

# **Ethical Issues in Research with Children**

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# What is the morally appropriate role for children in research?

- Historical overview:
  - Earliest guidelines written to protect against abuse.
- The miracles of modern medicine:
  - More recent guidelines seek to increase access.
- The 21<sup>st</sup> Century:
  - Striking the proper balance.

**“The history of pediatric experimentation is largely one of child abuse.”**

“Historical Overview: Pediatric Experimentation” SE Lederer and MA Grodin in *Children as Research Subjects: Science Ethics and Law*. New York: Oxford University Press, 1994, p. 19.

# Lessons from History

- Immunization Research often used children as subjects as they were more likely to be disease-naïve.
  - 18<sup>th</sup> century: Child-subjects were the researcher's children, servants, or slaves.
  - 19<sup>th</sup> century: Child-subjects were often institutionalized children.
  - 20<sup>th</sup> century: Subjects included the researcher, the researcher's children, and institutionalized persons, particularly institutionalized children with mental retardation.

**Research on institutionalized children offered scientific advantages because the standardized conditions in the asylum approximated those “...conditions which are insisted on in considering the course of experimentation infection among laboratory animals, but which can rarely be controlled in a study of infection in man.”**

Alfred Hess, Medical Director of the Hebrew Infant Asylum in NYC, 1914.

**“...cheaper than calves.”**

Explanation by a Swedish physician about why he chose to experiment on institutionalized children as reported by the Humane Society, n.d.

# The Lessons of History NOT Learned

- Post World War II
  - Nuremberg Code did not address research with children.
  - Declaration of Helsinki (1964) permitted surrogate decision making.
- Henry K Beecher M.D. “Ethics and Clinical Research” *New England Journal of Medicine*; 1966: 274: 1360-4.
  - 22 studies; 4 involved children including Willowbrook

**The focus of the 1970s  
and 1980s Guidelines  
was the protection of  
subjects, particularly  
vulnerable populations  
like children**

# Regulations for Children in Medical Research

- National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research, “Report and Recommendations: Research Involving Children”, 1977.
- American Academy of Pediatrics, “Ethics of Drug Research”, 1977.
- Federal Regulations, 1983, revised 1991, 1997, “Additional Protections for Children Involved as Research Subjects.” [Subpart D]

# National Commission

- National Commission report opens with a Recommendation that offers justification for a child's participation:
  - “The Commission recognizes the importance of safeguarding and improving the health and well-being of children, because they deserve the best care that society can reasonably provide.” (p. 1)
- Also acknowledges a child's vulnerability:
  - “Ethical problems arise from the dependence and immaturity of children which can be offset by establishing conditions that research must satisfy.” (p. 2)

# National Commission / Fed Regs

- Criteria for Children as Research Subjects
  - the research is scientifically sound and significant;
  - where appropriate, studies have been conducted first on animals and adult humans, then older children;
  - risks are minimized by using the safest procedures consistent with sound research design;
  - adequate provisions are made to protect the privacy of the children and their parents;
  - subjects will be selected in an equitable manner;
  - adequate provisions for the permission of the parents or guardians, and when appropriate, the assent of the child.
- Suggests that research be classified by degree of risk and whether it offers the prospect of direct benefit.
- Fed Regs, subpart D accepts the Commission's guidelines almost verbatim.

**The focus of the 1990s and 2000s policies is to promote access to research participation of all subjects, including vulnerable subjects.**

# Policy Changes that Promote Access

- Food and Drug Administration Modernization Act (FDAMA), 1997
- Best Pharmaceuticals for Children Act (BPCA), 2002
- NIH inclusion of children, 1998
- Pediatric Research Equity Act passed in 2003 (after the FDA's Pediatric Rule was found unconstitutional)

# Why the shift from Protection to Access?

- Concern that children were “therapeutic orphans”.
  - The acknowledgement that children are not little adults for whom we can simply “down-size dosages”.
- AIDS epidemic in which only those who participated in clinical trials received life-prolonging therapies.

**The focus of the 1970s and 1980s Guidelines was the PROTECTION of subjects, particularly vulnerable populations like children. The focus of the 1990s and 2000s Policies is ACCESS.**

**Are we misfocused?**

# **BEECHER REVISITED**

Case 1: A literary example



*Curious George  
gets a medal*

by

**H.A. REY**



MUSEUM OF SCIENCE

Dear George,

A small space ship has been built by our experimental station. It is too small for a man but could carry a little monkey. Would you be willing to go up in it?

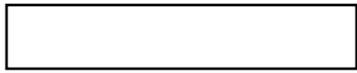
I have never met you but I hear that you are a bright little monkey who can do all sorts of things, and that is just what we need.

We want you to do something nobody has ever done before: bail out of a space ship in flight.

When we flash you a signal you will have to open the door and bail out with the help of emergency rockets.

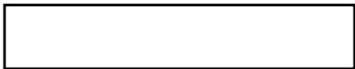
We hope that you are willing and that your friend will permit you to go.

Gratefully yours  
Professor Wiseman  
Director of the Science Museum.





“So YOU are George!” Professor Wiseman said. “If I had only known . . . Of course everything will be forgiven, if you are willing to go.”



# Lessons from Curious George

- The wrong lesson: Curious George is a successful astronaut, he is hailed as a hero, and (as the title foretells), he earns a medal!
- The real lessons:
  - Illiteracy makes you a vulnerable subject.
  - Informed consent documents should describe the RISKS as well as the benefits.
  - Subjects may feel coerced for many reasons.
  - “An experiment is ethical or not at its inception...ends do not justify means.” (Beecher, 1966).

# **Case 2: Experimental Stem Cell Transplantation for Newly Diagnosed Type 1 Diabetes [T1D]:**

When is a Children's First  
Policy appropriate?

**Autologous Nonmyeloablative  
Hematopoietic Stem Cell Transplantation  
in Newly Diagnosed Type 1 Diabetes  
Mellitus [T1D]. Voltarelli, JC. et al. *JAMA*.  
April 11, 2007: 1568–76.**

- **Objective:** To determine the safety and metabolic effects of high-dose immunosuppression followed by autologous nonmyeloablative hematopoietic stem cell transplantation (AHST) in newly diagnosed T1D.

# Stem Cell Transplantation in T1D

- **Design, Setting, and Participants:** A prospective phase 1/2 study of 15 patients with T1D (aged 14–31 yrs) diagnosed within the previous 6 weeks. Enrollment was 11/03–7/06 with observation until 2/07 at the Bone Marrow Transplantation Unit of the School of Medicine of Ribeirão Preto (Brazil). Patients with previous diabetic ketoacidosis were excluded after the first patient with DKA failed to benefit from AHST. Hematopoietic stem cells were mobilized with cyclophosphamide (2.0 g/m<sup>2</sup>) and granulocyte colony-stimulating factor (10 µg/kg per day) and then collected from peripheral blood by leukapheresis and cryopreserved. The cells were injected intravenously after conditioning with cyclophosphamide (200 mg/kg) and rabbit antithymocyte globulin (4.5 mg/kg).

# Ethical Issues

- Was the study design ethical?
  - Did the authors need a control group?
- Does it matter that the lead author (Dr. Burt) was from the US but he partnered with colleagues in Brazil and none from his own institution nor his own country?
  - When is it ethical to do research outside of the U.S.?
- Was the subject selection appropriate?
  - Do we need to enroll children in this first study of this therapy?

# Children First Policy

- The participation of children in research with adults is appropriate if:
  - It represents the best medical option
  - Early phase I and phase II studies in adults show safety and a promise of efficacy
  - Study is designed to include subset analyses
- Currently, children are being exposed to risks and harms of research, but there is no advance in pediatric medicine from their participation.

# **Case 3: Clinical Asthma Trials [CAT]**

Ethical issues in the need for equipoise, the use of placebos, and when research morally can enroll children

# Asthma: Background

- One of the most common chronic conditions of childhood
- Over 4.5 million children in U.S are affected.  
Accounts for:
  - > 10 million missed school days;
  - 5.8 million outpatient visits;
  - >867,000 emergency department visits;
  - 174,000 hospitalizations; and
  - >200 deaths annually in children.

# NHLBI Recommendations

- 1991 Guidelines for the Diagnosis and Management of Asthma
  - Anti-inflammatory medications (AIM) for all children and adults with more than mild asthma
    - Inhaled corticosteroids (ICS) for children and adults with severe asthma
    - ICS for adults with moderate asthma
- 1997 Guidelines, reaffirmed 2002 guidelines
  - First line of choice for all children and adults with more than mild intermittent asthma is an ICS.

# Study Objectives

- How often do children enrolled in CAT receive anti-inflammatory medications [AIM] in accordance with NHLBI guidelines?
- Are subjects, particularly children subjects, enrolled in placebo-controlled trials (PCT) harmed more than subjects enrolled in other types of CAT?
- Are children enrolled in the placebo arm of a PCT harmed more frequently than children enrolled in active-treatment arms?
- Is generalizable knowledge about children as a class procured when children are enrolled in studies with adult subjects?

# Methods

- Medline search between 1/1/98 and 12/30/01 for asthma trials
  - Exclusion criteria
    - Conducted outside of the US
    - Did not include subjects younger than 18 years
    - Did not include original data or involve active recruitment of subjects (e.g. meta-analyses)
    - Non-therapeutic (e.g. cost benefit analysis)
    - Focused on such related conditions as exercise induced asthma, allergic rhinitis or status asthmaticus.

# Results: Study Characteristics 1

Asthma studies 1998-2001	450
Eligible asthma studies	70
Trials using placebos	50
Placebo vs. experimental drug (PCT)	45
Placebo as add-on vs. experimental drug (add-on) study	5
PCT	45
Trials involving children and adults	31
Trials involving ONLY children	14

# Results: Study Characteristics 2

Trials involving children and adults	52
Trials differentiating between children and adults at baseline	8
Trials differentiating between children and adults in results	1
Avg duration of trials (excl. run-in) in weeks	26.8
Trials documenting withdrawal information	62
PCTs documenting withdrawal info	40
Trials documenting IRB review and approval	67
Trials documenting procurement of consent	68

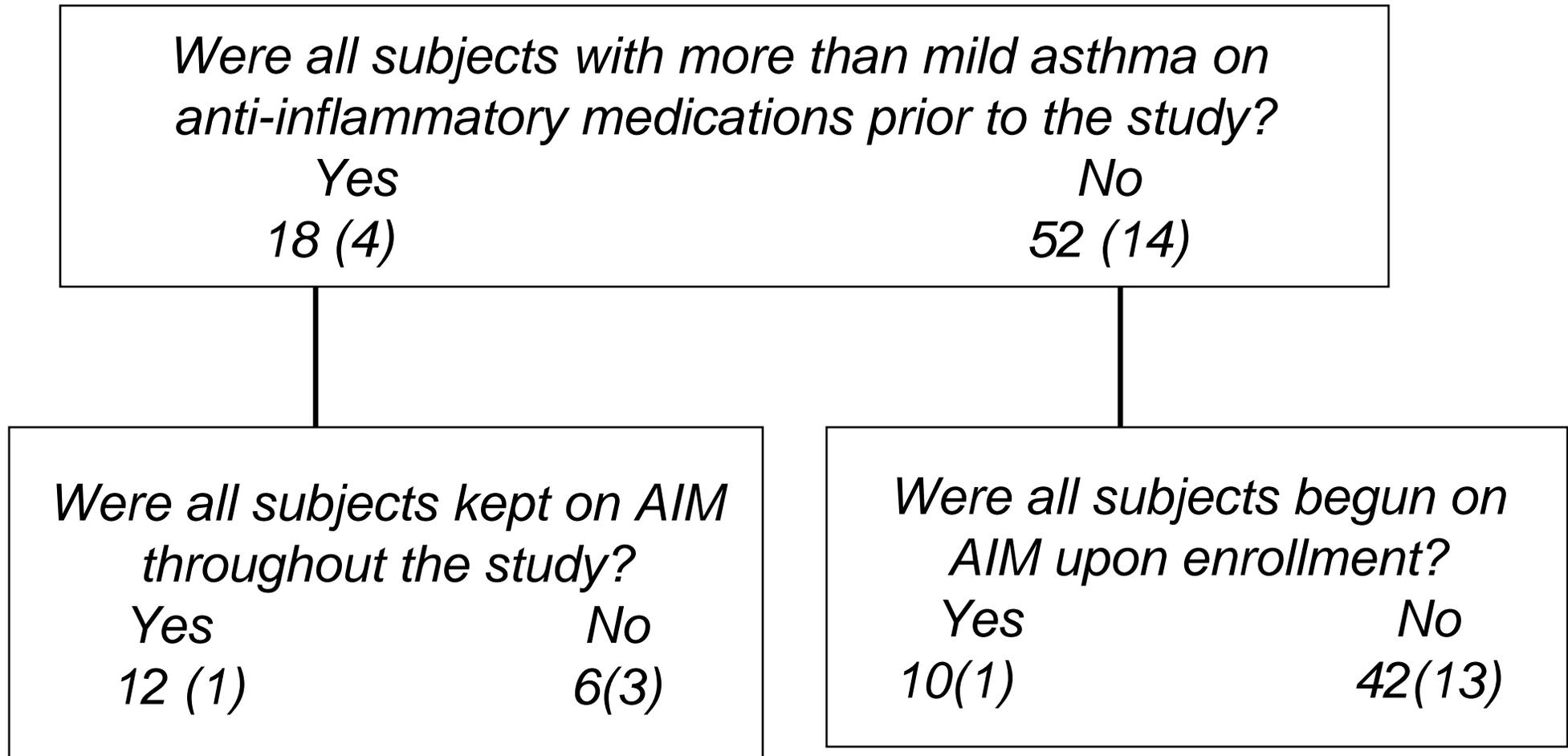
# Results: Study Characteristics 3

Trials documenting source of funding	67
Pharmaceutical company	63
NIH with pharmaceutical-sponsored drugs	3
Academic institution	1
PCT documenting source of funding	42
Pharmaceutical company	39
NIH with pharmaceutical-sponsored drugs	3
Academic institution	0

# Results: Study Characteristics 4

Trials performed by year # (# incl. only children)	
1998	15(7)
1999	22(4)
2000	20 (5)
2001	13 (2)
Subjects available for analysis (# counted more than once)	30,101 (218)
Subjects enrolled in 62 trials documenting withdrawal information	25,366 (218)

# NHLBI Asthma Guideline Adherence in Clinical Asthma Trials incl. children (n=70)



# Subject Withdrawals by Trial Design

	All Trials (n=62)	Add-on and Active controlled Trials (n=22)	PCT (n=40)
Subjects analyzed #	24,953	11,690	13,263
Withdrawn #(% )	4,653 (19)	1,849 (16)	2,804 (21)*
asthma exacerb'n	1,605 (34)	358 (19)	1,247 (44)*
adverse event	518 (11)	277 (15)	241 (9)*
other	2,069 (44)	1,177 (64)	892 (32)*
not discussed	461 (10)	37 (2)	424 (15)
Hospitalized #(% )	122 (<1)	108 (<1)	14 (<1)

# Subject Withdrawal in PCTs

	All Trials (n=40)		
Study arms	All arms	Active arms	Placebo arm
Subjects analyzed #	13,263	8,867	4,396
Asthma exacerbation # (%)	1,247 (9.2)	580 (6.5)	667 (15)*
Withdrawn # (%)	2,804 (21)	1,422 (16)	1,210 (28)*

\*p<.001

# Ethical Questions Raised by Current CAT

1. Do the studies begin in clinical equipoise?
2. When, if ever, are placebo-controlled trials ethical?
3. When should children be enrolled as “first line” participants in research?
4. Does the consent of the subjects ensure that the research was ethical?

# 1. Clinical Equipoise

- “...at the start of the trial, there must be a state of clinical equipoise regarding the merits of the regimens to be tested, and the trial must be designed in such a way as to make it reasonable to expect that, if it is successfully conducted, clinical equipoise will be disturbed.”

- B Freeman, “Equipoise and the Ethics of Clinical Research.”  
*New England Journal of Medicine* 1987; 317: 141.

- This means that researchers must be uncertain as to which arm of the trial is better.

- Individual equipoise versus community (clinical) equipoise

# 1. Clinical Equipoise?

- “Asthma symptoms would be expected to worsen in the placebo group during the treatment period because these patients were dependent on inhaled steroids but were not allowed treatment with inhaled steroids while in the study.”
  - Shapiro et al. Efficacy and safety of budesonide inhalation suspension (Pulmicort Respules) in young children with inhaled steroid-dependent, persistent asthma. *J Allergy Clin Immunol.* 1998; 102:789-96
- Clearly, the placebo-controlled trials (non add-ons) did not begin in equipoise.
- I doubt this perspective was shared in the consent process as well!

## 2. When are Placebos Ethical?

- International Codes of Research Ethics:
  - Declaration of Helsinki (1964)
  - Helsinki was revised in 1975 to address medical design: In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method.
  - Helsinki was revised again in 2000 (article 29): The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

## **2. When are Placebos Ethical?-2**

- **Modification to Declaration of Helsinki, 2002.**
  - **FOOTNOTE: NOTE OF CLARIFICATION ON PARAGRAPH 29 of the WMA DECLARATION OF HELSINKI, Washington DC 2002**
  - **The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:**
    - **- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or**
    - **- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.**
  - **All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.**

## 2. When are Placebos Ethical?-3

### ● AMERICAN ACADEMY OF PEDIATRICS

- No commonly accepted therapy.
- If the commonly accepted therapy is of questionable efficacy, carries a high frequency of undesirable side-effects, or generates greater risks than benefits.
- To determine incidence and severity of undesirable side-effects of add-on treatment to an established regimen.
- Disease process is characterized by frequent spontaneous exacerbations and remissions, and the efficacy of the therapy has not been established.

Committee on Drugs, American Academy of Pediatrics.  
“Guidelines for the Ethical Conduct of Studies to Evaluate  
Drugs in Pediatric Populations.” *Pediatrics* 1977; 60: 99.  
Reaffirmed and restated in *Pediatrics* 1995; 95: 294.

## 2. Asthma Research Involving Placebos: Which were Ethical?

- 50 studies used placebos
  - In 45 studies, an experimental drug was compared against placebo (Placebo-controlled Trial or PCT).
  - 5 studies used placebos as add-ons.
- PCT (n=45)
  - None ensured that all subjects who required AIM received them.
  - In 6 studies, subjects were taken off AIM for enrollment.
  - In 10 studies, subjects were not started on AIM unless they were randomized into an active study drug arm.
  - One could imagine studies that used an active control arm: comparing the experimental drug against an alternate ICS or cromolyn.
- Experimental drug versus placebo as add-on (n=5)
  - All were ethical.

### 3. When is a “Children-First” Policy Ethical?

- Trend of increasing participation of children in studies that previously enrolled only adults.
- Although these policies have succeeded in increasing the percentage of studies that enroll children, studies fail to show whether the therapies are safe and effective in children, the true goal of these initiatives.
  - Of the 52 studies enrolling children and adults, only one performed subset analyses.
  - Some studies enrolled a significant number of children, suggesting that subpopulation analysis might have been possible.
  - 44 (85%) studies that included both children and adults did not characterize subjects by age.

## 4. Does the Consent of the Participant Ensure that the Research was Ethical?

- No. Informed Consent of Subjects is necessary but NOT sufficient.
- Randomized clinical trials are an important research tool.
  - The need for placebo-controls needs to be carefully thought-out.
  - Ethical requirement to minimize risk.
  - Ethical requirement to have equipoise at the start of a trial.

**Case #4:**  
**Behavioral Research**  
**Serotonin, Fenfluramine,**  
**and Aggression**

# Serotonin and Aggression

- Animal studies consistently demonstrate that decreasing central serotonin levels result in increased aggressive behavior.
- Neurochemical studies to date in children have yielded inconsistent results.
  - Researchers use Fenfluramine which inhibits CNS neuronal uptake of serotonin.

# Serotonergic Response to Fenfluramine

- Hypothesis: Association between parent aggressive behavior and lower serotonergic function in aggressive boys with ADHD.
- Study design: 41 prepubertal boys with ADHD
  - Aggressive and nonaggressive subgroups based on parental histories and the presence or absence of a persistent pattern of physically aggressive behavior in the child.

JM Halperin et al. "Serotonin, Aggression, and Parental Psychopathology..." *Journal of the Amer Acad of Child and Adolescent Psychiatry* 1997; 36: 1391-8.

# Serotonergic Response to Fenfluramine

- Method: One month washout of any meds (12 children were being treated with medication for ADHD), 3 day low monoamine diet, and overnight fast. Children given one dose of fenfluramine and blood samples obtained.
- Results: Association between parental aggressive behavior and lower serotonergic function in aggressive boys with ADHD. Data cannot determine whether this is genetic or environmental.

# Serotonergic Response to Fenfluramine

- Similar study by Pine et al. involving 34 boys from ethnic minority, impoverished families. Study found that “...aggressive behavior and social circumstances conducive to the development of aggressive behavior are positively correlated with a marker of central serotonergic activity.”

DS Pine et al. “Neuroendocrine response to Fenfluramine Challenge in Boys:...” *Archives of General Psychiatry* 1997; 54: 839.

# What are the ethical issues?

1. Was the risk: benefit ratio appropriate?
2. Did the study minimize risk?
3. Was consent free of coercion?
4. Was subject selection fair?

# 1. Risk: Benefit Ratio

- Pediatric trials using a single-dose of Fenfluramine began in 1992 despite the fact that no data existed on short-term effects in children.
- Fenfluramine was later found to be associated with cardiac pathology in obese adults.
  - Pediatric studies continued.
  - FDA aware that study continued after drug pulled from the market.

## 2. Were the risks minimized?

- 12 children with ADHD were taken off their medication.
  - Was this during the school year?
  - Were the parents made aware that they were terminating effective medication for research that promised no benefit to their child?

### **3. Was Consent Voluntary; Free of Coercion?**

- New York City Department of Probation identified 6- to 10-year old boys whose brothers were incarcerated.
  - After one month, officials balked out of concern that families might find participation coercive.

## 4. Subject Selection

- Researchers given family court records which are supposed to be confidential.
- In Pine et al.'s study, 44% of the boys were African American and 56% were Latino reflecting potential racial bias.

# Denouement

American Civil Liberties Union (ACLU) became involved; case was settled in favor of child-subjects and their families.

# **Children in Research: Finding a Moral Equilibrium**

**Let us all remember that a slower progress in the conquest of disease would not threaten society, grievous as it is to those who deplore that particular disease be not yet conquered but that, society would indeed be threatened by the erosion of those moral values whose loss, possibly caused by too ruthless a pursuit of scientific progress, would make its most dazzling triumphs not worth having.**

Hans Jonas, "Philosophical Reflections on Experimenting with Human Subjects", 1970

# Conclusion

- Shift in federal policy from protecting subjects to ensuring access.
  - Shift has occurred for all populations.
  - In pediatrics, this means more children as research subjects, earlier in the process.
- Need to re-focus on our primary responsibility which is the protection of human subjects, particularly when the human subjects are children.