THE BUNDABERG DISASTER AND THE SUPREME COURT

immunization and its discontents

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Disclaimer

- Disclaimer ... I have no vested interest in anything I will say today. I expect to die a poor but honest man. (sigh)
Presentation goals …

- I hope to clarify the relationships between …
  - epidemic diphtheria
  - early vaccine manufacturing
  - the Massachusetts hard freeze of 1924
  - syphilis and meningococcal meningitis
  - a Yale School of Medicine training program
  - vomiting kittens
  - autism
  - $3,000,000,000 and 17¢
  - the US Supreme Court
21 children

- high fever
- vomiting
- profuse diarrhea
- circulatory collapse
- seizures
- rash (variable)
Patient characteristics and severity

Severity
- died (12)
- critically ill (5)
- moderately ill (1)
- not ill (3)

Age
- 1 .. 10 yrs

Individual patients
Details of severity

dose 1: 0.062 ml
dose 2: 0.123 ml
immunization

- sewage disposal
- immunization
- nutrition
- antibiotics
- CT scans
The Bundaberg vaccine

Immunizing a horse with gradually increasing doses of diphtheria toxin

Bleeding a fully-immune horse to collect toxin-neutralizing antibodies
Diphtheria toxin-antitoxin (TAT) vaccine
Diphtheria

CARRIER OF 
DIPHTHERIA

KEEP OUT OF THIS HOUSE

By Order of BOARD OF HEALTH

Any person removing this card without authority is liable to prosecution

HEALTH OFFICER
Diphtheria disease
The Bundaberg disaster
Friday, January 27, 1928
TAT vaccine – Batch 86
The disaster begins ...

Typical – though surely staged -- immunization scene in the ‘20s

Dr Thomson’s immunization clinic in Bundaberg – January 27, 1928
The Royal Commission is convened ...

Charles Kellaway; chairman of the Commission and head of the Walter and Eliza Hall Institute
F. MacFarlane Burnet ...
The obvious (but incorrect) explanation

- Diphtheria toxin
- Horse antibody
- Toxin-Antitoxin (TAT) vaccine
MacFarlane Burnet explains the Bundaberg Disaster

Staphylococcus aureus
Gram stain

Staphylococcus aureus
scanning EM
(false color to match the Gram stain)
Staphylococcus alpha-toxin

β hemolysis - blood agar

α hemolysin – penetrating a cell membrane
Recommendations from the Royal Commission

RECOMMENDATIONS.

1. That biological products in which the growth of pathogenic organisms is possible should not be issued in rubber-capped containers for repeated use unless there is present in the material a sufficient concentration of antiseptic to inhibit bacterial growth.

2. That all biological products not containing antiseptic, however issued, should bear a conspicuous printed notice, both on the container and on the package, to the effect that no antiseptic is present; that they should be used immediately on opening, and any remaining product discarded.

3. That biological products, should be distributed in bottles or ampoules of clear glass in which it is easier for the medical practitioner himself to detect turbidity or any other defect.

4. That the Commonwealth Department of Health should make full and careful enquiry as to whether it be advisable to substitute anatoxin or some similarly modified immunizing agent for toxin-antitoxin.

5. To ensure the adoption of the most approved technique, facilities for special post-graduate training should be afforded to all medical officers entrusted with the conduct of public campaigns to diminish the incidence of disease by immunization.
The end of the Bundaberg story?

- Dramatic story
- Medical mystery
- Brilliant investigation
- Mystery solved!
- Important lessons learned and applied
Twist 1 – the preservative problem

Paul Ehrlich
thimerosal

Morris Kharasch

sodium ethylmercurithiosalicylate
thimerosal
Merthiolate

Tincture of Merthiolate
Twist 2 – was alpha-toxin the real cause of the Bundaberg disaster?

- *Staphylococcus* toxins ...
  - alpha-toxin
  - beta-toxin
  - gamma-toxin
  - delta-toxin
  - enterotoxins (9 types including toxic-shock syndrome toxin)
  - leucocidin
  - coagulase
  - lipase
  - protease
  - staphyloxanthin
A new illness caused by staph

vomiting
diarrhea
high fever
diffuse rash
confusion
perilously low blood pressure
Toxic Shock Syndrome Toxin 1 (TSST-1)

- One of 9 toxins in the enterotoxin family
- Occasionally other enterotoxins produce TSS
- Superantigen
  - Promotes massive discharge of immune defensive materials causing ...
    - Dramatic fall in blood pressure ... circulatory collapse
    - Bowel wall muscle activation: vomiting and diarrhea
    - Fever
TSST-1 and Bundaberg

- Is TSST-1 the case of the Bundaberg Disaster?
  - Maybe, but we may never know
  - Clinically, similar or identical
  - Toxin production never characterized by modern methods

NCTC catalog #2669 ... £90
Twist 3 – making and selling vaccines

- Timeline … early diphtheria vaccine history
  - 1884 *Corynebacterium diphtheræ* (Loeffler)
  - 1913 TAT vaccine for human use (von Behring)
  - 1924 toxoid described (Ramon)
  - 1926 alum adjuvant described (Glenny)
  - 1927 CSL TAT batch 86 manufactured
  - 1928 Bundaberg disaster
  - 1928 Royal Commission report
  - 1929 alpha toxin discovered (Burnet)
Standard diphtheria vaccine

- 1930s -- standardization of the product
  - Replacement of TAT by toxoid
    - Toxin grown in liquid culture, purified by fractional precipitation with ammonium sulfate, detoxified with formalin
  - Preservative replacement of phenol by thimerosal
  - Alum adjuvant added
  - Packaged in 10- or 15-dose units
  - (similarly-made tetanus toxoid introduced)
DTP vaccine

- 1940s – diptheria toxoid replaced by DTP
  - diphtheria toxoid
  - tetanus toxoid
  - whole-cell thimerosal-killed pertussis vaccine
    - potent adjuvant for T-cell antigens
  - thimerosal preserved
  - alum as additional adjuvant
  - by 1950, 17¢ a dose
The pertussis component of DTP

- thimerosal-killed and partially heat-detoxified whole *Bordetella pertussis* cells
- contained endotoxin and a number of specific toxins and thousands of bacterial antigens
- increased risk of febrile seizures without sequelae first 24 hours
- maybe long-term neurological risk (1:140,000 or less)
  - pertussis disease: 1:333 risk of encephalopathy ... of these, 2/3 (=1:500) with brain damage or death
Whole-cell pertussis vaccine problems

- laborious to make
- excessive impurities and toxicity
  - high fever (sometimes febrile seizures)
  - swollen, hot, tender legs
  - high-pitched screaming for hours
  - pallid episodes with syncope or near-syncope
DTP (whole-cell) vaccine benefits

- Safe, effective, and cheap
  - 1950 - $ 0.17 per dose
  - 1955 - $ 0.17
  - 1960 - $ 0.17
  - 1965 - $ 0.17
  - 1970 - $ 0.17
  - 1975 - $ 0.19
  - 1980 - $ 0.26
  - 1985 - $ 2.80
  - 1990 - $ 10.62
DTP and DTaP pricing ...

- Change to liquid culture
- First lawsuits in 1978
- 1986: 250 lawsuits, National Childhood Vaccine Injury Act
- 2001: Multiple-dose vials replaced with preservative-free single dose vials
National Childhood Vaccine Injury Act of 1986

- federally-run insurance scheme to compensate people injured by immunization
- claims paid only for injuries known to be vaccine-related
- funded by an excise tax on vaccines – now $0.75 per disease covered (DTaP $2.25/dose)
- excise tax to Vaccine Injury Compensation Trust Fund – now about $3.5 billion held in trust
$3,500,000,000
Final twist: autism and the case just decided by the Supreme Court

April 1, 1992 ... Hannah Bruesewitz receives DPT #3
-- quickly suffers multiple seizures and developmental disabilities, including autism

April 3, 1995 ... Bruesewitz family seeks compensation from Vaccine Court for injuries
-- rejected: “residual seizure disorder” eliminated as attributable to DTP vaccine

October, 2005 ... attempt to bypass the Vaccine Court decision by suing in state court
-- rejected directly and on appeal in federal court
Hannah Bruesewitz and the Supreme Court

- 2010-2011 ... further appeal accepted by US Supreme Court; Hannah’s lawyers arguing ...
  - the DPT vaccine was “avoidably” unsafe because it was “outmoded” and the maker could have chosen to make a safer acellular product
    - Hannah Bruesewitz received DTP dose 3 in 1992
    - DTaP licensed in the US for infants in 1996
Vaccines and autism

- 1998 Andrew Wakefield in *Lancet* – assertion of role of measles vaccine in autism

2010 – *Lancet* withdraws Wakefield paper

The Hannah Bruesewitz decision
The Supreme Court
Immunization