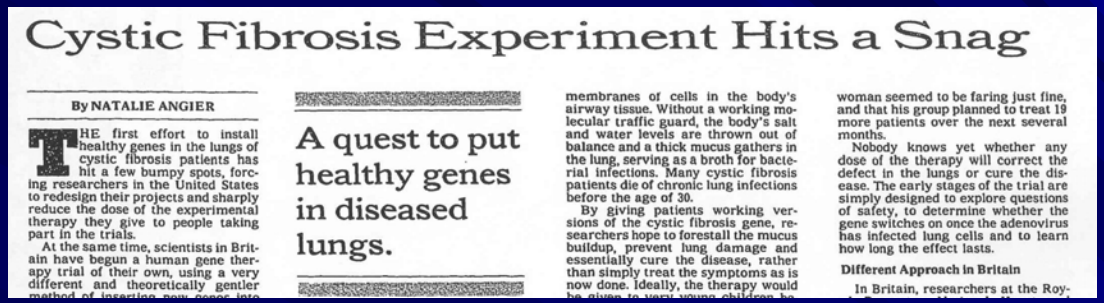


*Michael Knowles, M.D., removes nasal cells to determine if genetic changes have occurred in this patient who is undergoing gene therapy for cystic fibrosis.*

Photo by Scott Hoffman, Greensboro News & Record

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 September 1994, 10 patients had received the therapy and five more were expected to receive it.

Boucher; Michael Knowles, M.D., associate professor of medicine and leader of the clinical research team; and their colleagues are blinded as to the outcome of the study. The research team includes Larry Johnson, M.D., assistant professor of medicine; John Olsen, Ph.D., research associate professor of medicine and a member of the UNC Lineberger Comprehensive Cancer Center; and Raymond Pickles, Ph.D., post-doctorate fellow. Although these studies are designed to test the safety of the gene therapy and establish toxicity levels, the investigators hope to observe that the therapy restores normal CFTR function.



# 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

**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.

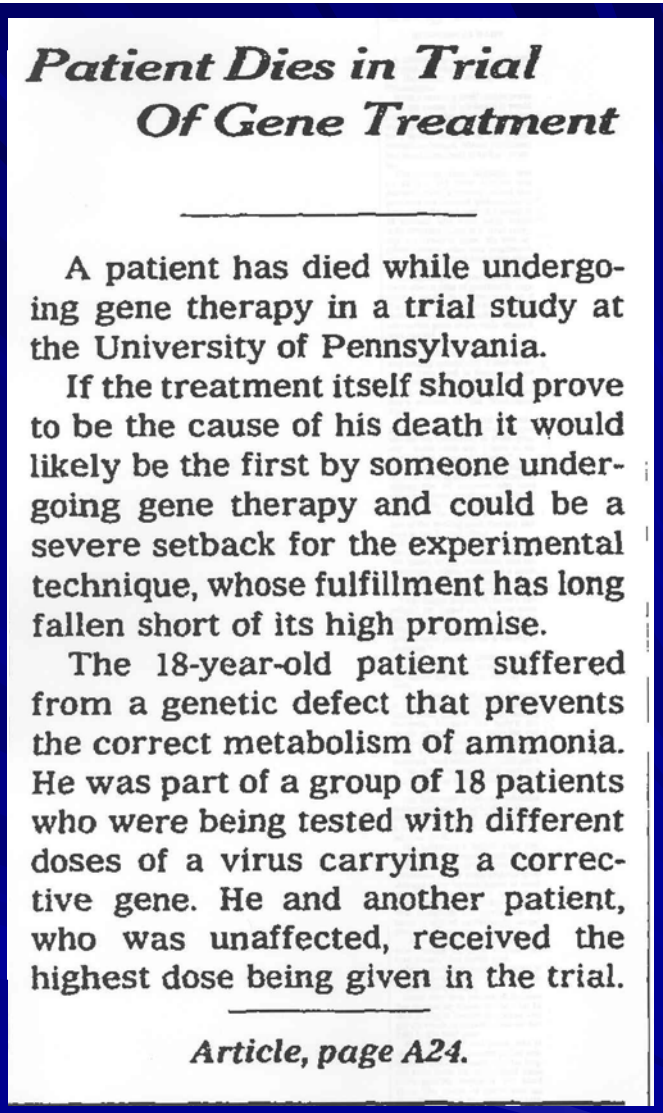
Nobody knows yet whether any dose of the therapy will correct the defect in the lungs or cure the disease. The early stages of the trial are simply designed to explore questions of safety, to determine whether the gene switches on once the adenovirus has infected lung cells and to learn how long the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

**Different Approach in Britain**

In Britain, researchers at the Roy-

Problems mount in adenoviruses used in "patients"… "When administered in low concentration [adenovirus] ineffective, at high doses causes acute inflammation…"

Experiments halted in CF… Crystal: GenVec "now concentrating on gene therapy for cardiovascular disease…" "Maybe the quickest route to solving cystic fibrosis is to take a detour" – Genzyme executive



# *Patient Dies in Trial Of Gene Treatment*

A patient has died while undergoing gene therapy in a trial study at the University of Pennsylvania.

If the treatment itself should prove to be the cause of his death it would likely be the first by someone undergoing gene therapy and could be a severe setback for the experimental technique, whose fulfillment has long fallen short of its high promise.

The 18-year-old patient suffered from a genetic defect that prevents the correct metabolism of ammonia. He was part of a group of 18 patients who were being tested with different doses of a virus carrying a corrective gene. He and another patient, who was unaffected, received the highest dose being given in the trial.

*Article, page A24.*

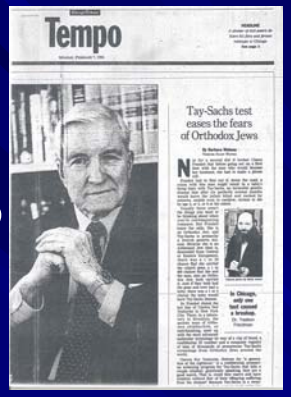
MAJOR CRISIS OF GENE THERAPY

**POSITIVE SPIN: 1995: "This commercial pressure may also account for some of the hype surrounding developments in gene therapy… If you're the leader of a gene-therapy company… 'you try to put as positive a spin as you can on every step of the research process… because you have to create promise out of what you have -- that's your value." James Q. Wilson, Inst for GT, Penn**

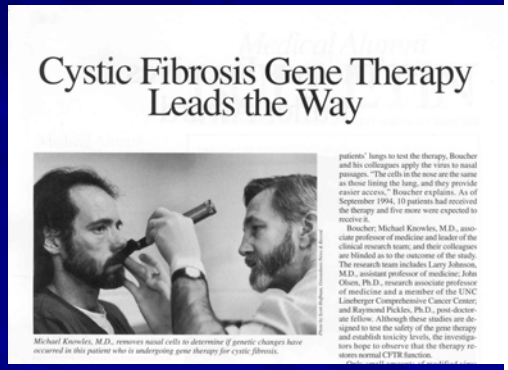
# DILEMMAS IN CARRIER SCREENING: Should the Dor Yeshorim be extended to CF testing and prevention?

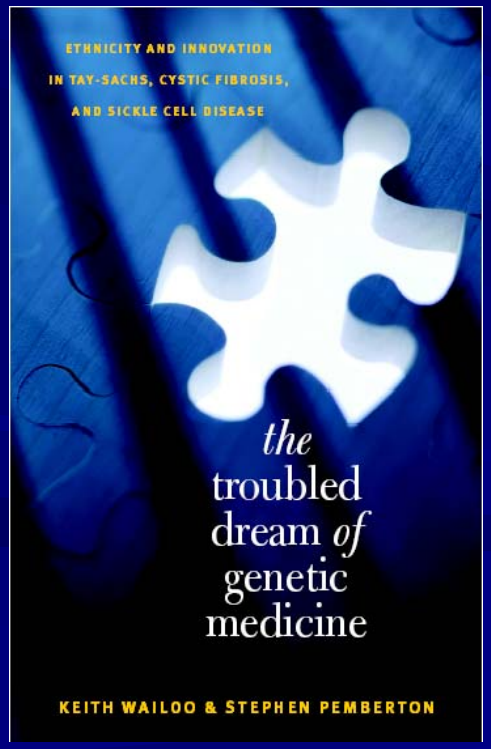
A clash of conflicting ideals, values, and histories

(Jewish Orthodox community health and preservation)
AND (The Question for a Genetic Cure)


Tempo

Tay-Sachs test eases the fears of Orthodox Jews


Cystic Fibrosis Gene Therapy Leads the Way

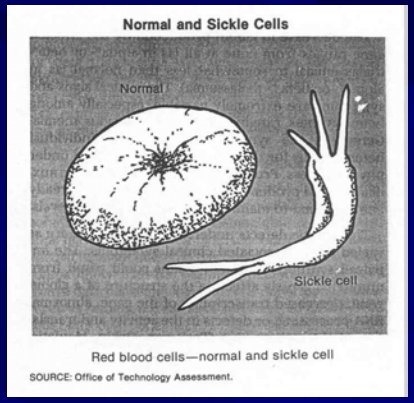



***EACH GENETIC DISEASE AND EACH POPULATION FOLLOWS A UNIQUE TRAJECTORY:***
***shaped by complex interaction of science, technology, medicine with values, subculture and society***

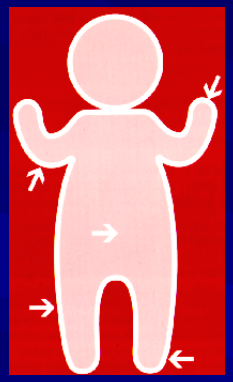
*Histories of therapeutic advancement – solving some problems, creating others in their wake*

*Different interests and social, political, economic investments in screening*

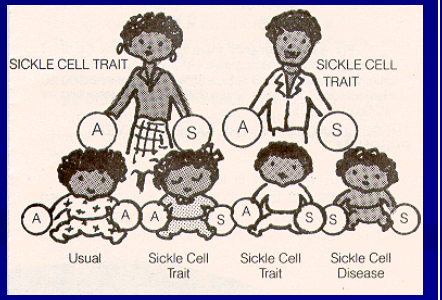
**Sickle Cell Disease – shares history with both CF and TSD**




- **Dramatic impact of antibacterial agents (great masquerader)**



- **Clinical description early in the century (James B. Herrick)**
- **Molecular Understanding and Inheritance Illuminated at mid century – Linus Pauling and J.V. Neel**




**Autosomal Recessive**

**THREE DISEASES TRAVELING DIFFERENCE HISTORICAL TRAJECTORIES:**

**DIFFERENT KINDS OF STIGMA, DIFFERENT MEANINGS FOR EACH POPULATION, AND CARRIER SCREENING COMES TO HAVE A DIFFERENT POLITICAL, SOCIAL, AND CULTURAL MEANING**

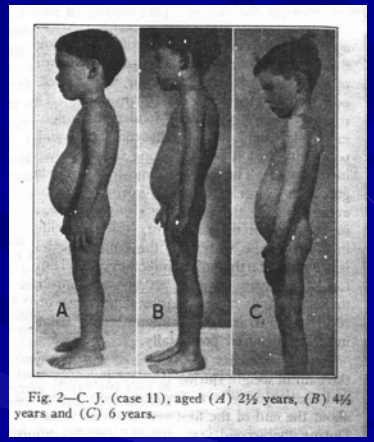
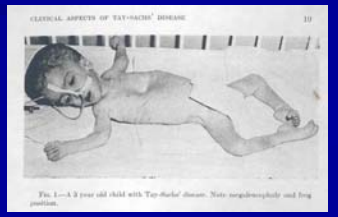


Fig. 2—C. J. (case 11), aged (*A*) 2½ years, (*B*) 4½ years and (*C*) 6 years.

*. . . my lower lip drops as the numbing effect of the pain takes over.*

**TSD: PREVENTING CERTAIN DEATH AND SUFFERING**



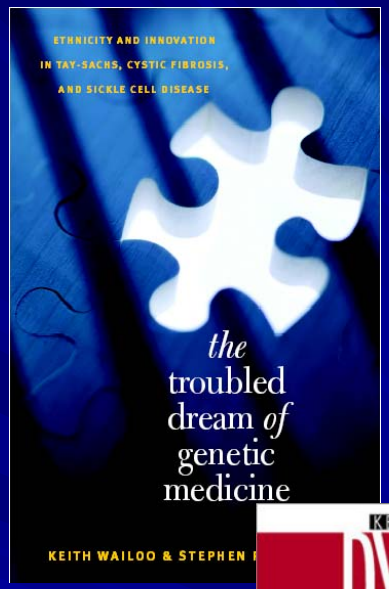
**CONTROVERSIES in CARRIER SCREENING, STIGMATIZATION, AND POPULATION – the case of sickle cell disease**

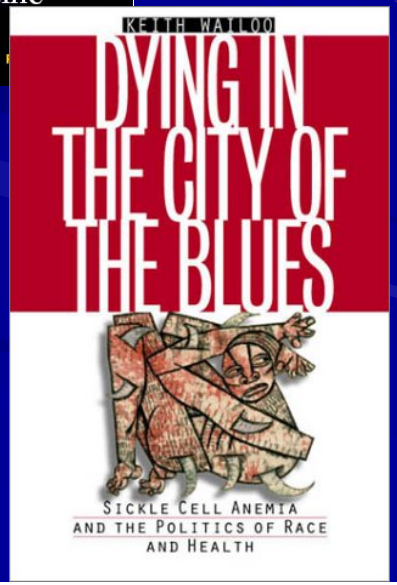
**• LINUS PAULING 1968: "I have suggested that there should be tatooed on the forehead of every young person a symbol showing possession of the sickle cell gene or whatever other similar gene… that he has been found to possess in a single dose… It this were done, two young people carrying the same seriously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

**• AIR FORCE POLICY ON TRAIT CARRIERS (1970s); UREA DEBACLE AND SEARCH FOR DESICKLING AGENTS**

**• Hydroxurea; Pain Management (80s/90s); Prophylactic Penicillin**

**SCA -- SCREENING CONTROVERSIES (PAULING, ETC.) EVOKE: EUGENICS, POPULATION CONTROL, GOVERNMENT AND RACISM**



**HYDROXYUREA – "genetic switch"; PROPHYLACTIC PENICILLIN**

**"I don't like the word breakthrough… But we can now show that this drug therapy can make a difference." (Reid, 1986)**

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**BONE MARROW TRANSPLANT (peril and promise)**

**(high-risk, high-gain intervention – Cure/Graft-vs-Host-Disease/Death from Procedure):**

**"Little would be gained by sickle cell disease patients if they merely traded the mortality associated with the primary disorder for a new set of disabling symptoms resulting from their treatment." (Beutler, 1991)**



SPECIAL ARTICLE

## BONE MARROW TRANSPLANTATION FOR SICKLE CELL DISEASE

### A Study of Parents' Decisions

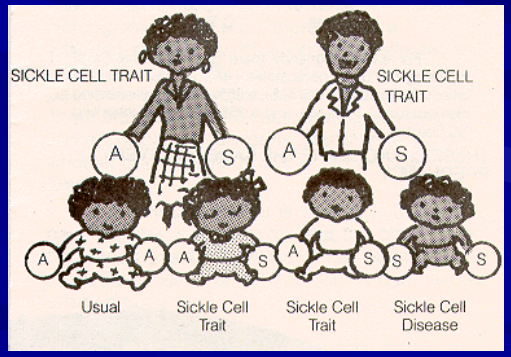
ERIC KODISH, M.D., JOHN LANTOS, M.D., CAROL STOCKING, PH.D., PETER A. SINGER, M.D., M.P.H., MARK SIEGLER, M.D., AND F. LEONARD JOHNSON, M.D.

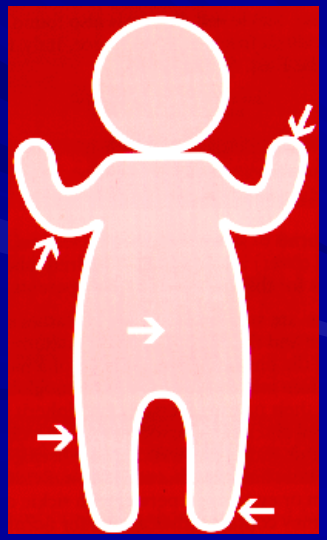
**Abstract** *Background.* Bone marrow transplantation has been shown to cure sickle cell disease, but it carries a 15 percent mortality risk. To determine whether parents would accept this risk to cure their children of sickle cell disease, we interviewed parents of children with sickle cell disease who were being followed in a university hospital clinic.

*Methods.* We assessed parents' attitudes by using questions based on the standard reference-gamble paradigm. After we gave them descriptions of bone marrow transplantation and graft-versus-host disease (GVHD), the parents were presented with a series of hypothetical situations. In the first situation, bone marrow transplantation was described as offering certain (100 percent) survival with cure of sickle cell disease. In subsequent descriptions, the mortality rate associated with bone marrow transplantation was increased by 5 percent increments. The parents indicated the highest mortality risk at which they would consent to the procedure in order to cure their children.

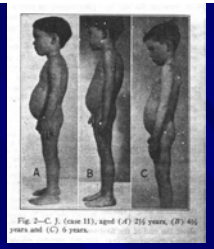
*Results.* In order to obtain a cure for their children, 36 of 67 parents (54 percent) were willing to accept some risk of short-term mortality, 25 of 67 (37 percent) were willing to accept at least the 15 percent short-term mortality risk we estimate to be the current figure for bone marrow transplantation, and 8 of 67 (12 percent) were willing to accept a short-term mortality risk of 50 percent or more. Nine parents (13 percent) said they would accept both a mortality risk of 15 percent or more and an additional 15 percent risk of GVHD. The parents' decisions were not related to the clinical severity of their children's illness.

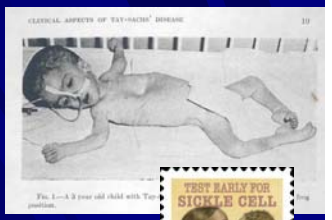
*Conclusions.* At current rates of mortality and morbidity with bone marrow transplantation, a substantial minority of the parents of children with sickle cell disease may consent to bone marrow transplantation for their children. Parental attitudes should be factored into decisions about whether to offer bone marrow transplantation to children with sickle cell disease. (N Engl J Med 1991;325: 1349-53.)

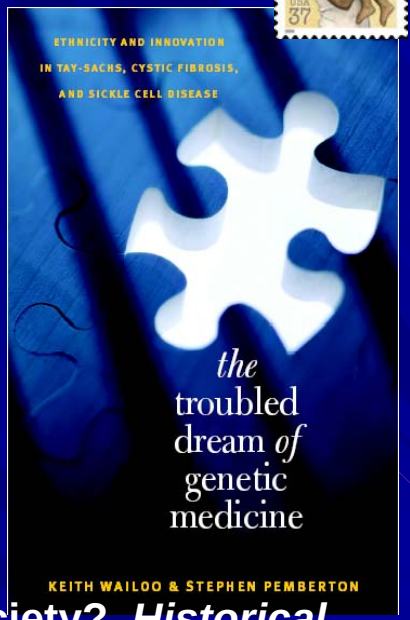


## CONCLUDING COMMENTS – TSD, CF, SCD CARRIER SCREENING






1. **CONFLICTING cultural values over DISEASE, and the best way to combat disease… (e.g., prevention or cure), and divergent cultural views of genetic medicine**

2. **All "genetic diseases" or heritable disorders considered in their own terms. "Genetic" or "Hereditary" disease, as a label, does not do justice to their complex, divergent trajectories and cultural meanings**

3. **LESSONS of the PAST: The Ethics of the DOR YESHORIM AND CF (right for Ultra-Orthodox…)**

**Lessons of the Past:**

- **Balancing the screening interests of individuals, communities, and society?** ***Historical sensitivity to values, and cultural competence among health practitioners who engage in screening***

- **How to target screening to "hidden" and obvious subpopulations?** ***One-size will not fit all***

- **When screening is not the answer. Other goals: treatment, relief, longevity?** ***Competent screening programs among populations whose group identities are invested in the maintenance of values that are distinctively different than that of the majority culture***