CLINICAL TRIALS: THE BASICS

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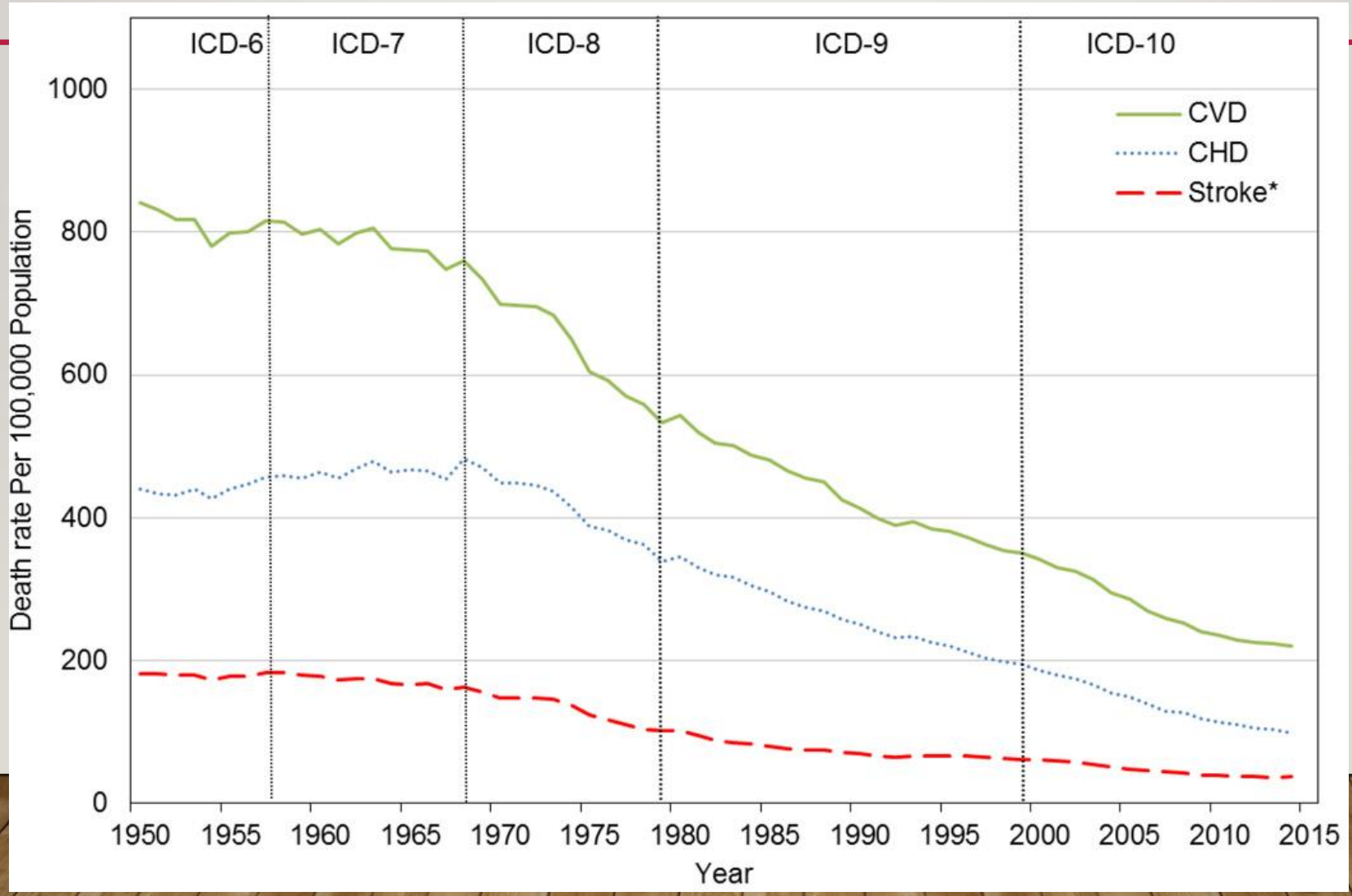
DEDICATION

- This talk is dedicated to the researchers who create the knowledge, the clinicians who practice it, the teachers who spread it, and the students who learn from it.

THE AIM OF SCIENCE IS NOT TO OPEN A DOOR TO ENDLESS WISDOM, BUT TO PUT A LIMIT TO ENDLESS ERROR.

BERTOLT BRECHT: THE LIFE OF GALILEO

WHAT HAPPENED HERE WITH CARDIOVASCULAR DISEASE?



ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN

- About 90% of children with ALL can be cured. Patients are considered cured after 10 years in remission.

CLOSTRIDIUM DIFFICILE BOWEL INFECTION

- Rectal infusion of donor feces resulted in >80% cure rate measured at 10 weeks
- "Standard of Care" treatment of oral antibiotics has a 30% cure rate at 10 weeks.
- N = 43 patients

The Women's Health Initiative: Risks outweigh benefits of combination hormone replacement therapy, 2002 JAMA.

Combination estrogen and progestin hormone replacement therapy (HRT) is associated with a 29% increased risk of cardiovascular disease, 110% increased risk of venous thromboembolism and 26% increased risk of invasive breast cancer.

Mean average age of participants was 63, ranged from 50 to 79. 16,000 participants

Participants received conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d

TYPES OF RESEARCH

- **Basic** or bench research – building knowledge
- **Translational** research - take some knowledge of a particular biological phenomenon (that the basic scientists discovered) and translate it into something that might eventually be used in a clinical setting.
- **Clinical research** – see next slide

WHAT IS CLINICAL RESEARCH?

- **Clinical research** helps doctors and researchers learn more about disease and improve health care for people in the future. Clinical research includes all research that involves people. **Types of clinical research include:**
  - **Epidemiology,** which improves the understanding of a disease by studying patterns, causes, and effects of health and disease in specific groups.
  - **Behavioral,** which improves the understanding of human behavior and how it relates to health and disease.
  - **Health services,** which looks at how people access health care providers and health care services, how much care costs, and what happens to patients as a result of this care.
  - **Clinical trials, which evaluate the effects of an intervention on health outcomes.**

Clinical trials are part of clinical research and are at the heart of all medical advances.

Clinical trials can study:

- New drugs or new combinations of drugs
- New ways of doing surgery
- New medical devices
- New ways to use existing treatments
- New ways to change behaviors to improve health
- New ways to improve the quality of life for people with acute or chronic illnesses.

TYPES OF CLINICAL TRIALS

- **Prevention trials** test ways to prevent diseases. Approaches may include medicines, vaccines, or lifestyle changes.
- **Screening trials** test ways to detect diseases.
- **Diagnostic trials** study tests or procedures for diagnosing a particular disease or condition.
- **Treatment trials** test new treatments or approaches.
- **Behavioral trials** evaluate behavioral changes designed to improve health.
- **Supportive care trials** look to improve comfort and quality of life.

Clinical trials are conducted in a series of steps called "**phases**." Each phase has a different purpose and helps researchers answer different questions.

- **Phase I trials**: Researchers test a drug or treatment in a small group of people (20–80) for the first time. The purpose is to learn about **safety** and identify **side effects**.
- **Phase II trials**: The new drug or treatment is given to a larger group of people (100–300) to determine its **effectiveness** and to further study its **safety**.
- **Phase III trials**: The new drug or treatment is given to large groups of people (1,000–3,000) to confirm its **effectiveness**, **monitor side effects**, **compare it** with standard or similar treatments, and determine how it can be used safely.
- **Phase IV trials**: After a drug is approved by the FDA and made available to the public, researchers track its **safety in the general population**, seeking more information about a drug or treatment's benefits, and optimal use.

FIRST IN HUMAN

- https://www.cc.nih.gov/ocmr/firstinhuman/

POTENTIAL BENEFITS FOR PARTICIPANTS

Well-designed and well-executed clinical trials provide the best approach for you to:

- Help others by contributing to knowledge about new treatments or procedures.
- Gain access to new research treatments before they are widely available.
- Receive regular and careful medical attention from a research team that includes doctors and other health professionals.

POTENTIAL RISKS TO PARTICIPANTS

- There may be unpleasant, serious, or even life-threatening effects of experimental treatment.
- The study may require more time and attention than standard treatment would, including visits to the study site, more blood tests, more procedures, hospital stays, or complex dosage schedules.

THE PARKINSON'S DRUG TRIAL: A MIRACLE CURE?

- https://www.bbc.co.uk/programmes/m0002tjw

SOME ESSENTIAL TERMS

- Protocol
- Randomized Clinical Trial (RCT)
- Standard of Care
- Placebo
- Single blinded, double blinded

THE RIGHTS OF CLINICAL TRIAL PARTICIPANTS

- Informed consent
- Can quit the trial at any time
- Free from coercion
- Extra protection for vulnerable populations
  - Prisoners
  - Pregnant women
  - Children

PROTECTION OF CLINICAL TRIAL PARTICIPANTS

- https://youtu.be/y7TDwbrD7GQ
- https://youtu.be/DGOHXJZtrjs
- https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html

WHAT HAPPENS WHEN THE CLINICAL TRIAL IS DONE?

- Results can take time – analysis is complex
- Clinicaltrials.gov
- Poster presentations at medical and research conferences
- Publish in peer-reviewed journals

• HOUSTON, WE HAVE A PROBLEM

Integrating clinical trial results into mainstream medicine

- Diffusion of Innovations theory by Rogers (1962)
  - Factors that affect the diffusion of Innovations:
    - The innovation itself
    - Adopters
      - Innovators, early adopters, early majority, late majority, laggards
    - Communication channels
    - Time
    - Social system

DEBUNKING

- Number of people in study?
- Randomized Clinical Trial?
- Methods of treatment and statistical analysis are clearly presented
- Not based on patients' recollections
- Sounds too good to be true

The Women's Health Initiative: Risks outweigh benefits of combination hormone replacement therapy, 2002 JAMA.

Combination estrogen and progestin hormone replacement therapy (HRT) is associated with a 29% increased risk of cardiovascular disease, 110% increased risk of venous thromboembolism and 26% increased risk of invasive breast cancer.
Over 1 year, 10 000 women taking combination HRT might experience 7 more cardiovascular events, 8 more strokes, 8 more pulmonary emboli, 8 more cases of invasive breast cancer, 6 fewer colorectal cancers and 5 fewer hip fractures.

Mean average age of participants was 63, ranged from 50 to 79. 16,000 participants

Participants received conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d

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 another. All 12 children had intestinal abnormalities, ranging from lymphoid nodular hyperplasia to aphthoid ulceration. Histology showed patchy chronic inflammation in the colon 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 (two). There were no focal neurological abnormalities and MRI and EEG tests were normal. Abnormal laboratory results were significantly raised urinary methylmalonic acid compared with age-matched controls (p=0·003), low haemoglobin in four children, and a low serum IgA in four children.

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

Lancet 1998; **351**: 637–41

See Commentary page 611

Inflammatory Bowel Disease Study Group, University Departments of Medicine and Histopathology (A J Wakefield FRCS, A Anthony MB, J Linnell PhD, 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 FRCPsych), **Neurology** (P Harvey FRCP), **and Radiology** (A Valentine FRCR), **Royal Free Hospital and School of**

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 bloating 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 (diarrhoea, abdominal pain, bloating and food intolerance), were investigated. All children were admitted to the ward for 1 week, accompanied by their parents.

Clinical investigations

We took histories, 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.[1] Developmental histories 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 somatry evoked potentials (where compliance made these possible), and lumbar puncture 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.[2] Chromatograms were scanned digitally on computer, to analyse the methylmalonic-acid zones 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.

ANDREW WAKEFIELD'S ARTICLE LINKING MMR VACCINE TO BOWEL PROBLEMS AND AUTISM

- small case series with no controls
- linked three common conditions
- relied on parental recall and beliefs
- numerous facts were altered about the patients' medical histories in order to support his claim to have identified a new syndrome

BONE MARROW TRANSPLANT FOR ADVANCED BREAST CANCER

- Dr Werner Bezwoda of South Africa admits he falsified data, and is retracting a widely publicized study claiming that bone-marrow transplantation and high-dose chemotherapy could prolong lives of women with advanced breast cancer; admission of fraud comes after a team of American scientists visit his laboratory at University of Witwatersrand in Johannesburg to examine his records, and find they do not match what he has reported; Bezwoda has resigned from his university positions. *The New York Times, 2000*

ISRAELI TEAM ANNOUNCES "CURE FOR CANCER WITHIN ONE YEAR"

- "We believe we will offer in a year's time a complete cure for cancer"
- The treatment, called MuTaTo, will use a combination of cancer-targeting peptides and a toxin that will specifically kill cancer cells.
- "Our cancer cure will be effective from day one, will last a duration of a few weeks and will have no or minimal side-effects at a much lower cost than most other treatments on the market."

HTTPS://CLINICALTRIALS.GOV/

- Search tips

FURTHER READING

- Saklayen, M. G., & Deshpande, N.V. (2016). Timeline of History of Hypertension Treatment. *Frontiers in cardiovascular medicine, 3, 3*. doi:10.3389/fcvm.2016.00003
- Clinicaltrials.gov
- DeVita, V.T., Chu, E. (2008). A History of Cancer Chemotherapy. *Cancer Res November* 1 2008 (68) (21) 8643-8653; DOI: 10.1158/0008-5472.CAN-07-6611
- Parkinson's Trial https://www.bbc.co.uk/programmes/m0002tjw
- First in Human https://www.cc.nih.gov/ocmr/firstinhuman/
- All of Us Research Study https://allofus.nih.gov/