BACK TO THE FUTURE – HOW GOOD IS YOUR MEMORY?

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“DURABLE SPECIFIC IMMUNOLOGICAL MEMORY IS THE BASIS OF SUCCESSFUL VACCINATION”

- Pasteur : Attenuated microbe → specific protection (mechanism unknown). Chicken cholera/anthrax/rabies

- Von Behring : Toxins stimulated specific humoral protection
- (passive & active immunization in diphtheria)

IMPACT OF VACCINATION IN AUSTRALIA (PATHOLOGY INVOLVES TOXIN OR VIRAEMIA)

TABLE 1

DEATHS IN AUSTRALIA FROM COMMON PREVENTABLE DISEASES, 1926 TO 1995

Period	Diphtheria	Pertussis	Tetanus	Poliomyelitis	Measles[a]	Population average
1926–1935	4,073[b]	2,808	879	430	1,102	6,600,000
1936–1945	2,791	1,693[b]	655	618	822	7,200,000
1946–1955	624	429	625[b]	1,013	495	8,600,000
1956–1965	44	58	280	123[b]	210	11,000,000
1976–1985	2	14	31	2	62	14,900,000
1986–1995	2	9	21	0	32	17,300,000

Notes:
(a) These numbers exclude deaths from subacute sclerosing panencephalitis.
(b) Decade in which community vaccination started for the disease.

Source:
Commonwealth year books. Canberra: Australian Government Publishing Service.

TABLE 2

REDUCTION IN MORTALITY WITH VACCINATION FOR COMMON PREVENTABLE DISEASES IN AUSTRALIA

Disease	Year of onset of public vaccination	Reduction in mortality rate (%)
Diphtheria	1932	100
Pertussis	1942	99
Tetanus	1953	99
Poliomyelitis	1956	100
Measles	1970	91

Source:

One hundred years of vaccination

► *Continued from page 61*

Limited shipping rapidly led to a shortage of these agents, and in 1915 the Commonwealth government decided to start a federal institute in Melbourne on the site of the present Commonwealth Serum Laboratories.

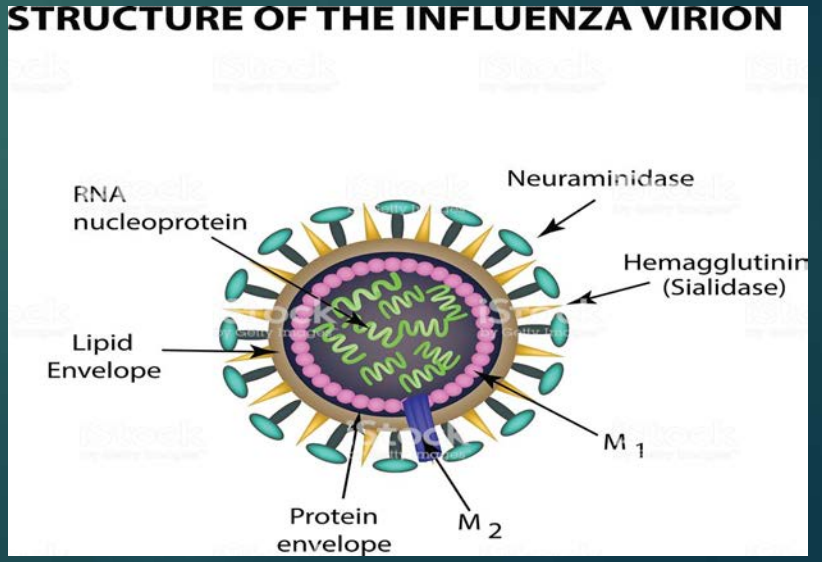
The first stimulus to the production of vaccines and antisera in Australia was the threat of shortages during the war. The second was the decision that all service personnel

THEN THERE WAS INFLUENZA!

- (i)Segregate nucleus without "proof-reading" → multiple intracellular infection → SHIFT antibody-induced DRIFT (variation around "haemagglutinin binding packet", especially for H2N3)

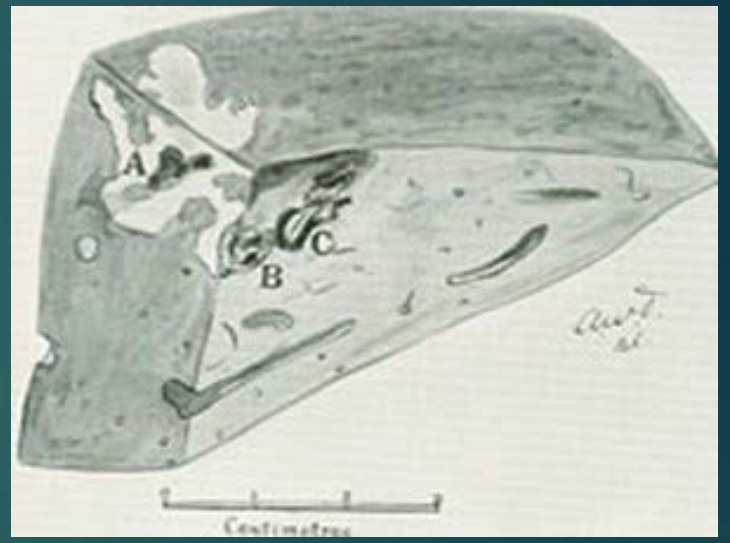
(ii)Vaccine strategy of matching H & N (but only 5-50% effective)

(iii) Natural Flu → CD8+ T memory (but not Vaccination, as no appropriate HLA repertoire)



AUSTRALIAN CONTRIBUTIONS TO VACCINOLOGY

- EARLY INTRODUCTION : Vaccinia, Anthrax (Loir/Pasteur), CSL – self-sufficient
- Arthur Turner: Pathogenesis and prevention of Black disease &PPLO cattle
- Complexity of influenza:
  (recognized 1919 Flu 2nd bacterial infection –40% less deaths with bacterial vaccine)



- Burnet :Flu- eggs/structure/biology; Immunol memory (Bundaberg disaster)
- T cell/HLA biology, mucosal immunology

IMMUNOLOGY AND INFLUENZA VACCINES

- ORIGIONAL SIN
- CONSERVED EPITOPES & CD8+ T CELL MEMORY
- MUCOSAL IMMUNOLOGY AND BACTERIAL/VIRAL CO-INFECTION

ORIGIONAL SIN

(Innitial exposure to flu shapes subsequent outcomes)

(i)2007/2009 H1N1 – less antibody to new isolate

(ii)Dengue – 4 serotypes. Disease/vaccine involves ltd repertoire : next infection →inappropriate CD+T response & shock syndrome

(iii)Hep C & HIV vaccines in circumstance of "changing antigens" → "trap" immunity with dominant response to earlier antigen

AIM: "GLOBAL" VACCINE TO CONSERVED EPITOPES

WHAT ABOUT CD8+ T CELL MEMORY?

- Natural Flu → CD8+ T Cell Memory

- Yellow Fever Live Vaccine → Persistent CD8 T Cell Memory – BUT Split Flu H/N vaccines do not

- SO": simply use conserved flu T cell epitopes : BUT- "global HLA repertoire" for antigen presentation limited eg caucasion 60% ; aborigional 15%. IF NOT MATCHED, Risk no response, or innapropriate one

- THUS: Select epitopes from bigger pool

The Unmet Need – COPD

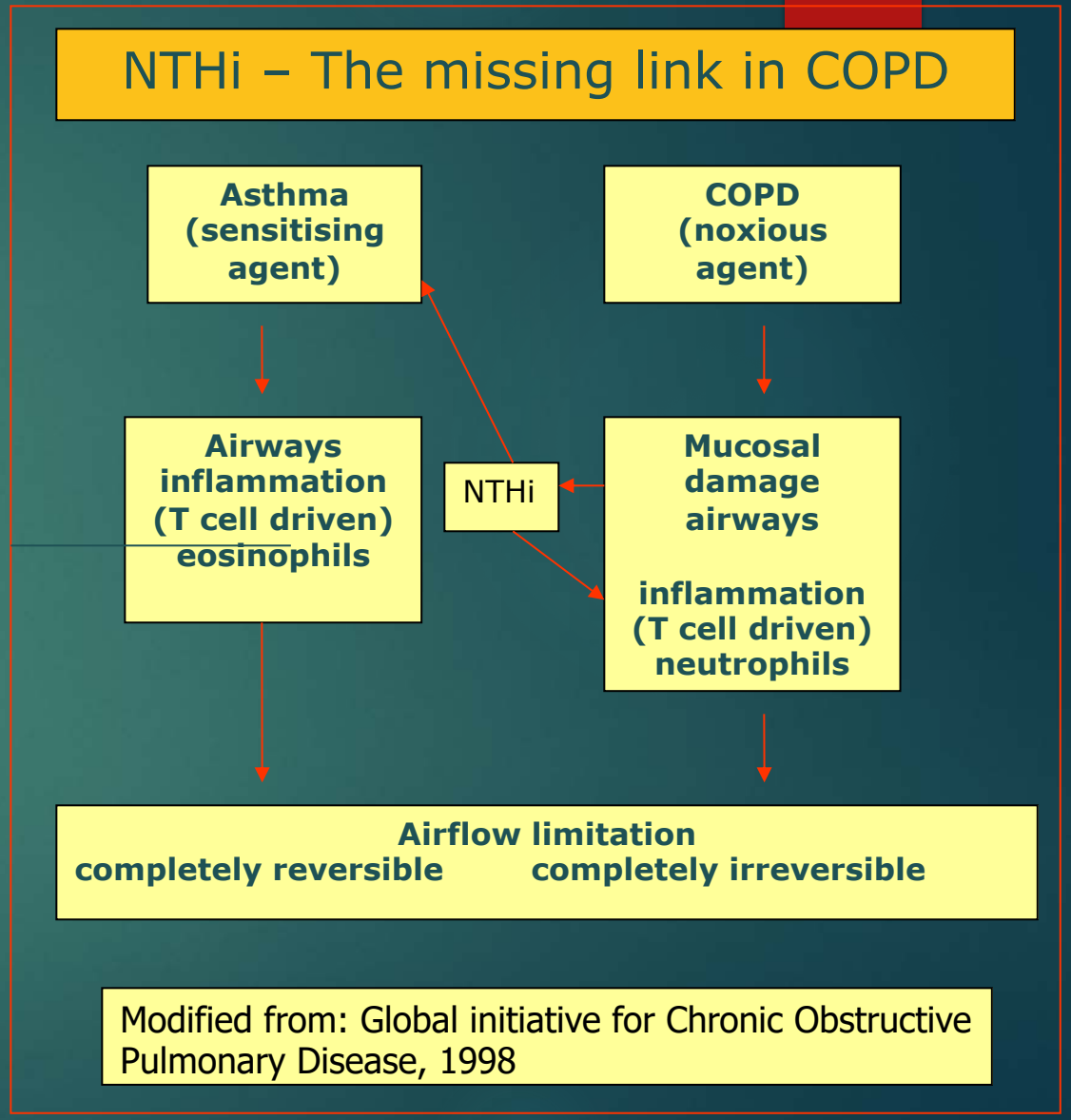
- arguably the greatest unmet medical need
- globally 20% over 60 y.o. have COPD
- major cause of medical hospital admissions (UK)
- $US18billion dollars/year (USA)
- 4th most common cause of death (global)
- existing therapy: costly, inconvenient, and of marginal clinical value. No distinct reduction in hospital admission (and attendant major costs)

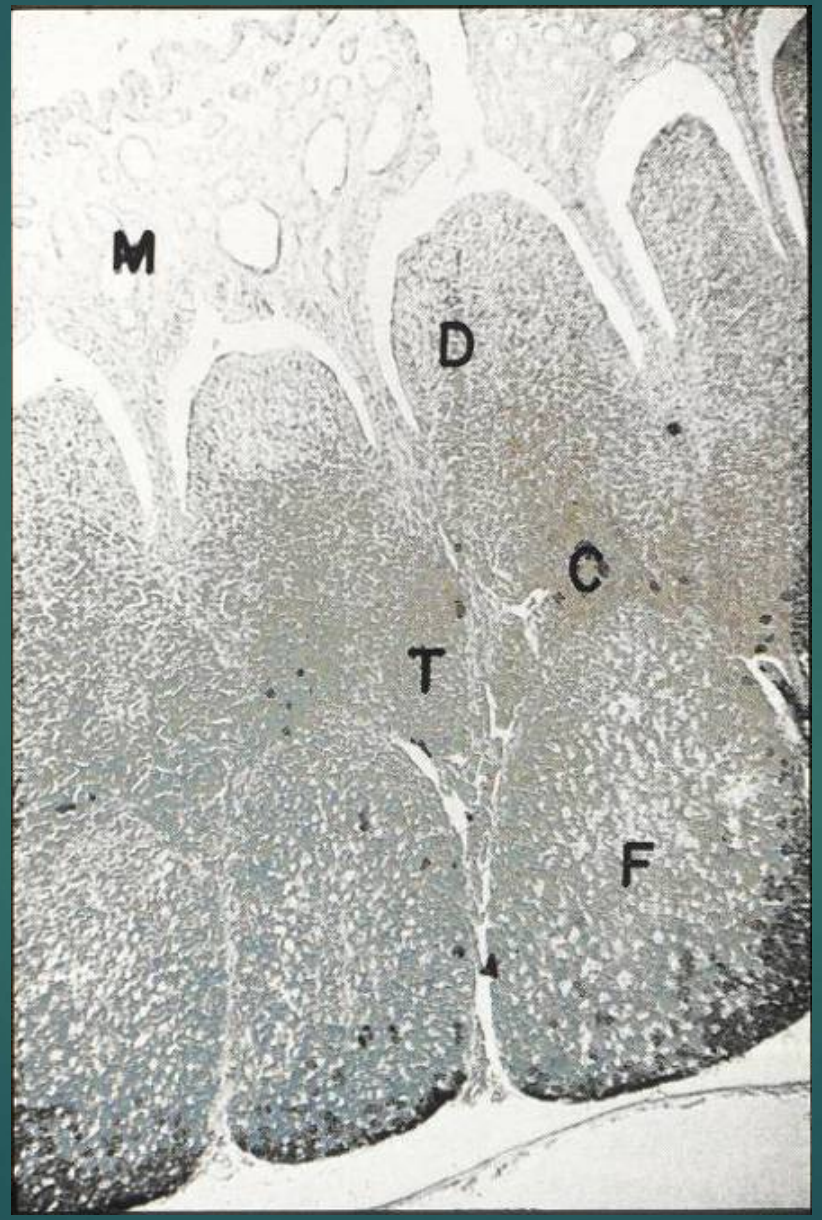
Influenza + NTHi → mutual stimulation

Oral Immunisation with NTHi abrogates increase in both flu and NTHi

Context : Peyers patch – dependent airways protection

Oral Immunisation with NTHi prevents virus-induced exacerbations of COPD

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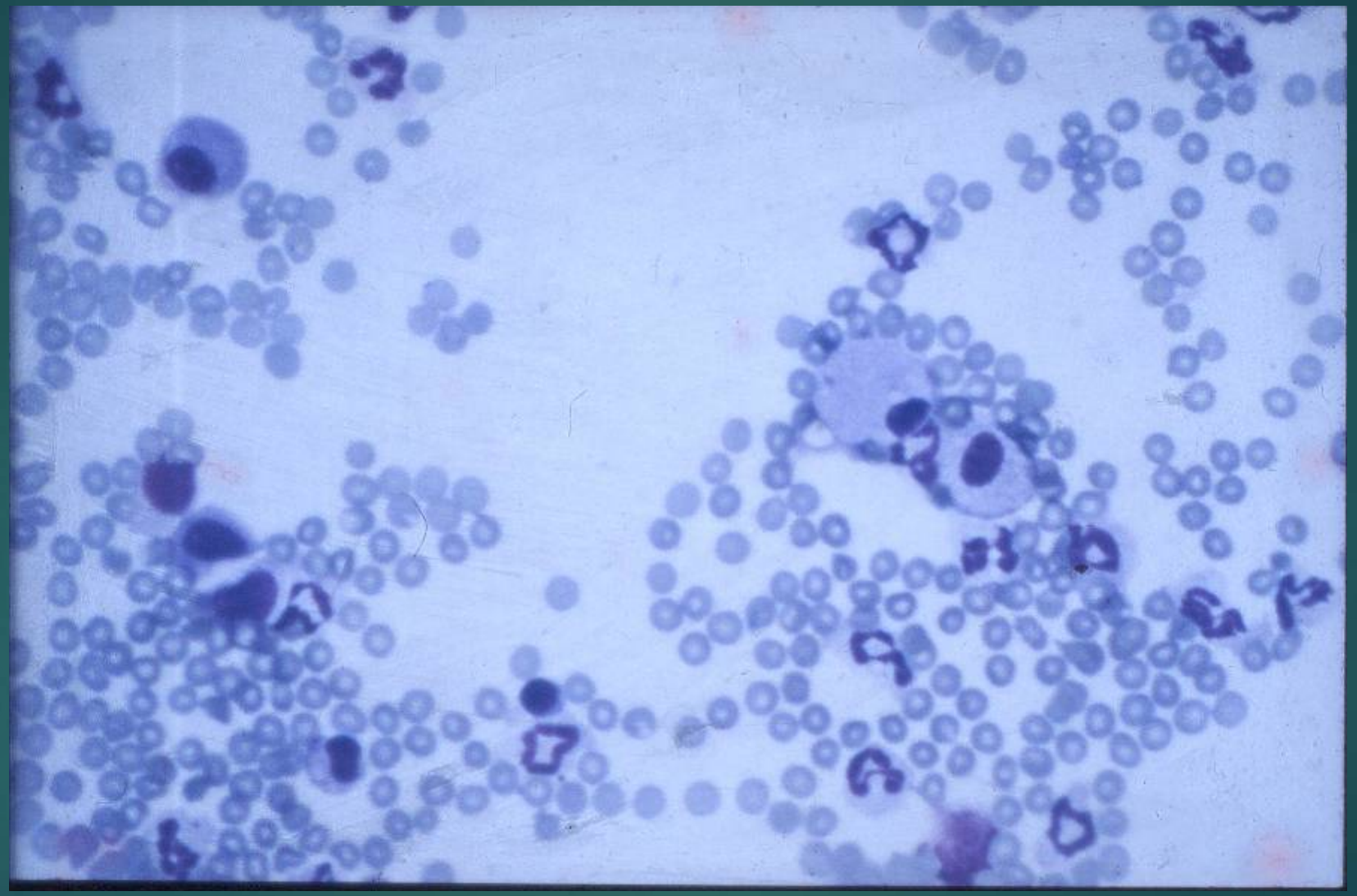
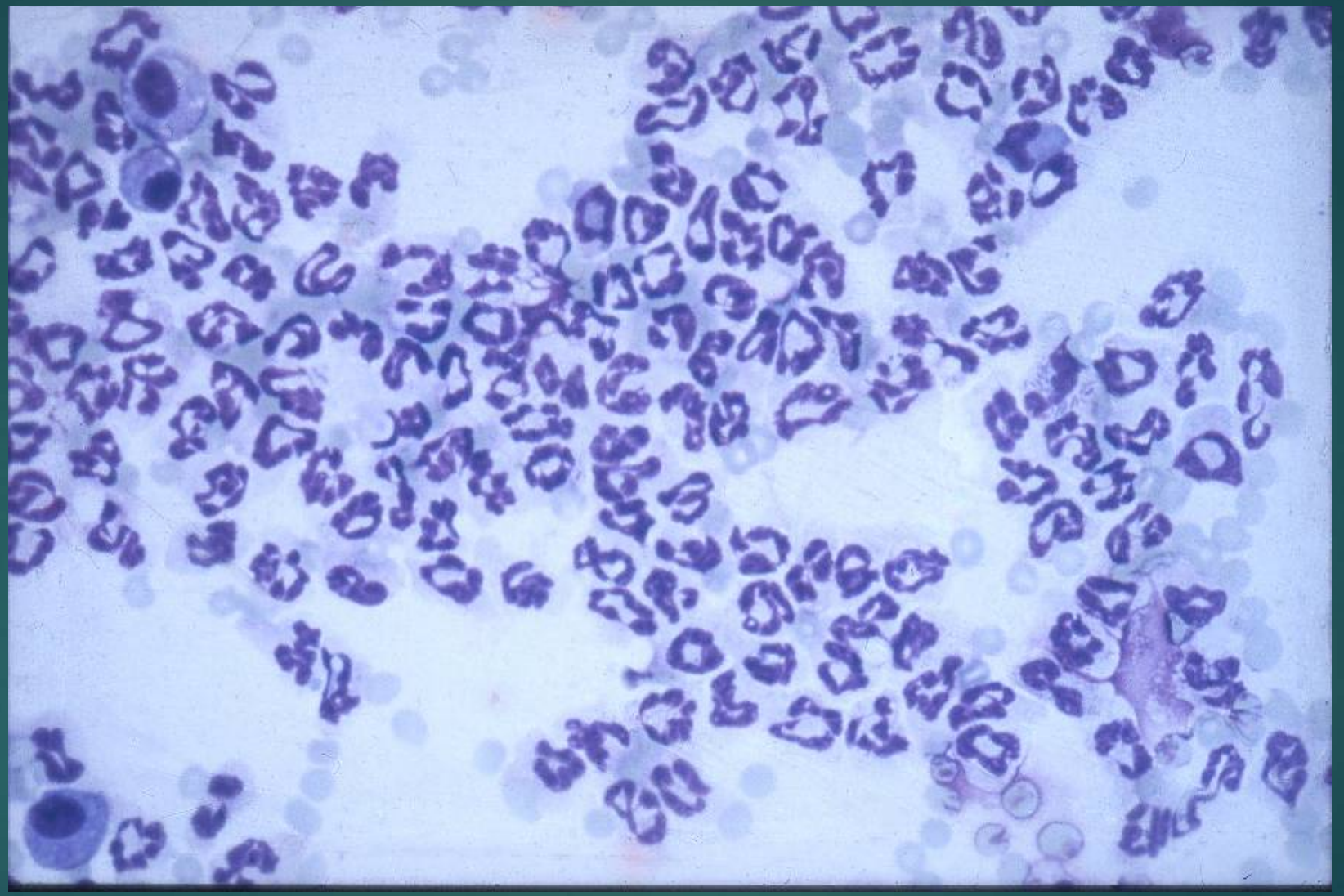
Obstructive Pulmonary



Washings post intratracheal NTHi from rat bronchus following i/v injection of thoracic duct T cells from placebo-fed donor

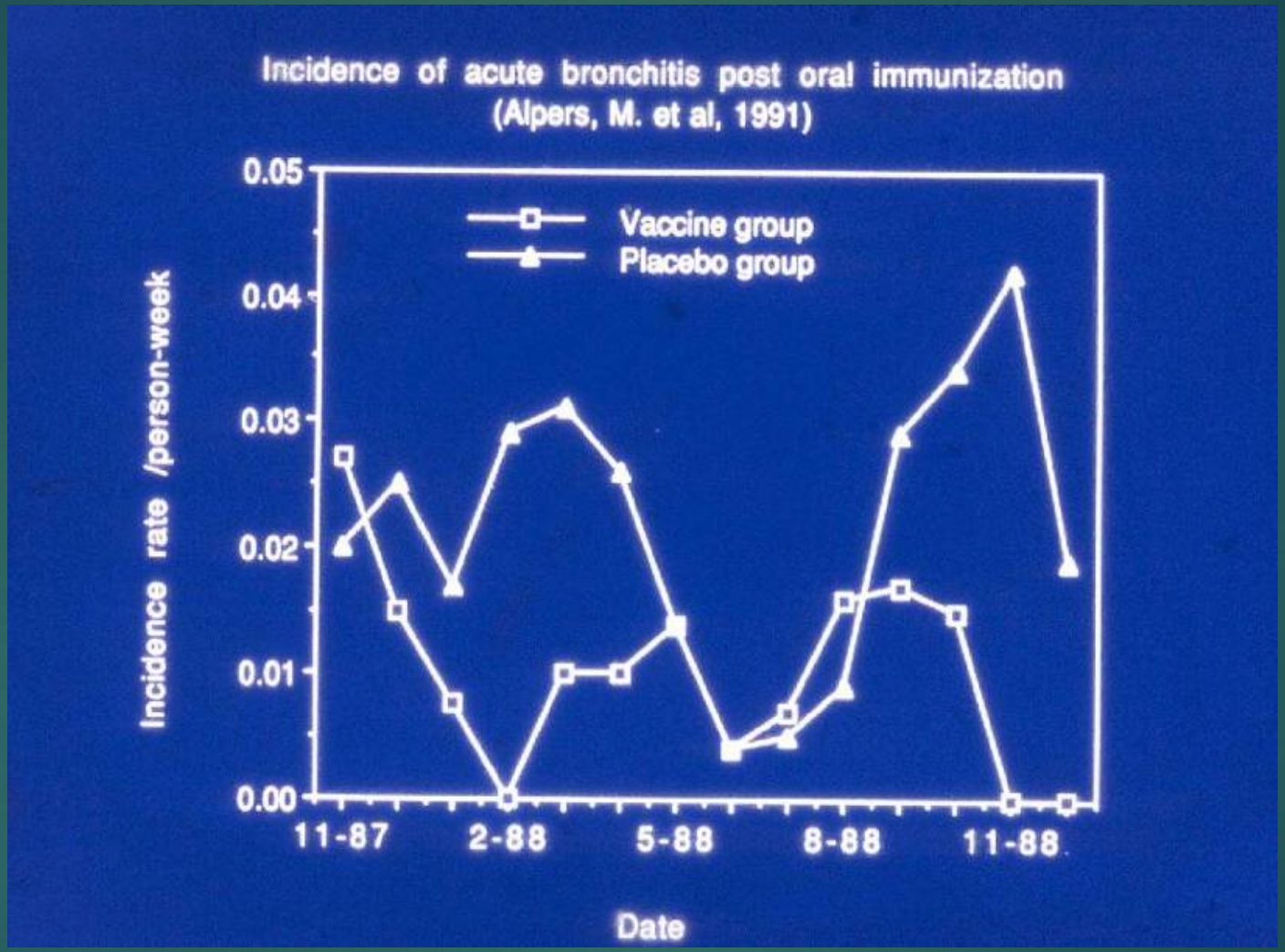


Washings post intratracheal NTHi from rat bronchus following i/v injection of thoracic duct T cells from NTHi-fed donor

Table 1. Summary of published data of NTHi oral immunotherapy studies in chronic bronchitis conducted before 1990

[a] Percentage of study subjects with a positive NTHi sputum culture, [b] Percentage of study subjects protected against acute exacerbations

Reference	Publication (year date)	Number in Study (n)	Mean Age (years)	FEV_1 (L/sec)	+ve NTHi [a] (%)	Protection [b] (%)	P value
1	1985	50	65	0.9	69	90	< 0.001
12	1991	64	72	0.9	36	30	<0.05
13	1991	62	53	1.4	81	45	<0.05



Lehmann et al. Reduction in the incidence of acute bronchitis by an oral *Haemophilus influenzae* vaccine in patients with chronic bronchitis in the Highlands of Papua New Guinea. Am Rev Resp Dis. 1991; 144: 324-330.

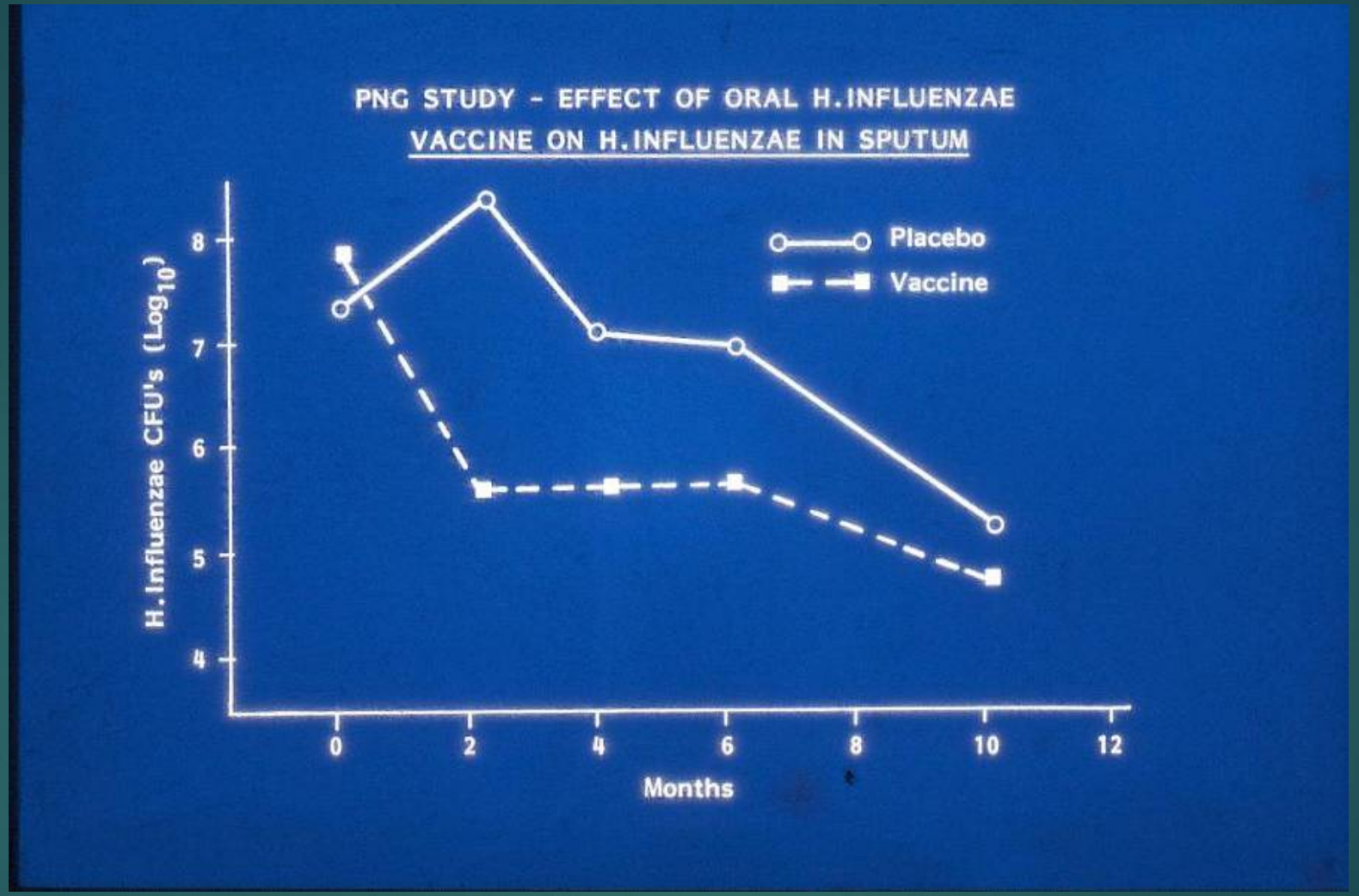


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Table 3. Protection against acute exacerbations of COPD by an oral whole killed cell NTHI immunotherapy[[24 and unpublished data]. This study was conducted in 2 parts. Previously only data from 38 subjects with moderate/severe exacerbations ($FEV_1 \leq 50\%$ of normal) were published. [24]. Here all subjects with $FEV_1 \leq 70\%$ are included.

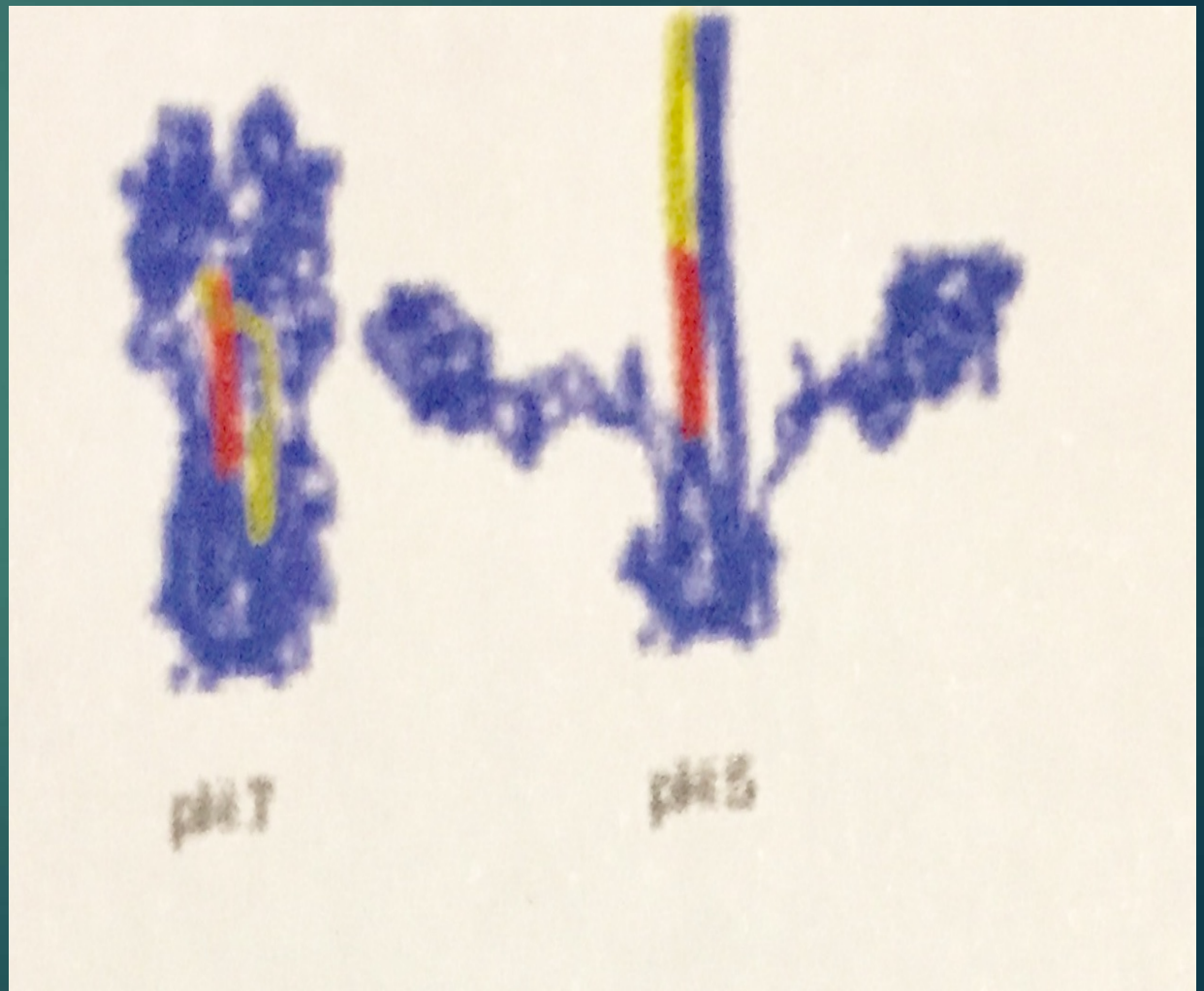
	Oral immunotherapy	Placebo	Protection (%) [a]	P value
Number of study subjects	68	72		
Exacerbations (all) [b]	1.10 [f]	1.50 [f]	26	0.09
Moderate exacerbation [c]	0.46 [f]	0.85 [f]	46	0.01
Severe exacerbation [d]	0.06 [f]	0.22 [f]	74	0.01
All hospital admissions [e]	0.09 [f]	0.29 [f]	70	0.003

[a] Percentage of study subjects protected against acute exacerbations. [b] Increase in cough and purulent sputum. [c] Increase in cough and purulent sputum

AUS BIO COMPOUND MD185 : Induces conformational Change in Haemagglutinin

- Reduces Plaque Formation
- Prevents Death in Mice
- Protects Ferret Airways from Infection

Note: Current anti-viral drugs block protein function. MD185 reproduces low pH of endosomes to prevent Haemagglutinin binding to sialic acid on cell surface



SUMMARY (1)

- Vaccines give protracted immunity if IgG memory to TOXINS or OBLIGATORY Blood Phase (eg Viraemia)
- Vaccines give poor response if: immune response and pathogen not matched/poor memory developed/regional disparity
- Need to develop vaccine strategy in relation to pathogenesis

SUMMARY (2)

- INFLUENZA :

- (I) Immune Senescence
- (ii) Global Memory : CD8+T Cell/B Cell/HLA
- (iii)Origional Sin
- (iv)Flu/NTHi symbiosis
- (v)Prevent virus cell entry