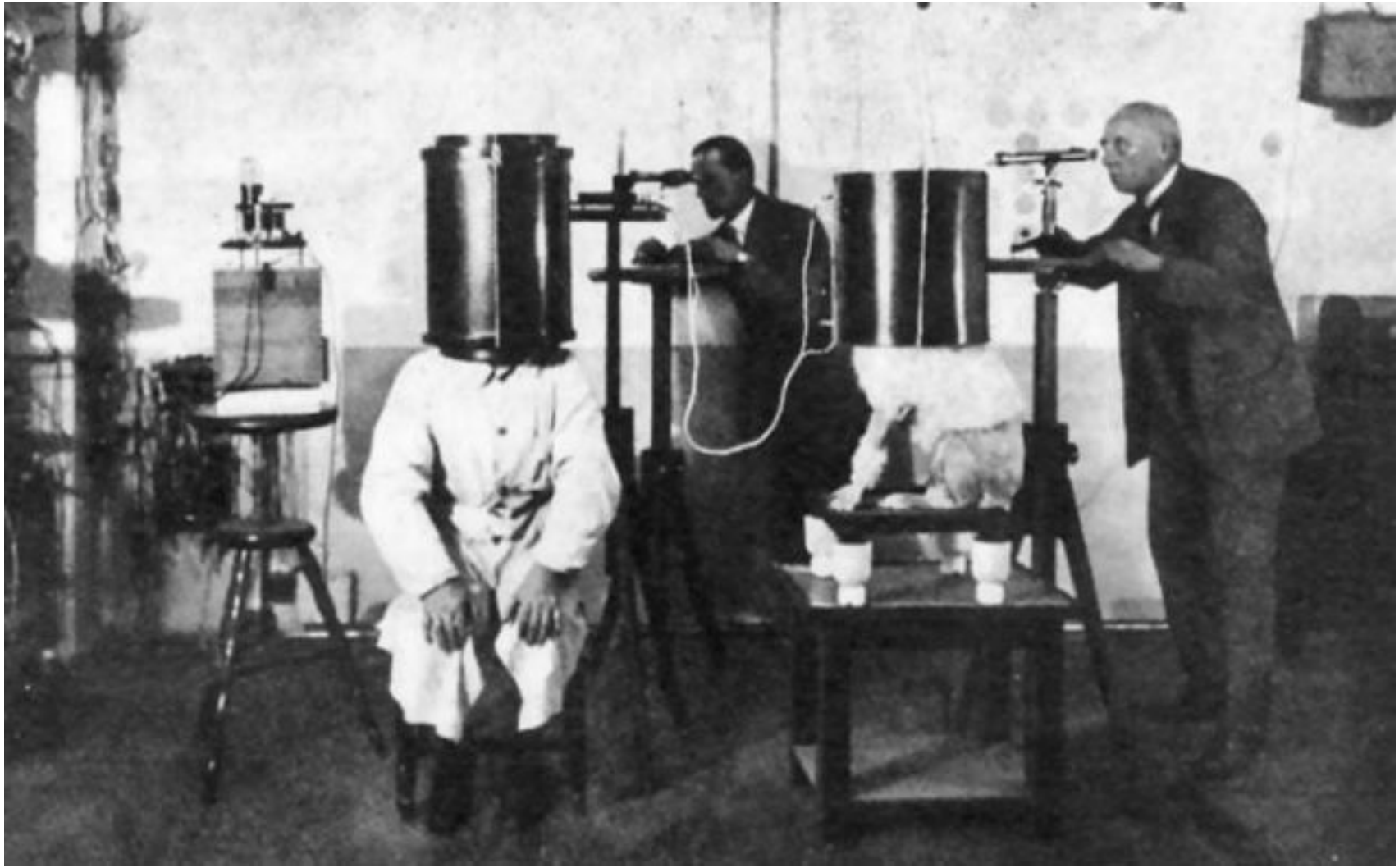
The Ethics Police?:
THE STRUGGLE TO MAKE HUMAN RESEARCH SAFE

Robert Klitzman, M.D.
Professor of Psychiatry
Director, Masters of Bioethics Program
Columbia University

COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK




RESEARCH ETHICS
Committee

Big Pharma *Bribery* Scandal

China investigates world's most powerful drug makers for rampant criminality

By Ronald L. Ray

The People's Republic of China is infamous for a variety of corrupt business practices, but recently the communist government has been cracking down, apparently intent on improving the nation's commercial sector and better protecting the Chinese consumer. The most prominent example is a massive scandal involving the British-based pharmaceutical giant, GlaxoSmithKline (GSK).

One of the world's largest drug producers, GSK is alleged to have spent $489 million bribing medical practitioners and government officials in order to

While the company conceded that some Chinese officials may have broken the law, CEO Andrew Witty claimed the "head office had no prior knowledge about the wrongdoing," said *International Business Times*.

The bribery and tax evasion could also subject GSK to criminal prosecution in London and New York under the UK Bribery Act and the U.S. Foreign Corrupt Practices Act. Seemingly for this reason, GSK refuses to take corporate responsibility for the alleged activities.

But GSK's concerned remarks ring like a hollow refrain. While the company moves to eliminate low-level employees caught by the law, a pattern of sys-

OBAMA IN POWER: A SECRET HISTORY BY JONATHAN ALTER

DOUBLE ISSUE: MAY 24 & 31, 2010

Newsweek

DESPERATELY SEEKING CURES

MEDICAL RESEARCH ISN'T MAKING PROGRESS RAPIDLY ENOUGH.

HERE'S WHY—AND HOW TO PUSH THINGS FORWARD.

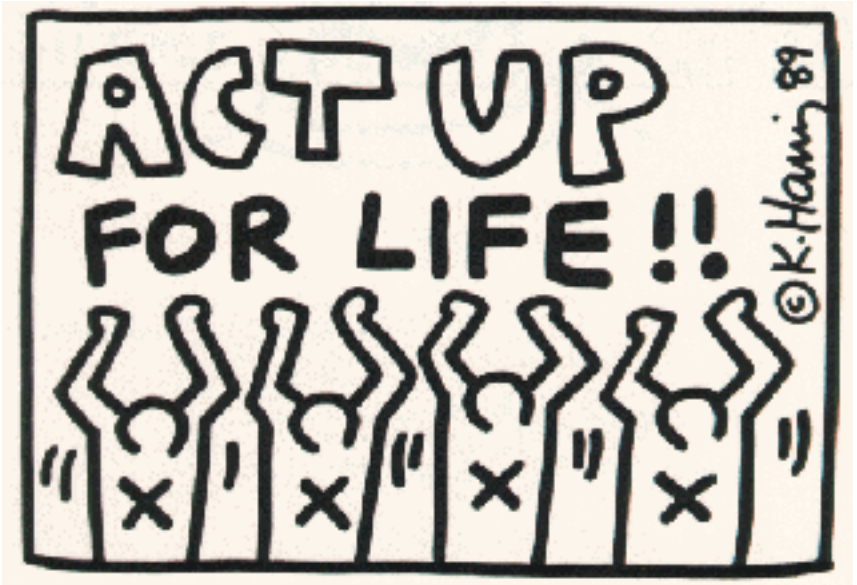
BY SHARON BEGLEY AND MARY CARMICHAEL

Newsweek
OCTOBER 18, 2013

THE DRUGS DON'T WORK

MORE AND MORE DEADLY PATHOGENS ARE BECOMING INCURABLE

by Kurt Eichenwald


ACT UP
FOR LIFE!!
©K.Haring 89

JANUARY 18, 2010

Joe Klein: The CIA's Afghan Disaster

Yemen: The New Center Of Terror

Why the Recession Hasn't Been Cool To Teens

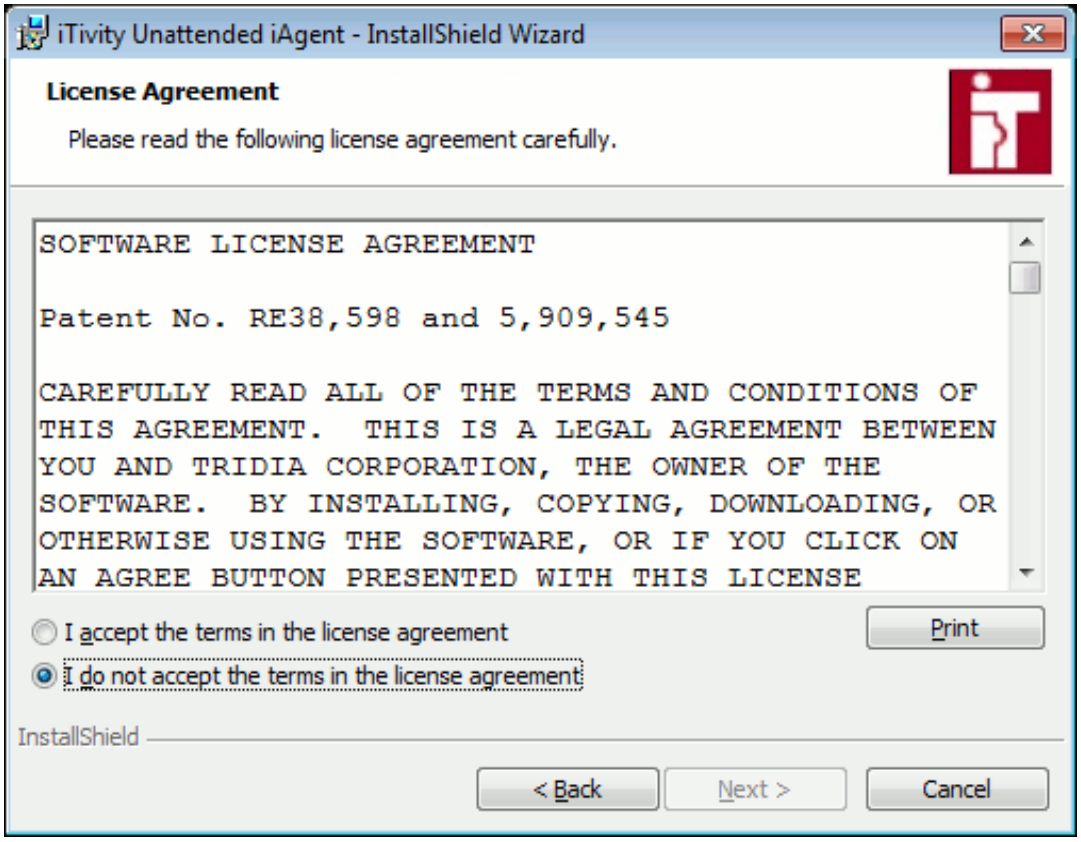
TIME

WHY YOUR DNA ISN'T YOUR DESTINY

The new science of epigenetics reveals how the choices you make can change your genes —and those of your kids

BY JOHN CLOUD

www.time.com


iTivity Unattended iAgent - InstallShield Wizard
License Agreement
Please read the following license agreement carefully.
SOFTWARE LICENSE AGREEMENT
Patent No. RE38,598 and 5,909,545
CAREFULLY READ ALL OF THE TERMS AND CONDITIONS OF THIS AGREEMENT. THIS IS A LEGAL AGREEMENT BETWEEN YOU AND TRIDIA CORPORATION, THE OWNER OF THE SOFTWARE. BY INSTALLING, COPYING, DOWNLOADING, OR OTHERWISE USING THE SOFTWARE, OR IF YOU CLICK ON AN AGREE BUTTON PRESENTED WITH THIS LICENSE
I accept the terms in the license agreement
I do not accept the terms in the license agreement
Print
InstallShield
< Back
Next >
Cancel

APRIL 22, 2002

Powell's Mission Impossible

TIME

HOW MEDICAL TESTING HAS TURNED MILLIONS OF US INTO ...

HUMAN GUINEA PIGS

www.time.com AOL Keyword: TIME

Background

- IRBs have been increasingly criticized
  - Discrepancies
    - Can impede research
  - Tensions with PIs

Recent Controversies

Since IRBs were created, research ethics "scandals" and controversies have occurred:

- Jesse Gelsinger
- Kennedy-Kreiger study, involving exposure of lead to children
- Hopkins "checklist" hand-washing study
  - Any need to inform IRBs or patients at 67 institutions?
- SUPPORT Study
  - Randomizing newborns to two levels of oxygen
  - OHRP: consent forms were insufficient
- Facebook experiment
  - Have users "signed away" all their rights to be involved in any research Facebook wants to do?
- Ebola
  - When is a new product proven enough to use instead of a placebo?

Policy debates

- Are IRBs broken?
- Unconstitutional?
- How much should they be centralized, and how might that work?
- Are other improvements needed, and if so, what?

Policy debates

- July 2011: ANPRM
  - Centralize IRBs more?
  - Exempt certain areas of minimal risk research
  - Let PIs self-determine minimal risk status
- December 2014: NIH
  - CIRBs for all multisite studies?

Policy debates

- September 8, 2015
  - Notice of Proposed Rule Making (NPRM)
  - CIRBs for multi-site studies
  - Post consent forms online
  - Questions about biobanks
    - Disclose whether biosamples may be used for profit, and if so, whether subjects will share it
  - 120-day comment period

Yet little empirical data exists

- Very few studies on views and experiences of IRBs
  - Several quantitative studies
  - But many questions remain:
    - How do IRBs make decisions?
    - What challenges do IRBs feel they face?
    - How do IRBs view these issues?

Larger questions

- How much should we trust researchers who experiment on human beings?
- Should government regulate or oversee these scientists in some way, and if so, how, and to what degree?
- How should we balance science vs. moral values?

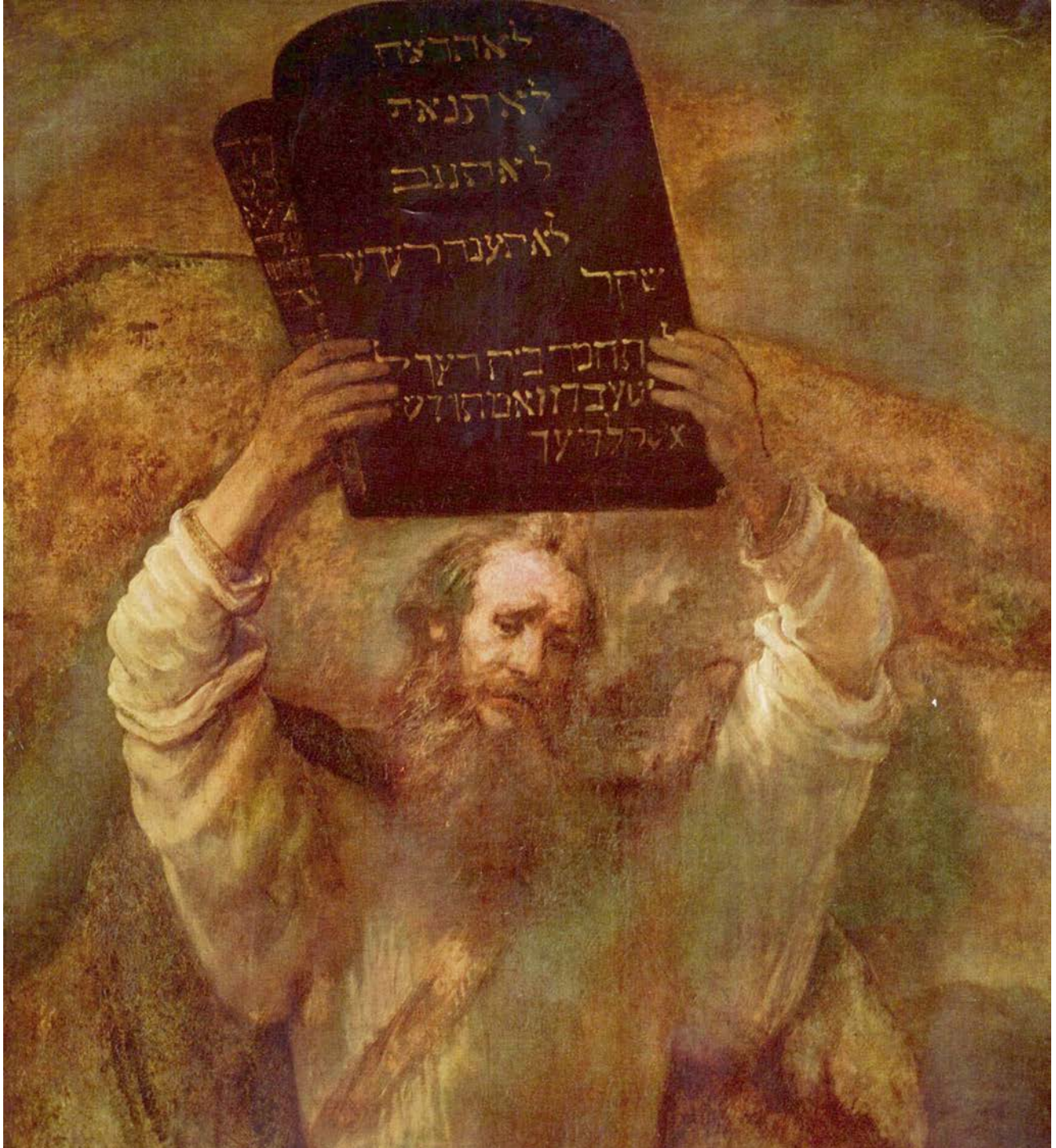
- Science has out-paced our understanding of its ethical and social implications.
- How should we understand this problem?
- What should we do about it?

ΙΠΠΟΚΡΑΤΟΥΣ ΟΡΚΟΣ.

HIPPOCRATIS IVSIVRANDVM.

Ο'ΜΝΥΜΙ 'Απόλλωνα ἰητρὸν καὶ Ἀσκληπιὸν καὶ Ὑγείαν καὶ Πανάκειαν, καὶ θεοὺς πάντας τε καὶ πάσας, ἵστορας ποιεύμενος, ἐπιτελέα ποιήσειν κατὰ δύναμιν καὶ κρίσιν ἐμὴν, ὅρκον τόνδε καὶ ξυγγραφὴν τήνδε. ἡγήσασθαι μὲν τὸν διδάξαντά με τὴν τέχνην ταύτην, ἴσα γενέτῃσιν ἐμοῖσι, καὶ βίου κοινώσασθαι, καὶ χρεῶν χρηίζοντι μετάδοσιν ποιήσασθαι, καὶ γένος τὸ ἐξ ωὐτέου, ἀδελφοῖς ἴσον ἐπικρινέειν ἄῤῥεσι. καὶ διδάξειν τὴν τέχνην ταύ-

PEr Apollinem Medicum, & Aesculapium, Hygiamque & Panaceam iureiurando affirmo, & Deos Deasque omnes testor, me quantum viribus & iudicio valuero, quod nunc iuro, & ex scripto spondeo planè obseruaturũ. Praeceptorem quidem qui me hanc artem edocuit, parentum loco habiturum, eique cum ad victum, tum etiam ad usum necessaria, grato animo communicaturum & suppeditaturum. Eius que posteros apud me eodem loco quo germanos fratres fore, eosque si hanc artem addiscere volent, absque mercede & syngrapha e-




We the People
Article. I

QUALITATIVE STUDY OF IRBS

Methods

- Contacted IRB leadership
- Every fourth institution of list of top 240 institutions by amount of NIH funding
- Response rate: 34/60 = 55%
- Asked 50% of these to distribute info to members and administrators
- Semi-structured, in-depth interviews

Characteristics of Qualitative Sample

	Total	**% (N=46)**
Type of IRB Staff		
Chairs/Co-Chairs	28	60.87%
Directors	1	2.17%
Administrators	10	21.74%
Members	7	15.22%
Gender		
Male	27	58.70%
Female	19	41.30%
Institution Rank		
1-50	13	28.26%
51-100	13	28.26%
101-150	7	15.22%
151-200	1	2.17%
201-250	12	26.09%
State vs. Private		
State	19	41.30%
Private	27	58.70%
Region		
Northeast	21	45.65%
Midwest	6	13.04%
West	13	28.26%
South	6	13.04%
Total # of Institutions Represented	**34**	

RESULTS

A wide range of issues concerning:

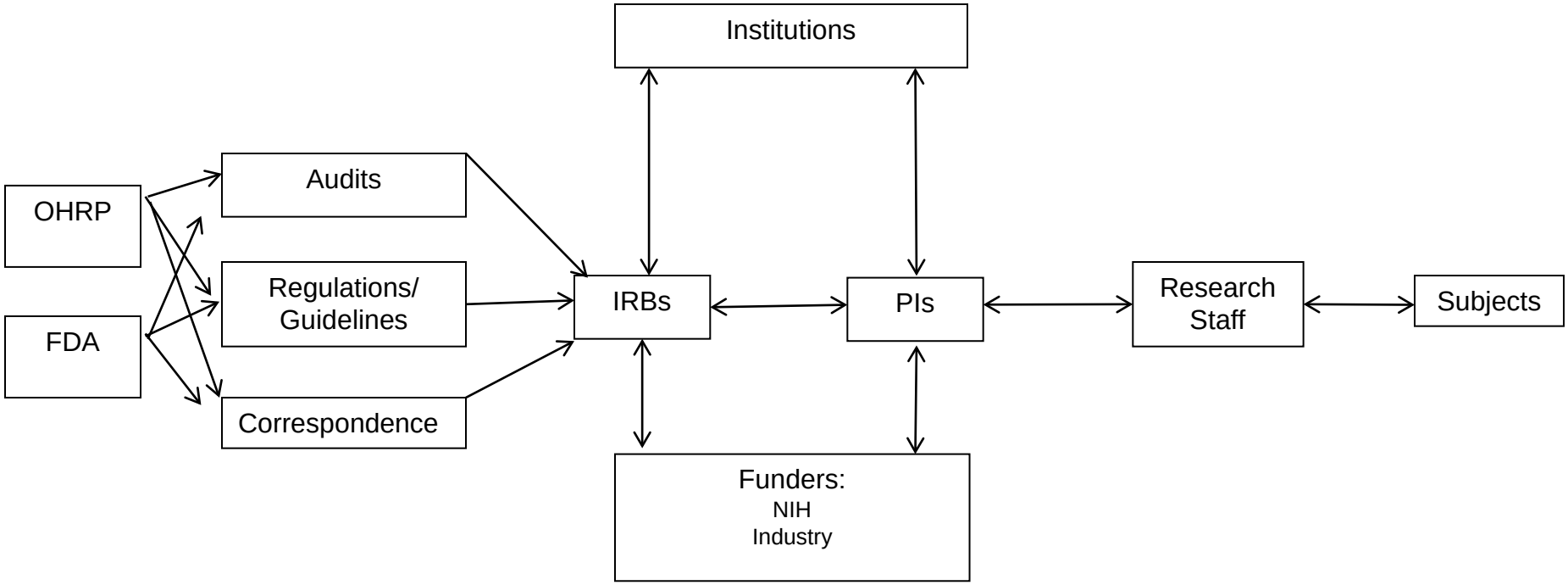
- Contexts of decisions
  - Who is on the IRB? How are they chosen?
    - Intra-IRB issues
  - Relationships with feds
  - Relationships with industry
  - Relationships with institutions

A wide range of issues concerning:

- Contents of decisions
  - Interpretations of principles and regulations
    - Assessing and weighing risks vs. benefits
    - Undue influence?
    - Is it research?
      - How good does the science need to be?
    - Informed consent
      - Is the form good enough?

A wide range of issues concerning:

- Relationships with researchers
    - Research integrity?
  - Additional issues in the developing world


Institutions
OHRP
Audits
FDA
Regulations/
Guidelines
Correspondence
IRBs
PIs
Research
Staff
Subjects
Funders:
NIH
Industry

Intra-IRB issues

- Very high degrees of commitment and dedication
- Some are “volunteered” for the IRB

Becoming members and chairs

Before appointment to IRB

Institutions vary

- Appointment may be due to variable reasons
- Individuals vary in prior education and experience:
  - In ethics
    - From some to none
  - In research
    - May have interest
  - May be chosen because of complex institutional factors:
    - Assignment “volunteered” by department as routine committee assignment
      - As remedial education/”punishment”
  - Turnover of chairs may occur because of:
    - Retirement
    - Scandal
    - Institutional wishes to change IRB
    - Roles may be fluid

THE CONTENTS OF DECISIONS:

Assessing and weighing potential risks and benefits of studies not yet conducted: Difficulties

Spectrums of Risk

- From major to minor
- "Significant" or not?
- From likely to unlikely
- From direct to indirect:
  - "Minimal risk"
  - "Minor increase over minimal risk"

Sources of Difficulties in Assessing Risks

- Because of inherent uncertainties of research (i.e., investigating "the unknown")
- Patients with ongoing, serious disease
- Therapeutic misconception
- Standards:
  - "Truly safe"?

Coercion and Undue Influence: Ambiguities and Dilemmas:

IRBs struggle with dilemmas concerning**:**

- o*Content*
  - ▪How much to give subjects
    - •Subjects get paid differently based on their income
    - •Will selection bias result?
    - •Provision of free care as coercive?
    - •What to give subjects (e.g., cash vs. vouchers)
    - •What types of studies
  - ▪Added challenges in several situations:
    - •Research on children
    - •Research on students
    - •Research in the developing world
  - ▪Whom to compensate
  - ▪When to compensate subjects
  - ▪Whether, when, and how to inform potential participants about compensation
  - ▪How to define undue influence:
    - •Based on “gut feelings” and “common sense”
    - •Can be subjective

Process of deciding about undue influence

- IRBs can take time to make these decisions
- Decisions often reflect compromises
- Underlying tensions arise:
  - "Undue inducement" is inherently subjective and difficult to assess in others
  - Questions arise of whether subjects should "volunteer" vs. do it for the money
  - Lack of a consistent standard:
    - Between IRBs
    - Even in one IRB over time

- Is the science good enough?
- Are consent forms legal documents?

COIs

- Standard:
  - Not having even the appearance of a COI?
  - Direct and indirect financial COIs
  - Rather than financial and non-financial COIs
  - Clearer or more rigorous standards for recusal?
    - Okay to stay in the room for this discussion, if not for the voting?

Variations between IRBs

- IRBs differ in their “colors” and “flavors”
- Vary from “nit-picky” to “user-friendly”

Locations of Variations

- Between IRBs
- Within a single institution
- Within a single IRB
- Within a single member

Causes of Variations

- Occasional perceived differences due to type of community (e.g., rural vs. urban)
  - Related to sexual issues ("other IRBs may be more prudish, and have trouble with HIV prevention studies among gay men, but we don't")
  - But very rare
- Differences that arise do not appear to reflect differences in values concerning research ethics
- Differences tend to concern procedural definitions, not community values

Causes of Variations

- Institutional differences
  - Types of studies the IRB has reviewed in the past
  - Past federal audits/“shut downs” of research
  - Differences in research intensiveness/size of institution/reliance on indirect costs
- Individual differences
  - Chairs and members make subjective interpretations
    - Rely on “gut feelings”, “intuition”, “sniff test”
    - Anxiety vs. psychological “comfort” (”peace of mind”)
    - Idiosyncrasies (“temperament”, “pet peeves”, “prudishness”)
    - “Nit-picky” vs. “user-friendly”/”pro-research”
    - “Good catches”: Effects of “many eyes seeing a protocol

Defending Variations

- Justifying differences
  - "Simply interpreting the regulations"
- A few acknowledge "minor differences"
  - As "fine-tuning"
  - But differences are often greater

Do IRBs Have Power?

- Power of chair and the IRB in the institution can vary
- Critical questions:
  - How much power do and should IRBs have?
    - What do these questions mean?
    - Who should decide?
    - Are IRBs the police, judge and jury?

IRB Perceptions of Their Power

- IRBs as having power
  - IRBs may acknowledge that PIs see them as having power
    - But may not acknowledge its full extent
  - IRBs may feel it is legitimate
    - It is based on overriding goals
    - They are trying to help PIs
  - IRBs may see problems but accept these as inevitable
  - IRBs may feel it is small because:
    - It's based on "the community's values"
    - But it may be based instead on institutional and/or personality factors.
- IRBs as not having power because:
  - They are "merely following the regulations"
  - They are themselves subject to higher administrative agencies
  - Their process is impersonal and not biased
  - Their process is "open"

IRBs' Perception of PIs' Views

- PIs may misperceive IRBs
- PIs may unfairly blame/inappropriately scapegoat IRBs
- IRBs cannot always publically respond to PI accusations
- PI claims that IRBs have power may not be fully valid

"Open Doors"?:
IRBs' Responses to Tensions with PIs

FORMS AND CONTENTS OF INTERACTIONS

- Protocol Reviews
  - IRBs vary in reviewer anonymity
  - Anonymity can reduce conflicts but make IRB seem a "faceless bureaucracy"

- IRB Meetings
  - Vary in whether PIs are invited and/or encouraged to attend
  - Presence of PIs can improve PI cooperation, but reduce candor in meetings

- Memos to PIs
  - Range in tone and content ("Using Southern Charm" vs. more bureaucratic).
  - More helpful memos can improve PI cooperation, but take more time

- PI Outreach Education
  - Varies in extent
  - Can improve PI cooperation, but take time and resources
- Toward best practices?
  - More “openness” and accessibility

Added challenges: Emerging economies:

Ethical Dilemmas for US IRBs

- How to interpret principles?
- How much to pay subjects?
- How much sustainability?
- Higher standards?

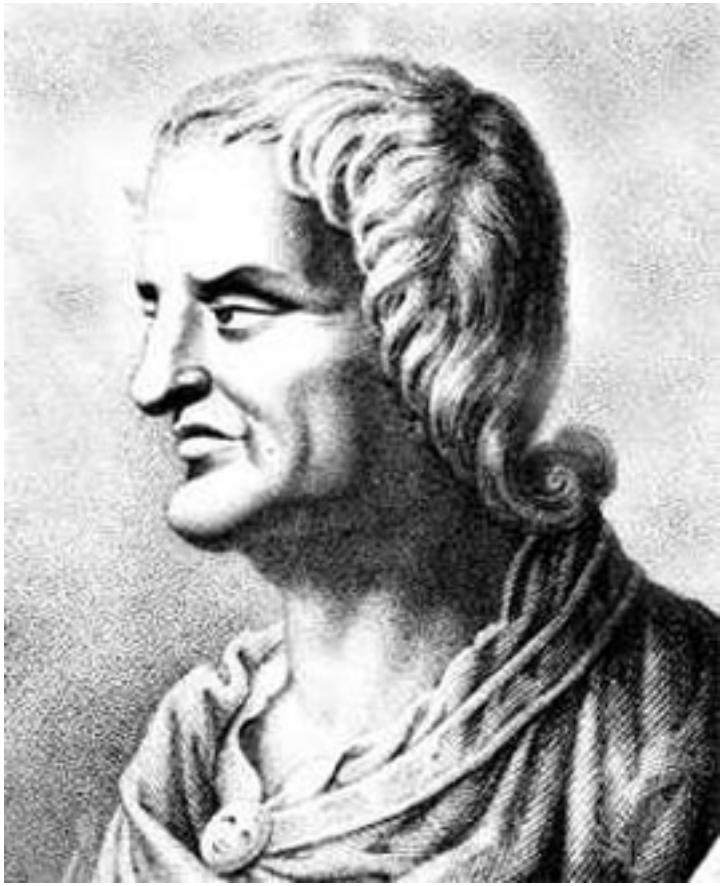
Added Challenges: Emerging economies:

Responses

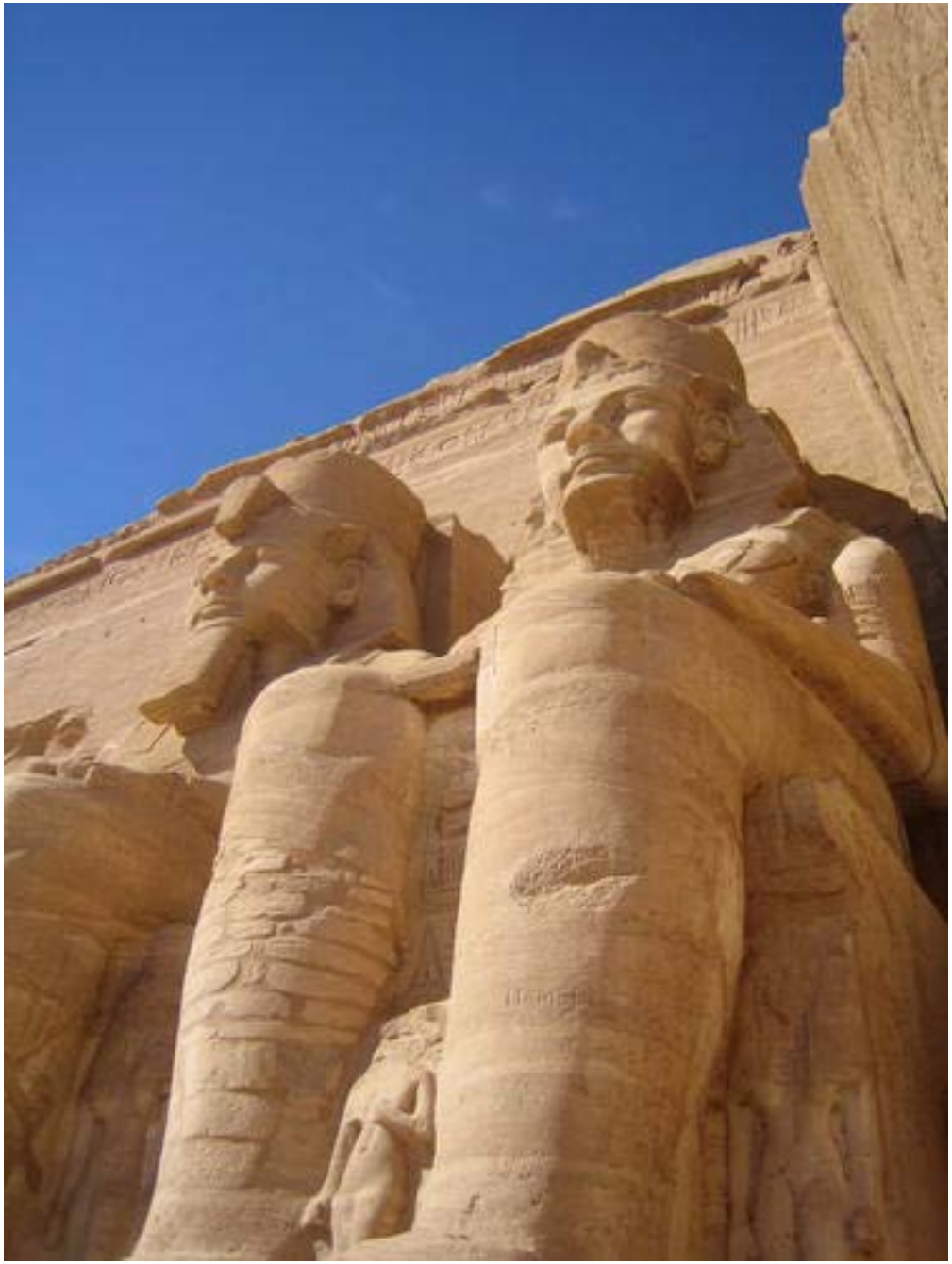
<u>Structural</u>

- Capacity building of overseas IRBs
- Monitoring IRBs
  - Not always welcome
- Infrastructure changes?
- Communicate more w/ local IRBs?
- Negotiating compromises
- Needs for more communication
  - IRBs communicate poorly in part because they do so via PIs

CONCLUSIONS




Two witnesses and a listener



Possible changes to improve subject protection:

Federal level:

- Centralization?
    - May offer several advantages and disadvantages
- Future of other proposals in the ANPRM?
    - Different rules for social science research?
    - Excuse certain minimal risk research?
        - But will PIs have COIs in making these determinations?

Other federal changes:

- More guidance and consensus
  - From OHRP, IOM, and/or others
- More case law/open, published precedents to establish consensus
  - Proprietary information can be redacted
- More consensus concerning areas where difficulties now arise
  - e.g., Is allergy skin testing minimal risk?
- Publishing decisions
  - Minutes or other summaries with proprietary information redacted
  - Similar to case law?
- External appeals process

- More regionalization
- More external (unaffiliated and non-scientific) members
- Improved informed consent
  - Shorter summary documents to accompany longer forms
    - Yet many details need to be addressed

- Training of IRB personnel, using protocols about which consensus has been reached
  - Is this informed consent “good enough”?
  - Is the quality of the science of this protocol “good enough”?
- More and different training
  - Reaching consensus and standardization on definitions, interpretations, and applications of key terms and principles
    - Testing to demonstrate adherence to these standards
- Will meet resistance
  - How then to proceed?

Institutional level:

- More resources
  - Compensating members
- Well-trained staff could make independent decisions about key issues
- Providing appropriate compensations to IRB members

Changes needed among BOTH IRBs and PIs

- IRBs and PIs would benefit from more fully understanding:
  - These tensions
  - The underlying causes

IRB Level: Needs for attitudinal changes

- Improving relationships with PIs
  - Needs to address current tensions
  - Better PR
    - Publicizing the benefits of IRBs
  - Some IRBs may misperceive PI complaints
  - Increased recognition of:
    - Ambiguous nature of regulations
  - Roles of interpretations
    - Acknowledgement of discretionary power?
  - Costs of variations

IRB Level:

- More transparency
  - Open doors
- Establishing institutional memory and a body of case law
  - Willingness to be studied
  - Sharing “best practices”
    - LISTSERVs
    - National or regional meetings
      - Not always attended

Researcher Level: Needs for change, too

- Changing attitudes
- May misperceive IRBs
- Enhancing understandings
  - Not “blaming the messenger”
- Avoiding inattentive and sloppy submissions to the IRBs

Public level

- Enhancing public education
- Enhancing media understandings
- Larger social/political questions:
  - How much should scientists be overseen?

Future research

- IRBs should be far more open enough to being studied
  - Many IRBs feel that they have nothing to gain
    - But that is incorrect
  - Some IRBs have required informed consent from all members

Broader implications

- How ethical principles get interpreted and applied differently in different settings
- How much of power is in the eyes of the beholder?
- Needs for more humanistic approaches

THE ETHICS POLICE?

The Struggle to Make Human Research Safe

ROBERT L. KLITZMAN

OXFORD

QUESTIONS?

Robert Klitzman, MD

Professor of Psychiatry
Director, Masters of Bioethics Program
Columbia University

Phone: (646) 774-6912
E-mail: rlk2@cumc.columbia.edu

COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK