Ethics in the Conduct of Research - How It Applies to You

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IPPCR – February 8, 2016

Scientific Integrity

- All scientists should be committed to the responsible use of the process known as the scientific method to seek new knowledge.
- All research staff in the Intramural Research Program should maintain exemplary standards of intellectual honesty in formulating, conducting and presenting research as befits the leadership role of the NIH.

Why is Scientific Integrity So Important?

The scientific community and the general public rightly expect adherence to exemplary standards of intellectual honesty in the formulation, conduct, and reporting of scientific research.

Without a high standard of *Scientific Integrity*, the scientific community and general public may become victims of *Research Misconduct*.

What is Research Misconduct?

- **Fabrication** – making up data or results and recording or reporting them
- **Falsification** – manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record
- **Plagiarism** – the appropriation of another person's ideas, processes, results, or words, without giving appropriate credit

Research Misconduct

- Research misconduct does not include honest error or difference of opinion
- Scientific collaborators cannot plagiarize from each other

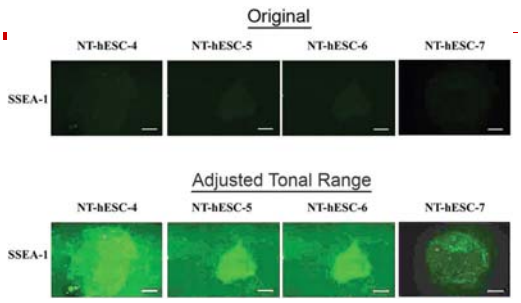
Real-life Examples of Research Misconduct

An infamous case, in 2006, involved the Korean investigator Woo Suk Hwang who claimed to have created the first-ever human embryonic stem cell lines whose DNA matched that of patients, promising great breakthroughs for diseases.

Real-life Examples of Research Misconduct

- This case involved questionable data management: 9 of 11 cell lines fabricated, images of cells were manipulated.
- One result is that major journals are changing their review processes to incorporate analyses of images that are submitted for publication.

Detecting image manipulation in the Hwang et al. Science 2009



Rossner M J Cell Biol 2007;176:131-132

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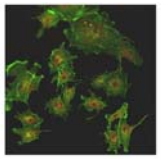
JCB

Inserting Additional Data



Rossner M, Yamada KM. "What's in a picture? The temptation of image manipulation" J Cell Biol. 2004 July 5; 166(1): 11–15.


Stem cells

What pushes scientists to lie? The disturbing but familiar story of Haruko Obokata

The spectacular fall of the Japanese scientist who claimed to have triggered stem cell abilities in regular body cells is not uncommon in the scientific community. The culprit: carelessness and hubris in the drive to make a historic discovery

The Guardian
18 Feb 2015

Real-life Examples of Research Misconduct

Breast Cancer Prevention Trial
A data coordinator falsified and fabricated the dates of tests and exams

Nat. Surgical Adjuvant Breast & Bowel Project
A data coordinator falsified and fabricated follow-up data

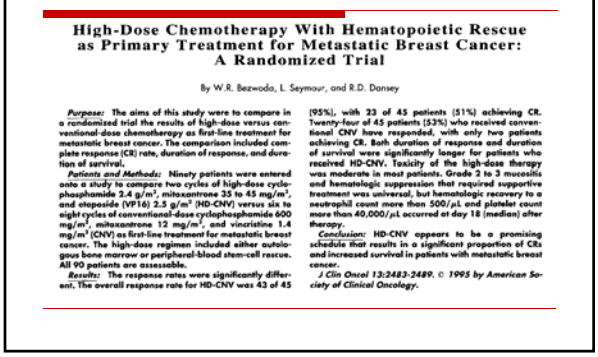
Why Does This Matter?

Inaccurate information regarding patient status and date of death could result in an over- or under-estimate of treatment benefits, especially when length of survival and length of disease-free survival are end-points

Real-life Examples of Research Misconduct

High Dose Chemotherapy for Breast Cancer

- HSCT for metastatic breast cancer widely performed by mid 1990's.
- 5 randomized studies completed
  - 4 negative
  - 1 strikingly positive (CR 51% vs. 4%)
    - Bezwoda JCO 1995



High-Dose Chemotherapy With Hematopoietic Rescue as Primary Treatment for Metastatic Breast Cancer: A Randomized Trial

By W.R. Bezwoda, L. Seymour, and R.D. Dansey

Purpose: **The aims of this study were to compare in a randomized trial the results of high-dose versus conventional-dose chemotherapy as first-line treatment for metastatic breast cancer. The comparison included complete response (CR) rate, duration of response, and duration of survival.**

Patients and Methods: **Ninety patients were entered onto a study to compare two cycles of high-dose cyclophosphamide 2.4 g/m², mitoxantrone 35 to 45 mg/m², and etoposide (VP16) 2.5 g/m² (HD-CNV) versus six to eight cycles of conventional-dose cyclophosphamide 600 mg/m², mitoxantrone 12 mg/m², and vincristine 1.4 mg/m² (CNV) as first-line treatment for metastatic breast cancer. The high-dose regimen included either autologous bone marrow or peripheral-blood stem-cell rescue. All 90 patients are assessable.**

Results: **The response rates were significantly different. The overall response rate for HD-CNV was 43 of 45 (95%), with 23 of 45 patients (51%) achieving CR. Twenty-four of 45 patients (53%) who received conventional CNV have responded, with only two patients achieving CR. Both duration of response and duration of survival were significantly longer for patients who received HD-CNV. Toxicity of the high-dose therapy was moderate in most patients. Grade 2 to 3 mucositis and hematologic suppression that required supportive treatment was universal, but hematologic recovery to a neutrophil count more than 500/μL and platelet count more than 40,000/μL occurred at day 18 (median) after therapy.**

Conclusion: **HD-CNV appears to be a promising schedule that results in a significant proportion of CRs and increased survival in patients with metastatic breast cancer.**

J Clin Oncol 13:2483-2489. © 1995 by American Society of Clinical Oncology.

PUBLIC HEALTH

Public health

High-dose chemotherapy for high-risk primary breast cancer: an on-site review of the Bezwoda study

Raymond B Weiss, Robert M Rifkin, F Marc Stewart, Richard L Theriault, Lori A Williams, Allen A Herman, Roy A Beveridge

Summary

Background The efficacy of high-dose chemotherapy with progenitor-cell rescue for women with breast cancer is a controversial issue. Although historically controlled trials have suggested a survival advantage for high-dose chemotherapy, several randomised studies have yet to confirm this advantage. Two studies, however, by Bezwoda, of patients with high-risk and metastatic disease, seemed to show a significant survival advantage for high-dose compared with conventional-dose chemotherapy for metastatic and high-risk primary breast cancer.

Methods To corroborate the study results before starting a large international confirmatory study, a US team did an on-site review of records for patients in the high-risk study. Limited numbers of records were made available for review, all of which were for patients who received the high-dose chemotherapy regimen.

Findings There was much disparity between the reviewed records and the data presented at two international meetings. In addition, the reviewers saw no signed informed consent, and the institutional review committee had no record of approval for the investigational therapy. After the site visit, Bezwoda admitted scientific misconduct by using a different control chemotherapy regimen from that described in presented data.

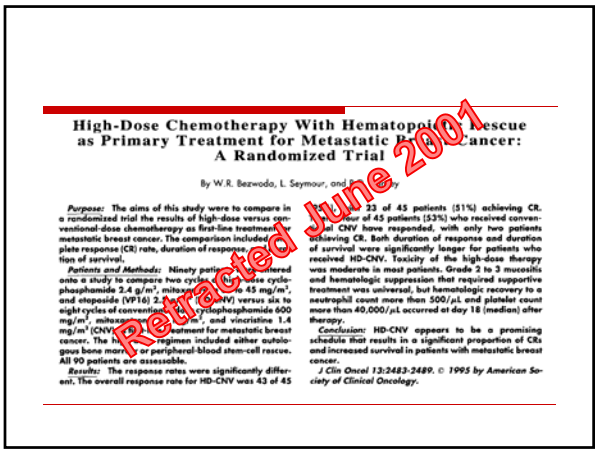
Interpretation The Bezwoda study should not be used as the basis for further trials to test the efficacy of the cyclophosphamide, mitoxantrone, etoposide regimen for high-dose chemotherapy in women with high-risk primary breast cancer. This review validates the essential nature of on-site audits, especially in single-institution studies.

Lancet 2000; **355**: 999–1003

Introduction

One of the most controversial issues in medical oncology has been the use of high-dose chemotherapy and autologous progenitor-cell transplantation for the treatment of breast cancer. Phase II trials in patients with metastatic disease[1] or high-risk primary disease[2,3] have suggested significant disease-free and overall survival benefits from this therapeutic approach. As a result of such studies, breast cancer became the most common disease for which transplant therapy was given in the 1990s.[4] Thousands of women worldwide underwent transplant therapy, frequently as routine medical care. In December, 1990, randomised trials assessing the efficacy of high-dose chemotherapy in metastatic and high-risk primary breast cancer were begun at the University of Witwatersrand, Johannesburg, South Africa, by Werner Bezwoda. The protocols involved two cycles of high-dose chemotherapy (tandem transplants) with progenitor-cell support and no intervening standard-dose chemotherapy.[5,6] The high-dose chemotherapy regimen consisted of a combination of cyclophosphamide, mitoxantrone, and etoposide given in doses requiring progenitor-cell support. This upfront tandem-transplant programme was unique because other randomised trials involved induction chemotherapy followed by high-dose chemotherapy.[10–13] Patients with metastatic and high-risk, primary breast cancer were reported to have survival in the high-dose-chemotherapy groups superior to that in the standard-dose groups.[5,6]

The results of the trial in women with high-risk, primary breast cancer were presented at the plenary session of the 1999 meeting of the American Society of Clinical Oncology (ASCO) and at the 1999 European Cancer Conference ECCO-10[14] (slides available at www.conference-cast.com/ascolecture_frame.htm at time of publication, until April 5, 2000). This trial was the only randomised study at the ASCO meeting that showed an



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Results: The response rates were significantly different. The overall response rate for HD-CNV was 43 of 45 ... 23 of 45 patients (51%) achieving CR. ... of 45 patients (53%) who received conventional CNV have responded, with only two patients achieving CR. Both duration of response and duration of survival were significantly longer for patients who received HD-CNV. Toxicity of the high-dose therapy was moderate in most patients. Grade 2 to 3 mucositis and hematologic suppression that required supportive treatment was universal, but hematologic recovery to a neutrophil count more than 500/μL and platelet count more than 40,000/μL occurred at day 18 (median) after therapy.

Conclusion: HD-CNV appears to be a promising schedule that results in a significant proportion of CRs and increased survival in patients with metastatic breast cancer.

J Clin Oncol 13:2483-2489. © 1995 by American Society of Clinical Oncology.

Retracted June 2001

Why Does This Matter?

- HSCT is very costly both in terms of monetary amounts and side effects.
- Treatment related mortality is significant
  - (10-20%)

HOW THE CASE AGAINST THE MMR VACCINE WAS FIXED

In the first part of a special *BMJ* series, **Brian Deer** exposes the bogus data behind claims that launched a worldwide scare over the measles, mumps, and rubella vaccine, and reveals how the appearance of a link with autism was manufactured at a London medical school

- 1998 Lancet paper by **Wakefield** links MMR to autism / diarrhea syndrome (n=12)
- Multiple groups can not replicate findings
- Reporter (Deer) uncovers multiple inconstancies

BMJ 2011; 342:c5347

HOW THE CASE AGAINST THE MMR VACCINE WAS FIXED

Comparison of three features of the 12 children in the *Lancet* paper with features apparent in the NHS records, including those from the Royal Free hospital

	Regressive autism		Non-specific colitis		First symptoms days after MMR		All three features	
Child No	Lancet	Records*	Lancet	Records†	Lancet	Records‡	Lancet	Records
1	Yes	?	Yes	Yes	Yes	No	Yes	No
2	Yes	Yes	Yes	Yes	Yes	No	Yes	No
3	Yes	?	Yes	No	Yes	?	Yes	No
4	Yes	?	Yes	No	Yes	No	Yes	No
5	Yes	?	Yes	No	No	No	No	No
6	Yes	No	Yes	Yes	Yes	?	Yes	No
7	Yes	No	No	No	Yes	No	No	No
8	No	No	Yes	No	Yes	No	No	No
9	No	No	Yes	No	No	No	No	No
10	No	No	Yes	No	No	No	No	No
11	Yes	?	Yes	No	Yes	No	Yes	No
12	Yes	No	Yes	No	No	No	No	No
Total	9/12	1a/12	11/12	1/12	8/12	12/12	6/12	0/12

See supplementary data on bmj.com for a version of this table with detailed footnotes.
*Regressive developmental disorder—autism.
†Royal Free hospital pathology service.
‡First behavioural symptoms ≤ 14 days after MMR.

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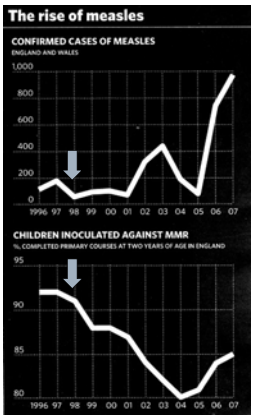
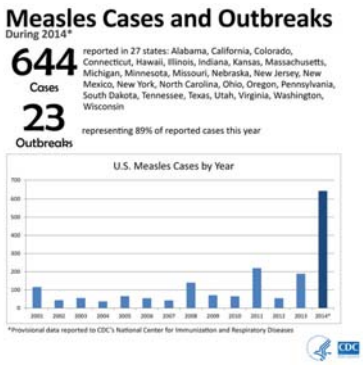
- Wakefield failed to disclose that he was working on a lawsuit of the manufacturer of MMR and was paid over £435,000.00
- Wakefield is stripped of license and Lancet paper is retracted 2010

BMJ 2011; 342:c5347





In 2015 by Feb 20 154 cases reported

Real-life Examples of Research Misconduct

A clinician, Eric Poehlman, who was involved in several different clinical protocols, admitted to falsifications and fabrications of clinical results.

One of his staff detected inappropriate data management and reported it

Real-life Examples of Research Misconduct

- Longitudinal Menopause Study
  - Reportedly studied 35 women at baseline and 3 years later.
  - All but 3 patients had fabricated and falsified data
  - Published in Annals of Med (and 6 other academic journals) and used in 9 NIH and 2 USDA grant applications

Real-life Examples of Research Misconduct

- Longitudinal Study of Aging
  - Exaggerated number of patients tested
  - Changed values to create a trend in the aging process
  - Presented in 3 grant applications
- Prospective Hormone Replacement Study
  - Double blinded study
  - Presented preliminary data in 2 grant applications when he did not have access to unblinding

Real-life Examples of Research Misconduct

- He had applied for about $11.6 million in funding (and was awarded $2.9 million)
- From 2000-2004 U Vermont and NIH investigated Dr. Poehlman
- They found that he presented false testimony and documents and influenced other witnesses to provide false documents.
- He eventually admitted to destruction of electronic evidence of his falsifications and fabrications

Real-life Examples of Research Misconduct

The finding of misconduct resulted in a 366-day Federal prison term for Dr. Poehlman because his actions led to loss of government funds, obstruction of justice, and abuse of a position of trust.

He was also *barred for life* from receiving any funding from any Federal agency and was *permanently* excluded from any Federal health care program

Real-life Examples of Research Misconduct

Dr. Poehlman justified his actions as follows:

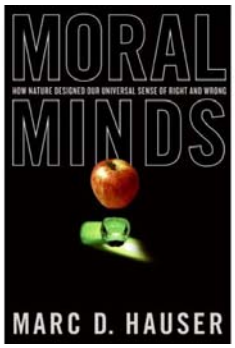
- Minor points were misrepresented to ensure the grant was re-funded
- His lab staff were dependent on the grant for their salaries
- He wanted to be recognized as an important contributor to his field

Marc Hauser, Harvard professor of Psychology and Director of Harvard's Cognitive Evolution Laboratory.

Questions arose when a lab assistant was asked to analyze the results of an experiment.

August 20, 2010 Harvard investigated and found Hauser guilty of misconduct. Case turned over to Fed Authorities (ORI)

Ironically, Dr. Hauser was at the time working on another book entitled *Evilicious: Why We Evolved a Taste for Being Bad*



Harvard University

MARC D. HAUSER
PROFESSOR OF PSYCHOLOGY
DIRECTOR, COGNITIVE EVOLUTION LAB

33 KIRKLAND STREET, WILLIAM JAMES HALL
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DEAN MICHAEL SMITH
HARVARD UNIVERSITY
UNIVERSITY HALL
CAMBRIDGE, MA, 02138

7 JULY 2011

Dear Dean Smith,

I am writing to let you know that I have decided to resign my position as a faculty member at Harvard effective August 1, 2011. While on leave over the past year, I have begun doing some extremely interesting and rewarding work focusing on the educational needs of at-risk teenagers. I have also been offered some exciting opportunities in the private sector. While I may return to teaching and research in the years to come, I look forward to focusing my energies in the coming year on these new and interesting challenges.

During my eighteen years at Harvard, it has been a great pleasure to teach so many bright and talented students and to work with so many dedicated colleagues. I will greatly miss them.

Sincerely,

Marc Hauser

What is the fall-out from these acts of research misconduct?

- Other scientists are angry because they have spent time and resources trying to replicate manipulated data
- Institutional reputations are also damaged
- Entire disciplines may be tarnished (e.g., hematopoetic stem cell transplant for solid tumors)

What is the fall-out from these acts of research misconduct?

- Patients and their families cannot understand why promising results they had heard about are no longer valid and lose their trust in researchers
- The Public relies on our truthfulness as investigators, so misconduct can undermine science in general

How is Research Misconduct Handled at the NIH?

- Allegations are reported to the AIRIO (NIH Agency Intramural Research Integrity Officer)
- An assessment is carried out to determine if the allegation meets the definition of misconduct
- An Inquiry Committee examines the evidence to determine if an Investigation is needed
- An Investigation Committee determines if research misconduct occurred
- The ARILO (NIH Agency Research Integrity Liaison Officer) concurs and imposes sanctions

http://sourcebook.od.nih.gov/ResEthicsCases/NIH%20Misconduct2.pdf

Data Management
Why would someone manipulate data?

1. **They want to make their data appear more convincing**
   Yes, improving the quality of the data is a common reason for data manipulation.

2. **They need a specific result to support their hypothesis**
   It is not uncommon for scientists to be so convinced of their hypothesis that they manipulate data to make it fit their model.

Data Management, continued

3. **They need the experiment to finish a manuscript**
   The pressure to finish a manuscript and submit for publication, especially if a lab is in stiff competition with another lab, may result in data manipulation since that is easier and faster than doing the actual experiments.

4. **They had to give a talk the next day and did not have all the data**
   This could happen as an individual might want impressive data to convince an audience of the novelty of their results.

Research Misconduct Penalties

Remember:

If you are caught manipulating data, you could be barred for life from ever receiving government financial support for your research, or even be sentenced to jail.


THE CANCER LETTER

Jan. 9, 2015 • www.cancerletter.com • Vol. 41 No. 1

"In raising these concerns, I have nothing to gain and much to lose." — Bradford Perez

Internal Emails Raise New Questions

Duke Officials Silenced Med Student Who Reported Trouble in Anil Potti's Lab

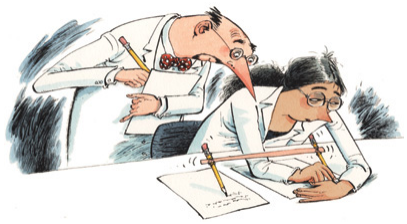
"Brad Perez is a Hero" . . . Page 5

A New Perspective on Nevins and Potti . . . Page 9

Research Concerns Nevins and Potti Respond to Perez's Questions and Worries . . . Page 14

A Timeline How the Perez Case Fits Into the Duke Scandal

Plagiarism



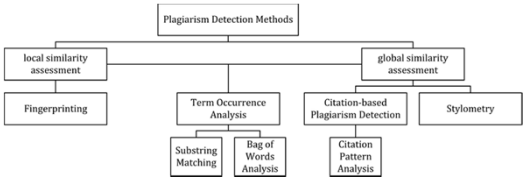
Plagiarism: the appropriation of another person's ideas, processes, results, or words, without giving appropriate credit

duplication, co-submission and plagiarism

Duplication

- Legitimate
  - Clinical Trial Updates
  - Meeting Proceedings
  - Errata
- Illegitimate
  - Plagiarism
  - Co-submission

Plagiarism Detection

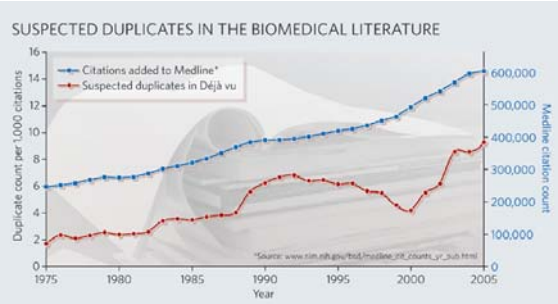


Wikipedia

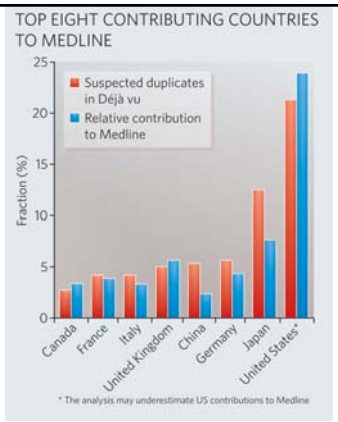
NIH Supported Database

http://dejavu.vbi.vt.edu/dejavu/

Duplication



Errami and Garner, *Nature* 2008



Errami and Garner, *Nature* 2008

Authorship Questions

Is authorship appropriate if?

1. **You wrote the paper**

   Yes, if you wrote the paper, you should be an author.

2. **You grew the cells used in the study**

   No, if you merely provided cells used in the paper, this would not warrant authorship.

http://sourcebook.od.nih.gov/ethic-conduct/Conduct%20Research%206-11-07.pdf

Answers: Authorship

3. **You performed 1/2 of the experiments**

   Yes, if you performed half of the experiments, authorship would be warranted.

4. **You identified and ordered the commercial supplies used in the project**

   No, if you merely helped find the reagents used, this would not warrant authorship.

5. **Your girlfriend worked on the project**

   No, personal relationships do not warrant authorship.

http://sourcebook.od.nih.gov/ethic-conduct/Conduct%20Research%206-11-07.pdf

Answers: Authorship, continued

6. **You thought up the idea for the project**

   This is the most difficult question. If you conceived the basic hypothesis, authorship might be warranted. If you casually mentioned an idea in a hallway conversation, authorship might not be appropriate.

Remember: Authorship is a privilege, not a right, and you must have made a meaningful contribution to the manuscript to earn it.

http://sourcebook.od.nih.gov/ethic-conduct/Conduct%20Research%206-11-07.pdf

Annals of Internal Medicine Authorship Criteria

The following, by themselves, are not criteria for authorship:

- holding position of administrative leadership
- contributing patients or reagents
- collecting and assembling data

Processes for Authorship Dispute Resolution

- **Direct Dialogue**
- **Mediation**
  - Office of the Ombudsman
- **Peer Panel**
  - Voluntary, 3+ member panel of experts
  - Binding decision
- **Binding SD/DDIR Decision**

http://sourcebook.od.nih.gov/ethic-conduct/Authorship%20Dispute%20Resolution%20Panel.pdf

Summary

Investigator	Description	Fabrication	Falsification
Hwang	Cloning	✓ 9 of 11 cell lines	✓ Image manipulation
Bezwoda	Transplant	✓ Made up patients	✓ Stated he had consent
Wakefield	Measles Vaccine	✓ Colitis	✓ Date of reaction
Poelman	Longitudinal Studies	✓ Patients	✓ Destroyed data
Hauser	Monkey Studies	✓ Sounds for Monkeys	✓ Monkey response

Fabrication – making up data or results and recording or reporting them
Falsification – manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record

Summary

The ethical conduct of science is your personal responsibility

You must not commit falsification or fabrication of data or plagiarize the work of others

Performing scientific research as a career is a privilege. By performing it in an ethical manner, you will maintain the highest standards of scientific integrity.

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http://portfolios.aiga.org/gallery/Science-is-Truth/176891