Australia’s Role on the Global Vaccine Stage

Sir Gustav Nossal
Department of Pathology
The University of Melbourne

7 September 2016
In 1928, twelve children died through receiving a diphtheria toxin-antitoxin mixture heavily contaminated with *Staphylococcus aureus*.

Burnet isolated the pathogen both from the vaccine vial and survivors’ wounds.

Burnet studied primary and secondary antibody responses in experimental animals.

The results did not fit the direct template hypothesis.
The exponential rise of antibody levels needs explaining.

So does the higher, faster secondary response.

So does a failure to form antibody to “self”.

The 1957 Clonal Selection Theory brings it all together.

N.B.; Jerne and Talmage deserve and receive much credit.
BURNET’S MAIN EXPERIMENTAL INTEREST WAS VIRUS GROWTH

- Burnet perfects Goodpasture’s method of growing viruses in fertile hen’s eggs.

- Burnet prepares live attenuated influenza virus and trials it as a live, attenuated vaccine in military personnel (World War II). The vaccine fails.

- Burnet isolates numerous other pathogens including poliomyelitis virus, showing for the first time that there is more than one strain.
FRANK FENNER FOLLOWS IN BURNETIAN TRADITION

- Fenner comprehensively dissects the epidemiology and pathophysiology of mousepox (ectromelia).

- Fenner closely follows the Australian rabbitpox (myxomatosis) pandemic.

- Insights gained materially help to guide W.H.O.’s smallpox eradication campaign.

- In 1980, Fenner signs the historic document declaring the global eradication of smallpox.
Inspired by these examples of a global approach, I develop close relationships with W.H.O., culminating in a long period of chairmanship of SAGE, the Strategic Advisory Group of Experts guiding W.H.O. in Vaccine strategy.

This occasions the Gates Foundation to ask me to chair the Strategic Advisory Council of their nascent vaccine programme.

After much deliberation, the Global Alliance for Vaccines and Immunisation is launched in 2000.

It aims to bring the common vaccines to poor children; to accelerate the introduction of newer vaccines; and to catalyse research into new and improved vaccines.
Q FEVER VACCINE: BARRIE MARMION

- Q fever is a costly and severe zoonotic disease in Australia involving people working with cattle, sheep and goats.

- Cause is a small intracellular bacterium, Coxiella burnetii.

- Acute disease can be followed by nasty complications such as endocarditis or Q fever fatigue syndrome.

- The Q-VAX Q Fever Vaccine is formalinised purified whole cell *C. burnetti* from embryonated eggs. Vaccination starting in 1994 materially lowers the risk in abattoir workers. Efficacy in 7 trials varies from 83% to 100%.

- A national Q fever management program has been in place since 1993.
Scottish physician Ian Frazer moves to Melbourne in 1980 attracted to the Walter and Eliza Hall Institute. Ian Mackay puts him in charge of HIV. He notes that HPV can cause pre-cancerous anal and rectal lesions.

In 1985 Frazer moves to Brisbane. Together with Jian Zhou, the concept of a genetically engineered HPV vaccine is born.

The HPV major capsid protein L1 is made in yeast cells and self-assembles into virus-like particles that resemble authentic HPV virions. Collaboration with CSL and Merck.

The Gardasil vaccine contains proteins of HPV types 16 and 18, responsible for 70% of cervical cancers, and types 6 and 11, responsible for 90% of genital warts. Most anal, vulval, vaginal and penile cancers are also prevented.

In December 2014 Gardasil 9 is approved including 5 other HPV strains.
AUSTRALIA’S ROTAVIRUS VACCINE HAS A LONG HISTORY

- In 1973, Ruth Bishop and colleagues identify a new virus in the cytoplasm of duodenal epithelial cells in cases of severe diarrhoea in young children. This rotavirus is responsible for 40-50% of severe, acute diarrhoea in young children worldwide.

- Early work by Ian Holmes and Mike Dyall-Smith in the 1980s with Wallace International proves disappointing.

- “Low titre” RV3 vaccine well tolerated in infants in early Phase I/II trials, but insufficiently immunogenic. CSL declines to collaborate

- RV3-BB vaccine phase 2a trial in New Zealand shows vaccine to be immunogenic and well tolerated when given as a 3 dose neonatal or infant schedule. No problems with the birth dose.
Group A streptococci cause >500,000 deaths per year, >600 million annual sore throats and >600,000 new cases of rheumatic fever, rheumatic heart disease. The latter affects 651/100,000 Australian Aboriginal people.

Vaccine consists of carrier protein and an important neutralizing antibody determinant from the cell surface GAS M protein incorporated onto liposomal vesicles.

The B cell epitope induces potent serum and mucosal antibodies after intranasal administration. Mice are protected from GAS challenge.

Development with Chinese firm Olymvax Pharmaceuticals.

Clinical trials in China and Australia.
• Alan Cowman: Live attenuated malaria vaccine using sporozoites of *Plasmodium falciparum* with a triple gene deletion (the P52, P36 and SAP1 genes).

• Humanised mouse model shows no progress to blood stage infection. Parasites show normal production of gametocytes, normal development in mosquitoes, normal invasion of salivary glands, normal infection of hepatocytes but failure to complete liver stage development.

• Barry Marshall: Use attenuated *Helicobacter pylori* as a vector for HIV antigens. Antigen presentation for many months.

• So far, no totally harmless *Helicobacter* has been found.

• ONDEK formed to exploit these ideas, including desensitisation to allergens.