Collaborating with a Statistician Series

SESSION 2:

Research Integrity & Preventing Research Misconduct

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Objectives

- Describe research misconduct federal regulations
- Provide examples of research misconduct
- Overview how to prevent research misconduct
- Outline resources available to UTHSC investigators for maintaining research integrity and preventing research misconduct

What Is Scientific Integrity?

Scientific integrity refers to maintaining the quality and objectivity of the research activities, such that they are sound and worthy of the public's confidence.

In fostering scientific integrity, one must assure:

- scientific findings are objective, accurate, honest and readily available to the public
- the development of policies based on science is conducted with appropriate transparency.

42 CFR 50 Subpart F and 42 CFR 93 – governs institution that receive PHS support

- 42 CFR 50 Subpart F – Conflict of interest
  - Institutional responsibilities regarding management and reporting investigator of conflicts of interest
- 42 CFR 93 Research Misconduct
  - Defines the responsibilities for compliance for institutions receiving PHS support
  - Establishes the Office of Research Integrity

Research Misconduct 42 CFR 93.103

- Fabrication – make up data or results and 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
  - Selective excluding data from analysis
  - Misinterpreting data to obtain desired results, (i.e., inappropriate use of statistical methods)
  - Doctoring images in publications
- Plagiarism – use ideas, information, process or results by others without giving appropriate credit
- Does not include honest error or differences of opinion or in interpretations of data, act must be committed intentionally
- From 1992 – 2018, 284 people have been sanction by the US Office of Research Integrity (ORI), 90% for falsification/fabrication, 10% for plagiarism

Key elements of Research Misconduct

- Intentional
- Knowing
- Reckless
- Significant departure from accepted research practice
- Proven by a preponderance of the evidence

42 CFR 93.104

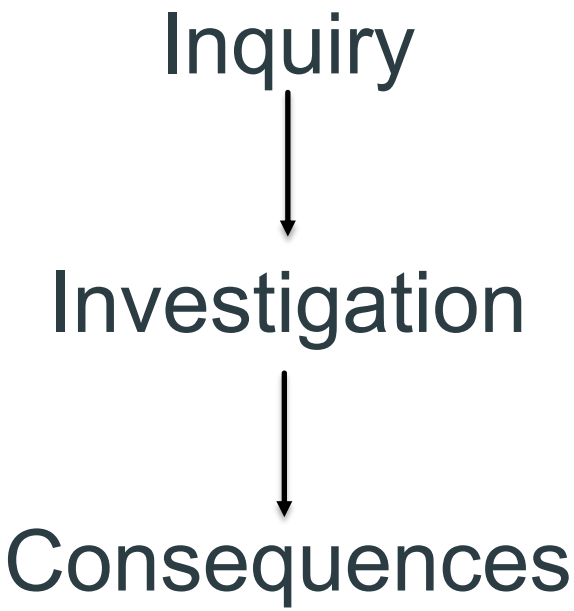
Research Misconduct

- Using inappropriate, harmful, dangerous research methods
- Poor research design
- Violation of human subject protocols
- Abuse of laboratory animals
- Not preserving data, bad data management, withholding data
- Claiming undeserved authorship, denying authorship to contributors
- Failure to correct the publication record
- Personal misconduct and financial misconduct

Motives for Misconduct

- Academic pressure to publish
- Low funding levels
- Financial gain
- Pressure on trainees to produce favorable research results
- Professional vanity
- Lack of understanding of the research process
- Psychiatric illness
- Pressure to accrue participants
- Low funding level puts pressure on researchers
- Pressure on mentees to produce research results

Research Misconduct Process



Research Misconduct Process

Inquiry: determines whether sufficient evidence exists to warrant an investigation

- Confidential
- Within the university
- Determines merit
- If no merit found no notification required

Research Misconduct Process

Investigation:

- Determines whether or not misconduct was committed and its scope
- Assesses the integrity of the scientific record and recommends remediation
- Recommends sanctions
- Institution must notify the sponsor
- Can be conducted by university or ORI

Research Misconduct Process

Consequences:

- sanctions, including termination of employment and debarment from federal research participation
- remediation of scientific record
- public notification
- imprisonment

Benefits of Whistleblowing

- To ensure that the scientific record is correct
- To comply with regulations
- To prevent future misconduct
- To protect one's own reputation or the reputation of another
- To punish wrongdoer

Risks of Whistleblowing

- Allegations are not borne out
- Time, effort and emotionally intensive
- Retaliation by respondent or respondent's institution
- Gain reputation as a trouble-maker

Whistleblower Protection

- Institutions are required to protect the whistleblower to the maximum extent possible, the privacy of those in good faith report apparent misconduct and to undertake diligent efforts to protect the positions and reputations of those persons, who in good faith report apparent misconduct

- Federal Whistleblower Protection Act of 1989

Office of Research Integrity (ORI)

- Formed in 1993
- Responsible for PHS grants (NIH, CDC, ect)
- Responds to reports of misconduct
- Responsible for promoting Integrity
- Reports to the Secretary of the US DHHS

ORI has statutory authority to respond to allegations of research misconduct when supported by *Public Health Service funds,* 42 USC 289b

https://ori.hhs.gov/

ORI Functions and Activities

- Receive and assess allegations of research misconduct
- Determine ORI jurisdiction
- Oversee institutional inquiry and investigation reports and procedures
- Make determinations of misconduct or recommendations for settlement
- Participate in civil or criminal cases of alleged research misconduct directly or through other offices, including HHS OIG, US Attorney's Office or in collaboration with other federal agencies

ORI Functions and Activities

- Protect the confidentiality of respondents, complainants, and witnesses
- Protect the complainant from retaliation through regulatory obligations imposed on the research institutions
- Provide education in the responsible conduct of research
- Collaborate with the research community to improve biomedical research
- Exclude dishonest investigators from PHS and Federal agency funded research
- Make public findings of misconduct so that institutions and individuals will be aware of wrongdoing

42 CFR 93.300 (d)

Case Summaries

This page contains cases in which administrative actions were imposed due to findings of research misconduct. The list only includes those who CURRENTLY have an imposed administrative actions against them. It does NOT include the names of individuals whose administrative actions periods have expired. Each case is categorized according to the year in which ORI closed the case.

2022

Case Summary: Brand, Toni M.
Case Summary: Chen, Shuo
Case Summary: Jarrett, Stuart G.
Case Summary: Jiang, Janina
Case Summary: Kaushal, Deepak
Case Summary: Leong, Daniel
Case Summary: Magnuson, Terry

Misconduct Case Summaries
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ORI Functions and Activities

- Participate in civil or criminal cases of alleged research misconduct directly or through other offices, including HHS OIG, US Attorney's Office or in collaboration with other federal agencies
- Maintain the assurance of 4,000 research institutions for responding to misconduct
- Correct or retract scientific papers to protect the integrity of the published literature and the public

Consequences of Research Misconduct

Scientific research is built on a foundation of trust. Public trust will only endure if the scientific community devotes itself to the values associated with ethical scientific research and reporting.

- Harm to individual and society with the introduction of an unsafe product (drug) or therapy or the failure to receive effective therapy (anti-vaccine).
- Damage to science itself – fortunately, the research record is inherently self-correcting through replication and validation, but this may take time.
- Damage to science and public trust – we are currently living through an assault on science with the COVID pandemic.
- Damage to careers of Co-investigators

Famous Fraud Cases

Andrew Wakefied (UK) physician published series of papers in Lancet (1998) linking MMR vaccine to autism and inflammatory bowel disease “autistic enterocolitis”. Led to sharp decline in vaccination and outbreaks of measles around the world. Data was derived from 12 children and parenteral observation only

- Undisclosed financial conflicts of interest funding from lawyers working on antivaccine cases
- British General Medical Council found Wakefield dishonest in his research, subjected minors to unwarranted procedures and mischaracterized their samples

Famous Cases

- Hwang Woo-Suk faked claims of cloning human embryonic stem cells published in Science 2005. Oocytes came from 2 junior members of his laboratory. Seoul University determined that none of the DNA in the cell lines matched the DNA from the somatic cell donors.
- Lessons Learned
  - Responsible conduct of research is an international issue
  - Conduct of research education is important. PHS requires all graduate students on training grants to received education.
  - Peer review is no panacea, difficult to detect research misconduct
  - Audit data and research records
  - Authorship and accountability

Resnik DB. Account Res 2006;13:101

https://science.howstuffworks.com/innovation/science-questions/database-18000-retracted-scientific-papers-now-online.htm

Database of 18,000 Retracted Scientific Papers Now Online

By: Oisin Curran | Nov 6, 2018

Early report

Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

A J Wakefield, S H Murch, A Anthony, J Linnell, D M Casson, M Malik, M Berelowitz, A P Dhillon, M A Thomson, P Harvey, A Valentine, S E Davies, J A Walker-Smith

Summary

Background We investigated a consecutive series of children with chronic enterocolitis and regressive developmental disorder.

Methods 12 children (mean age 6 years [range 3–10], 11 boys) were referred to a paediatric gastroenterology unit with a history of normal development followed by loss of acquired skills, including language, together with diarrhoea and abdominal pain. Children underwent gastroenterological, neurological, and developmental assessment and review of developmental records. Ileocolonoscopy and biopsy sampling, magnetic resonance imaging (MRI), electroencephalography (EEG), and lumbar puncture were done under sedation. Barium follow-through radiography was done where possible. Biochemical, haematological, and immunological profiles were examined.

Findings Onset of behavioural symptoms was associated by the parents, with measles, mumps, and rubella vaccination in eight of the 12 children, with measles infection in one child, and otitis media in seven. At 11 children had intestinal abnormalities ranging from lymphoid nodular hyperplasia to aphthoid ulceration. Histology showed patchy chronic inflammation in 11 children and reactive ileal lymphoid hyperplasia in seven, but no granulomas. Behavioural disorders included autism (nine), disintegrative psychosis (one), and possible postviral or vaccinal encephalitis (one). There were no focal neurological abnormalities and CT and EEG tests were normal. Abnormal laboratory results were significantly raised urinary methylmalonic acid compared with age-matched controls, low haemoglobin in four children, and low IgA in four children.

Interpretation We identified associated gastrointestinal disease and developmental regression in a group of previously healthy children, which was generally associated in time with possible environmental triggers.

Lancet 1998; **351**: 637–41
See Commentary page

Introduction

We saw several children who, after a period of apparent normality, lost acquired skills, including communication. They all had gastrointestinal symptoms, including abdominal pain, diarrhoea, and vomiting and, in some cases, food intolerance. We describe the clinical findings, and gastrointestinal features of these children.

Patients and methods

12 children, consecutively referred to the department of paediatric gastroenterology with a history of a pervasive developmental disorder with loss of acquired skills and intestinal symptoms, presented abdominal pain, bloating and food intolerance(s), were investigated. All children were admitted to the ward for a week, accompanied by their parents.

Clinical investigations

A history including details of immunisations and exposure to infectious diseases, and assessed the children. In 11 cases the history was obtained by the senior clinician (JW-S). Neurological and psychiatric assessments were done by consultant staff (PH, MB) with HMS-4 criteria.[7] Developmental assessment included a review of prospective developmental records from parents, health visitors, and general practitioners. Four children did not undergo psychiatric assessment in hospital; all had been assessed professionally elsewhere, so these assessments were used as the basis for their behavioural diagnosis.

After bowel preparation, ileocolonoscopy was performed by SHM or MAT under sedation with midazolam and pethidine. Paired frozen and formalin-fixed mucosal biopsy samples were taken from the terminal ileum; ascending, transverse, descending, and sigmoid colons, and from the rectum. The procedure was recorded by video or still images, and were compared with images of the previous seven consecutive paediatric colonoscopies (four normal colonoscopies and three on children with ulcerative colitis), in which the physician reported normal appearances in the terminal ileum. Barium follow-through radiography was possible in some cases.

Also under sedation, cerebral magnetic-resonance imaging (MRI), electroencephalography (EEG) including visual, brain stem auditory, and sensory evoked potentials (where compliance made these possible), and lumbar punctures were done.

Laboratory investigations

Thyroid function, serum long-chain fatty acids, and cerebrospinal-fluid lactate were measured to exclude known causes of childhood neurodegenerative disease. Urinary methylmalonic acid was measured in random urine samples from eight of the 12 children and 14 age-matched and sex-matched normal controls, by a modification of a technique described previously.[8] Chromatograms were scanned digitally on computer, to analyse the methylmalonic-acid ionex from cases and controls. Urinary methylmalonic-acid concentrations in patients and controls were compared by a two-sample *t* test. Urinary creatinine was estimated by routine spectrophotometric assay.

Inflammatory Bowel Disease Study Group, University Departments of Medicine and Histopathology (A J Wakefield FRCS, A Anthony MB, J Linnell MD, A P Dhillon MRCPath, S E Davies MRCPath) **and the University Departments of Paediatric Gastroenterology** (S H Murch MB, D M Casson MRCP, M Malik MRCP, M A Thomson FRCP, J A Walker-Smith FRCP), **Child and Adolescent Psychiatry** (M Berelowitz MRCPsych), **Neurology** (P Harvey FRCP), **and Radiology** (A Valentine FRCR), **Royal Free Hospital and School of**

Table 1: **Clinical details and laboratory, endoscopic, and histological findings**

before. Stool samples were cultured for *Campylobacter* spp, *Salmonella* spp, and *Shigella* spp and assessed by microscopy for ova and parasites. Sera were screened for antibodies to *Yersinia enterolitica*.

Histology

Formalin-fixed biopsy samples of ileum and colon were assessed and reported by a pathologist (SED). Five ileocolonic biopsy series from age-matched and sex-matched controls reports showed histologically normal mucosa were obtained comparison. All tissues were assessed by three other clinical experimental pathologists (APD, AA, AJW).

Ethical approval and consent

Investigations were approved by the Ethical Practices of the Royal Free Hospital NHS informed consent.

Results

Clinical details of the children are given in tables 1 and 2. None had neurological abnormalities on clinical examination; MRI scans, EEGs, and cerebrospinal-fluid profiles were normal; and fragile X was negative. Prospective developmental records showed satisfactory achievement of expected developmental milestones in all children. The only girl (child number 6) noted to be a slow developer compared with her older sister. She was subsequently found to have coarctation of the aorta. After surgical correction at the age of 14 months, she progressed rapidly, and learnt to talk. Speech was lost later. Child number 6 was kept under review for the first year of life because of wide bridging of the nose. He was discharged from follow-up as developmentally normal at age 1 year.

In eight children, the onset of behavioural problems had been linked, either by the parents or by the child's physician, with measles, mumps, and rubella vaccination. Five had had an early adverse reaction to immunisation (rash, fever, delirium; and, in three cases, convulsions). In these eight children the average interval from exposure to first behavioural symptoms was 6·3 days (range 1–14). Parents were less clear about the timing of onset of abdominal symptoms because children were not toilet trained at the time because behavioural features made children unable to communicate symptoms.

Child (child number) had received monovalent measles vaccine at 14 months, after which his development slowed (confirmed by professional assessors). No association was made with the vaccine at the time. He received a dose of measles, mumps, and rubella vaccine at age 4·5 years, the day after which his mother noticed a striking deterioration in his behaviour that she did link with the immunisation. Child nine received measles, mumps, and rubella vaccine at 16 months. At 18 months he developed recurrent antibiotic-resistant otitis media and the first behavioural symptoms, including disinterest in his sibling and lack of play.

Table 2 summarises the neuropsychiatric diagnoses; the apparent precipitating events; onset of behavioural features; and age of onset of both behaviour and bowel symptoms.

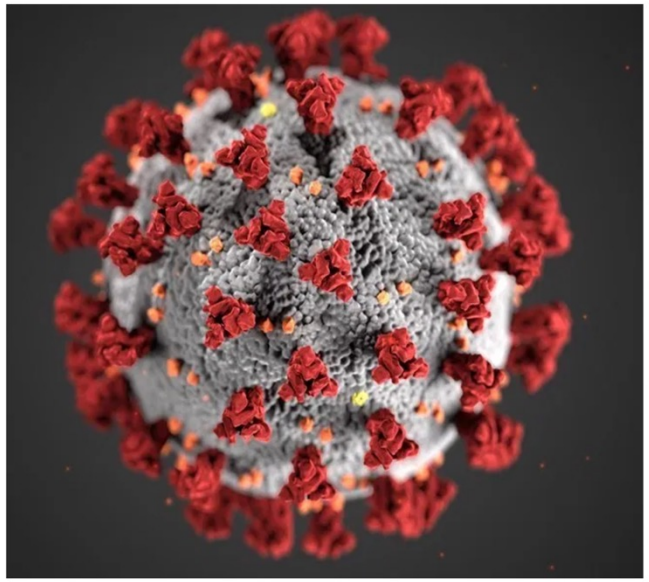
Laboratory tests

All children were antiendomysial-antibody negative and common enteric pathogens were not identified by culture, microscopy, or serology. Urinary methylmalonic-acid excretion was significantly raised in all eight children who

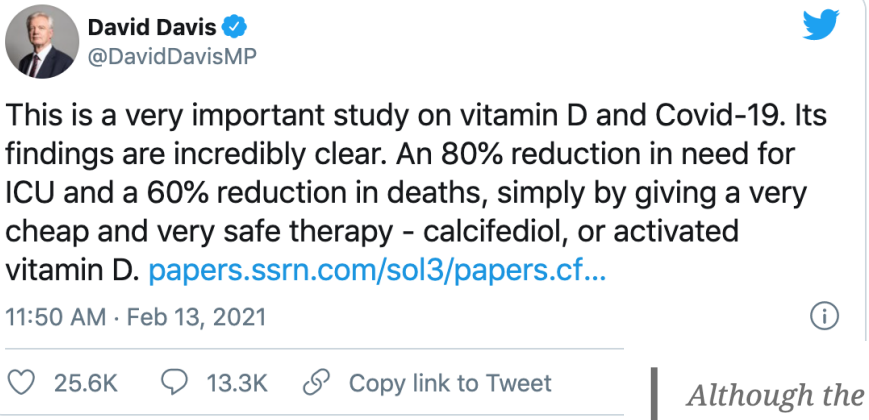
Figure 1: **Urinary methylmalonic-acid excretion in patients and controls**
p=Significance of mean excretion in patients compared with controls.

https://retractionwatch.com/retracted-coronavirus-covid-19-papers/

Widely shared vitamin D-COVID-19 preprint removed from Lancet server



A preprint promoted by a member of the UK Parliament for claiming to show that vitamin D led to an "80% reduction in need for ICU and a 60% reduction in deaths" has been removed from a server used by The Lancet family of journals.



> *Although the paper claims it is a randomised study, it also says that all patients treated in 5 wards received calcifediol treatment, while all three of the other wards received no calcifediol. How this study can be considered randomised is therefore questionable (maybe the wards were randomised but that is a very poor level of randomisation). It is also presumably open label, meaning that the attending physicians and decision makers would have been well aware whether the patients were receiving calcifediol or not. Its concerning to me that that in the calcifediol group more patients apparently died than were referred to the ICU. In the control group approx. 50% of the patients referred to the ICU died (assuming all those who died were ICU patients). This raises some troubling questions about the decision making process in the calcifediol group, were patients not referred to ICU who should have been?*

- **75 papers have been retracted**
- **87,000 papers published - US News 3/1/21**

Institutional Responsibility

- Institutions are required to have policies for handling scientific misconduct to be eligible to receive federal funds (42 CFR 50)

The University of Tennessee Policy and Procedures on Responsible Conduct in Research and Scholarly Activities*

(Effective September 15, 2016)

How to Prevent Research Misconduct

- Oversight/supervision by senior researcher
- Policy and Procedure Manual
- Methods of Operations
- Clean and Complete Source Documentation
- Record Retention policy
- Processes for early detection and self-correction on non-compliance
- Periodic research integrity training – currently require certain training for researchers, i.e. human subjects, animal use, lab safety

Office of Research Compliance

- Institutional Review Board
  - Human subjects research
- Institutional Animal Care and Use Committee
  - Animal research
- Institutional Biosafety Committee
  - Research utilizing rDNA and other biohazardous material
  - Infectious organisms, toxins, allergen, venoms
- Export Control
  - Covers release of covered technologies to foreign nationals in US
- Research Safety Affairs
  - Promotes regulatory compliance among researches with diversity of regulations from the CDC, OSHA, EPA, NIH, NRC, et al
- Research Integrity
  - Research Integrity Officer

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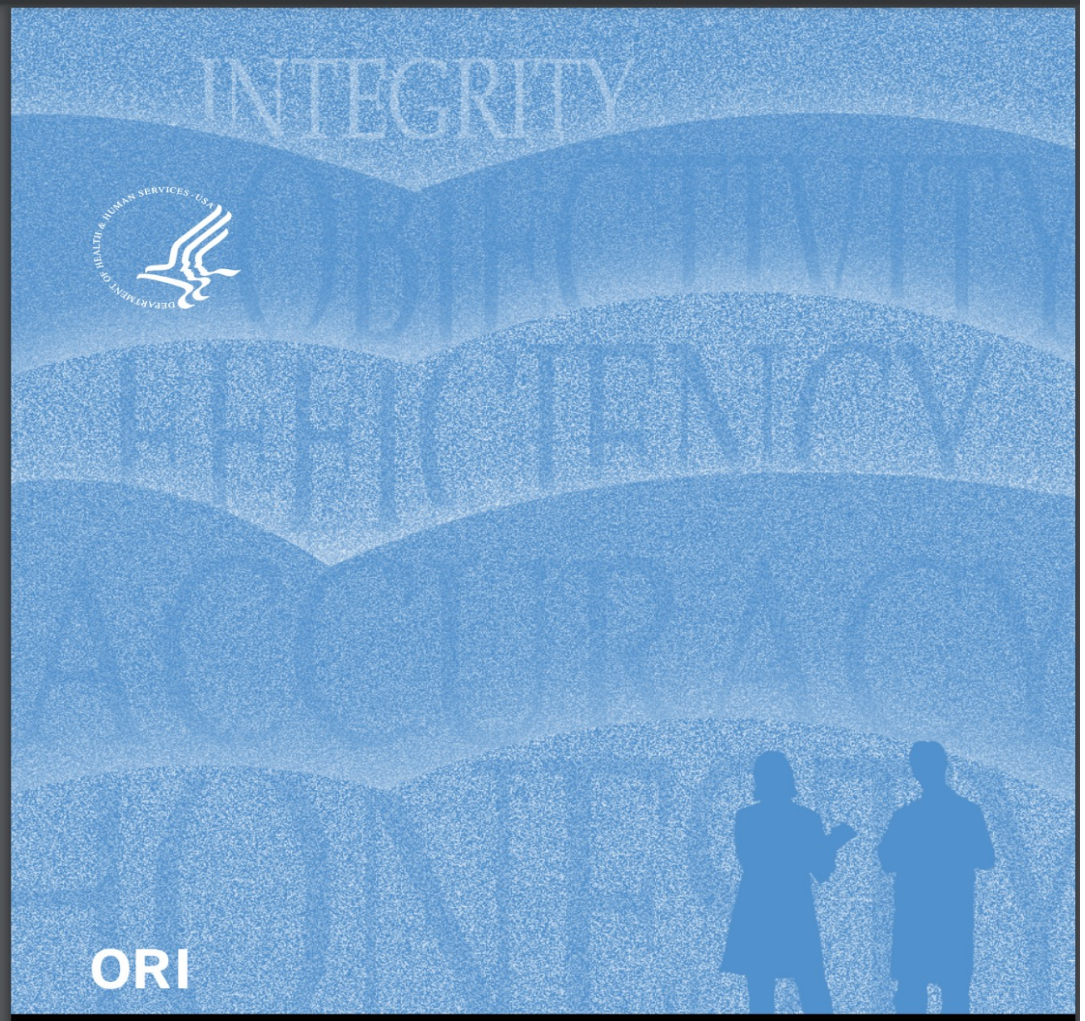

Introduction to the Responsible Conduct of Research

Nicholas H. Steneck
illustrations by David Zinn