



From Genes to Communities – Improving Child Health through Research & Education

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Chair Professor of Paediatrics

Doris Zimmern Professor in Community Child Health

LKS Faculty of Medicine, The University of Hong Kong



家姐代母職 (1960)



制水時期 (1961)



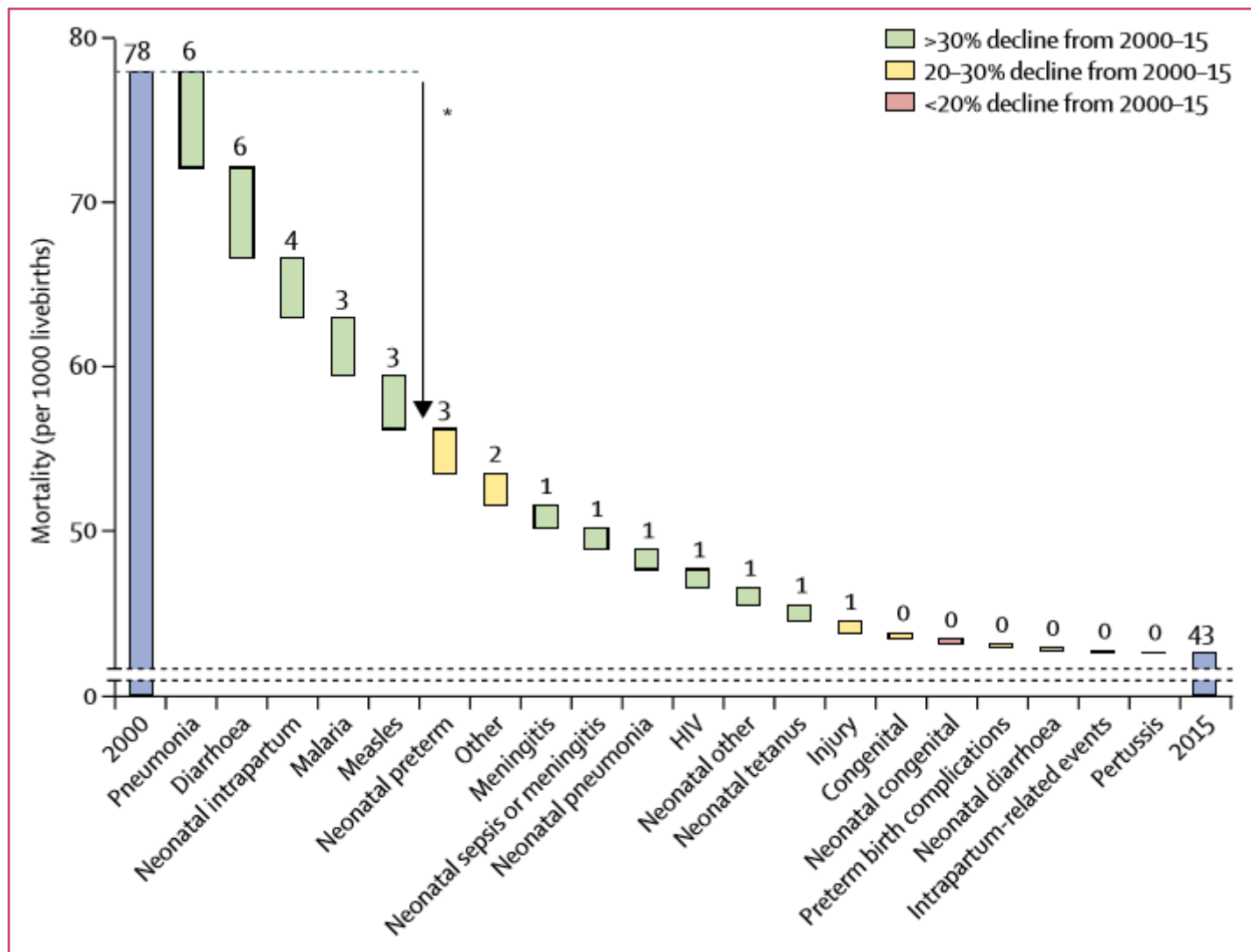
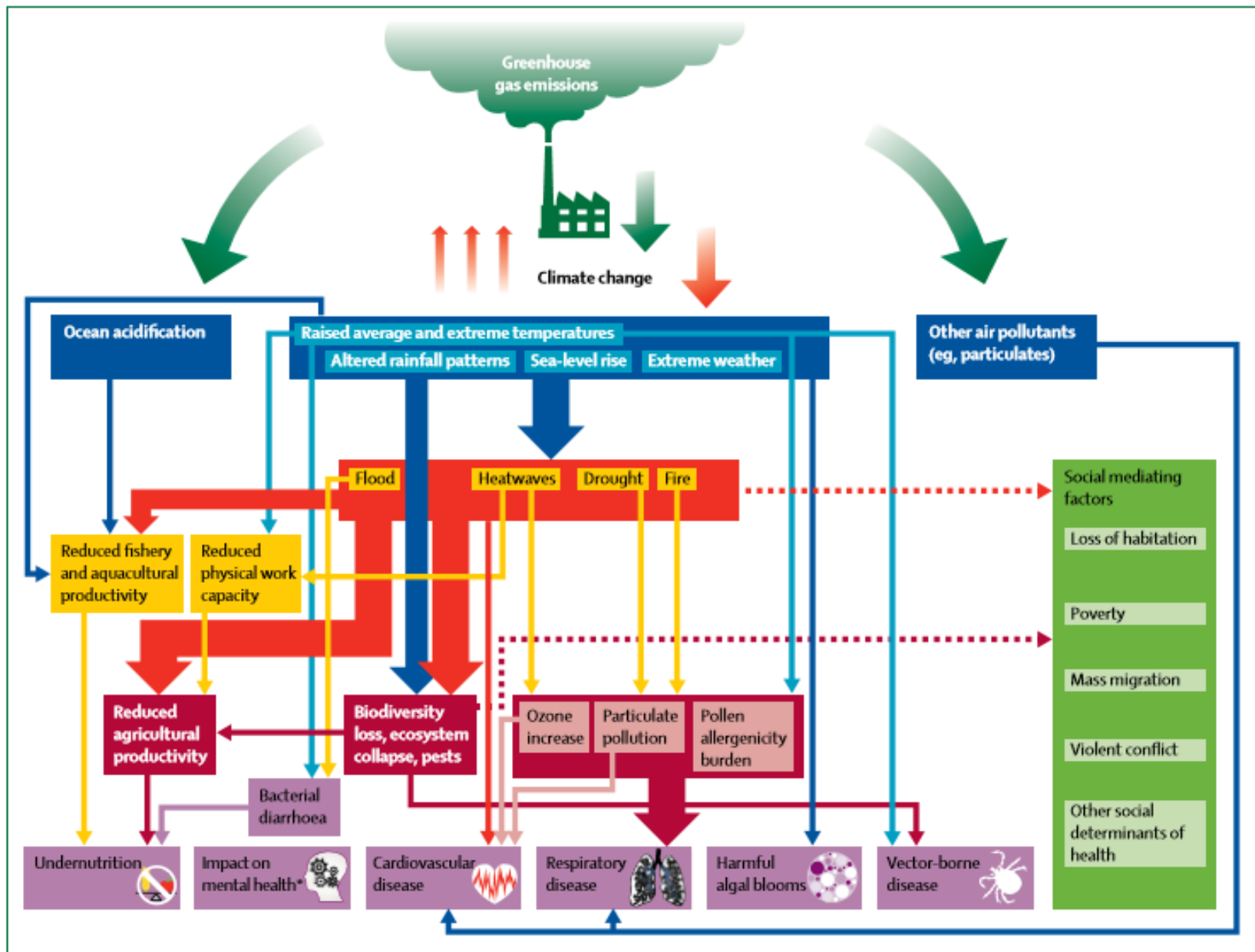


Figure 2: Global trends in cause-specific mortality rates in neonates and children aged 1-59 months, 2000-15

*About 61% of the reduction comes from pneumonia, diarrhoea, malaria, and measles among 1-59-month olds and neonatal intrapartum related events.

The health impacts of climate change





SUSTAINABLE DEVELOPMENT GOALS

1 NO POVERTY



2 ZERO HUNGER



3 GOOD HEALTH AND WELL-BEING



4 QUALITY EDUCATION



5 GENDER EQUALITY



6 CLEAN WATER AND SANITATION



7 AFFORDABLE AND CLEAN ENERGY



8 DECENT WORK AND ECONOMIC GROWTH



9 INDUSTRY, INNOVATION AND INFRASTRUCTURE



10 REDUCED INEQUALITIES



11 SUSTAINABLE CITIES AND COMMUNITIES



12 RESPONSIBLE CONSUMPTION AND PRODUCTION



13 CLIMATE ACTION



14 LIFE BELOW WATER



15 LIFE ON LAND



16 PEACE, JUSTICE AND STRONG INSTITUTIONS



17 PARTNERSHIPS FOR THE GOALS



SUSTAINABLE DEVELOPMENT GOALS

Sustainable Development Goal 3.2

Calls for ending

“preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce under-5 mortality to at least as low as 25 per 1000 live births” by 2030

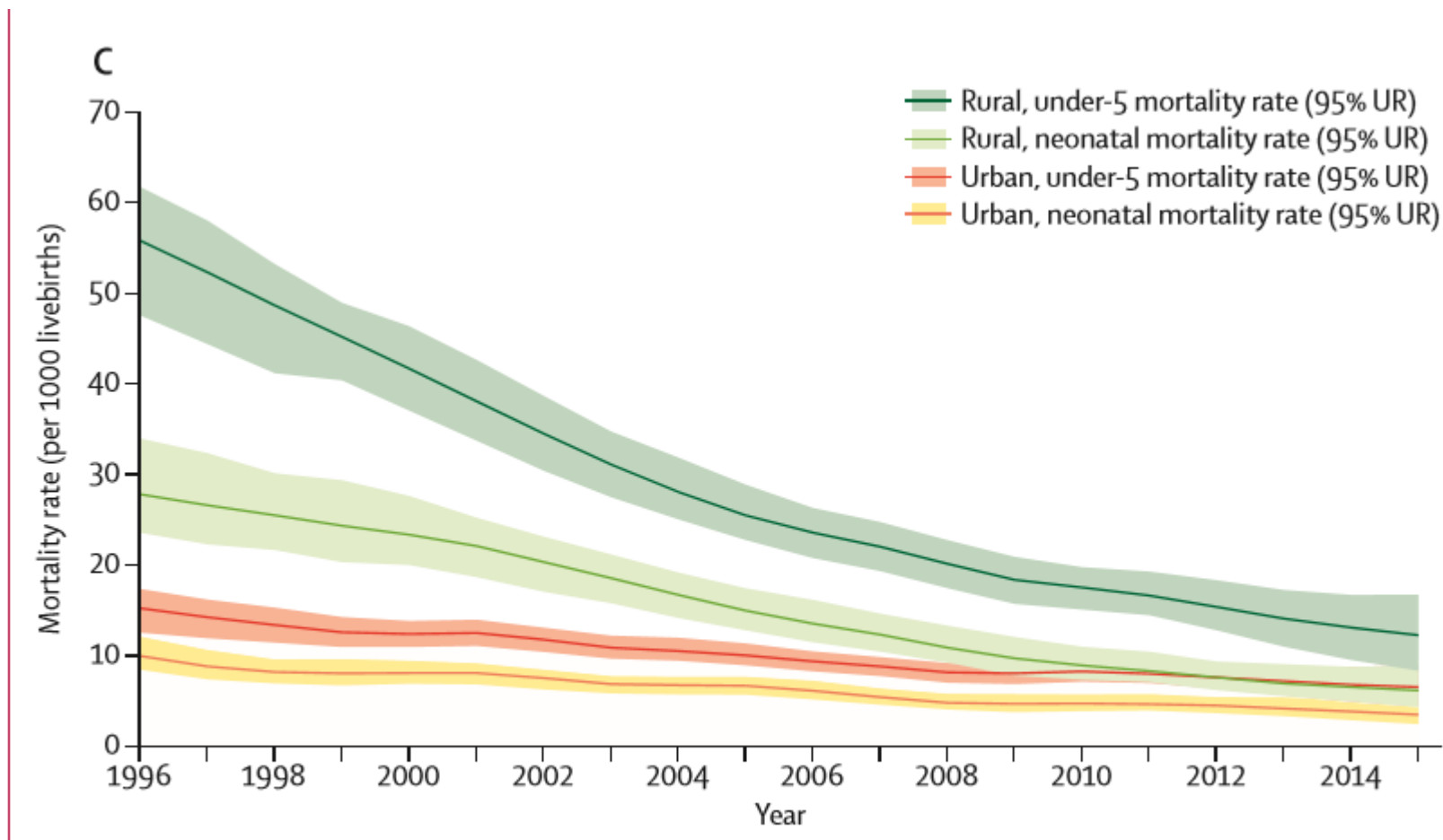


Figure 2: Age-specific mortality rates in children younger than 5 years in China, 1996–2015
 (A) National. (B) By region. (C) By residency. UR=uncertainty range.

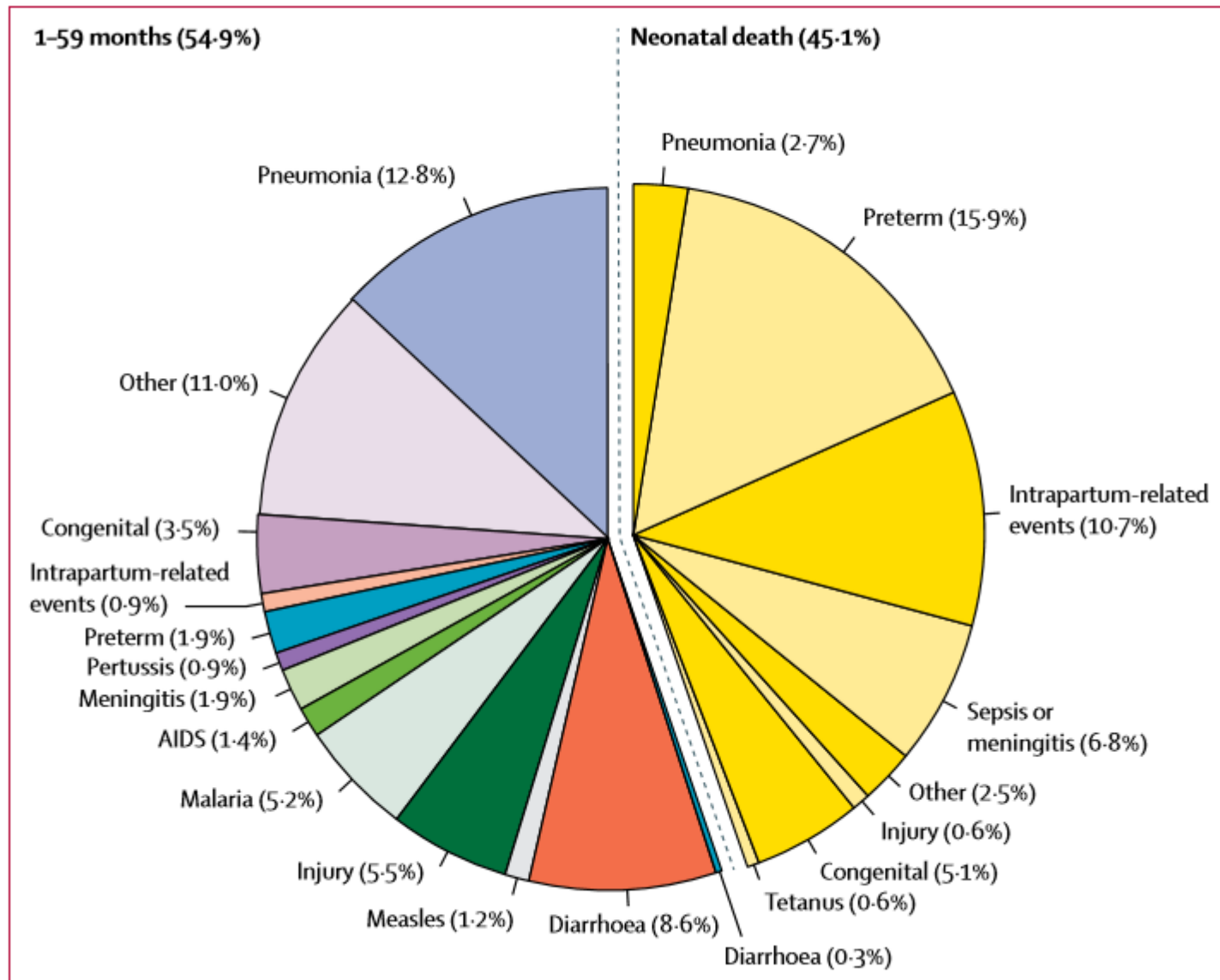


Figure 1: Global causes of under-5 deaths in 2015



Definition of Rare Disease

A disease of low prevalence

Defined in USA, <200,000 people (≤ 1 in 1,500)
in Europe, diseases of such low prevalence that special combined efforts
needed to address them (≤ 1 in 2,000)

Rare Disease Act 2002
European Commission

EURORDIS – Rare Disease Europe

- Individual disease might be labelled as “rare”
- With 6000 to 7000 different rare diseases, 30 million Europeans have rare disease (6% to 8% of EU population)
- 80% of rare diseases are genetic, affecting 3% to 4% of birth

EURORDIS 2005

Primary Immunodeficiencies (PID)

- Inborn errors of the immune system



David Vetter, born with X-linked SCID, lived 12 years in a sterile bubble (1972 – 1984)

Challenges in the care for rare diseases

- **Lack of knowledge & recognition**
- **Lack of access to diagnostic tests**
- **Lack of referral network for treatment**
- **High cost of drugs and care**
- **Inequities in availability of treatment & care**

Asian PID Referral Network: Mission

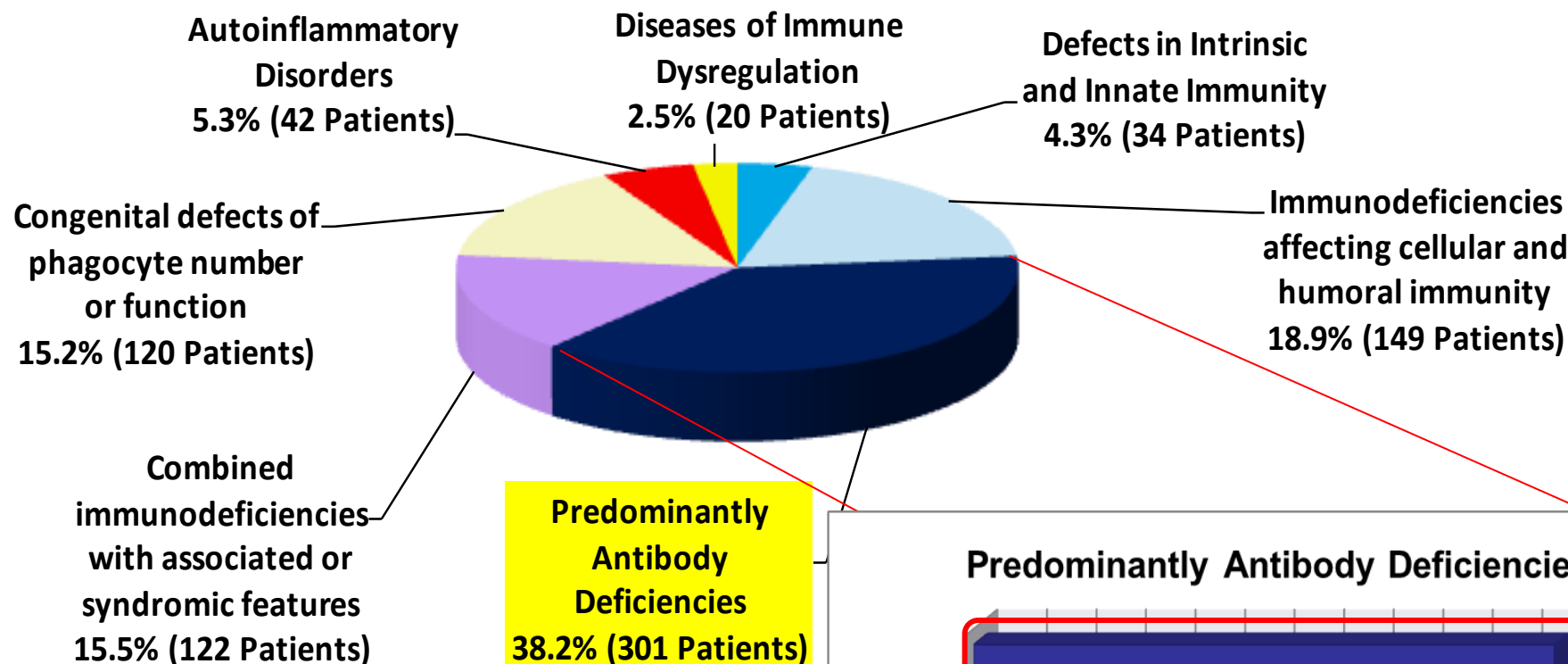
- To help patients and families affected by PIDs, by providing genetic testing for confirmation of diagnosis and carrier screening
- To facilitate sharing of experience among clinicians caring for patients with PIDs
- To promote multi-center collaboration to characterize the phenotypic and molecular features of PIDs in the Asian population

ANNALS of the New York Academy of Sciences 2011; 1238:33-41
Cellular & Molecular Immunology 2009;6(6):397-406
Stiehm's textbook

Asian PID Network

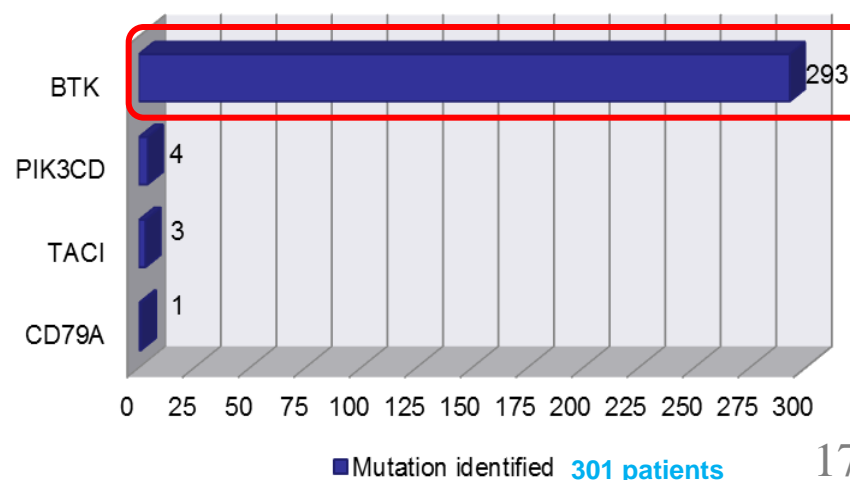


Asian PID Referral Network

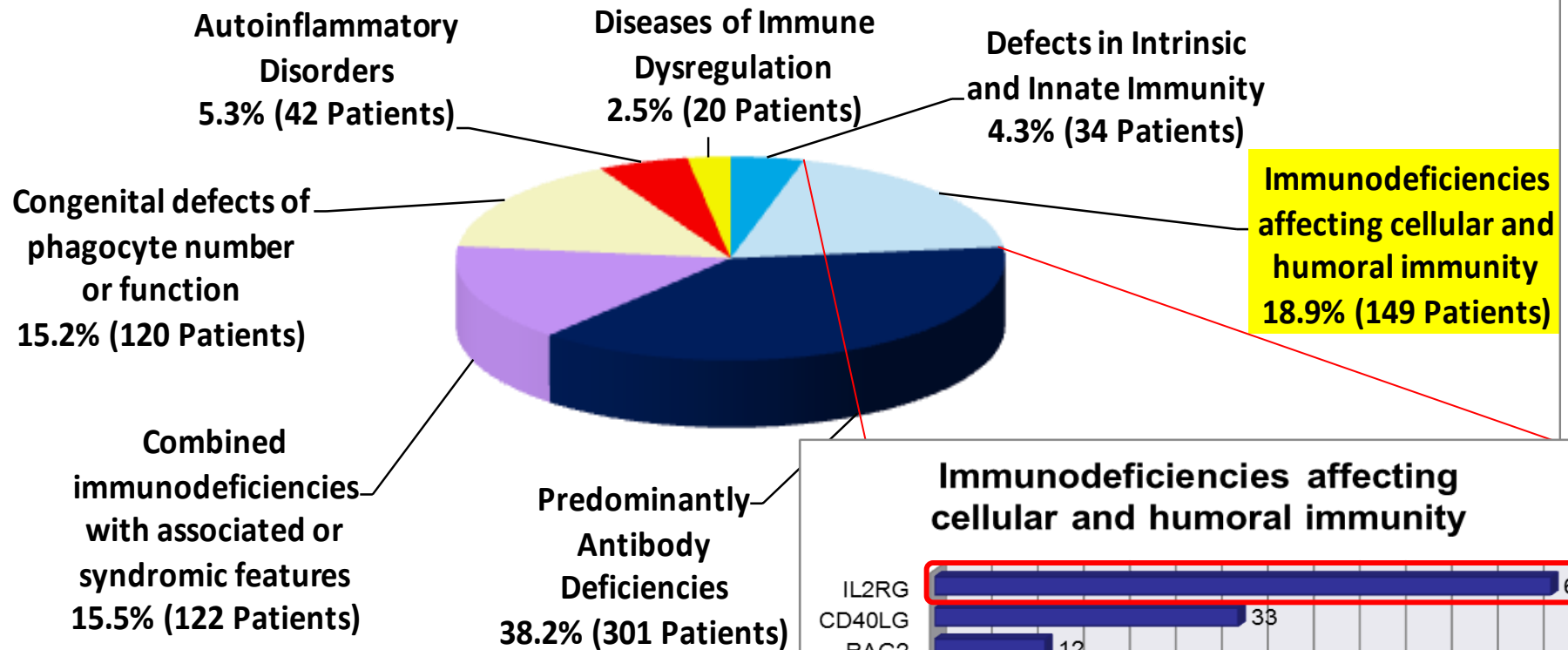


Patients referred: 1605
Patients with PID tests done: 1317
(Total 2252 PID tests done):
Patients with mutation identified: 788

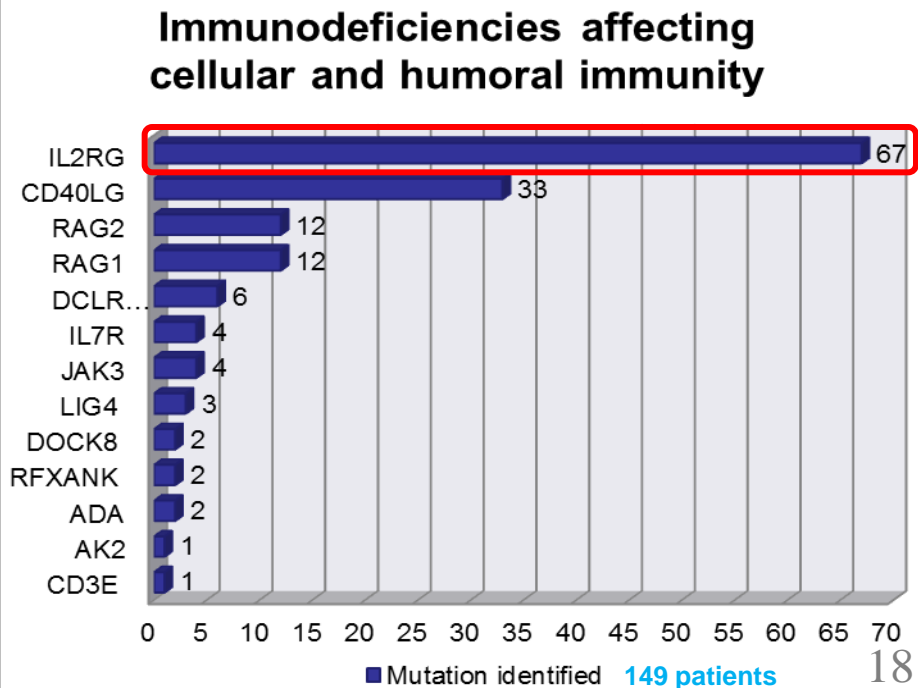
Predominantly Antibody Deficiencies



Asian PID Referral Network



Patients referred: 1605
Patients with PID tests done: 1317
(Total 2252 PID tests done):
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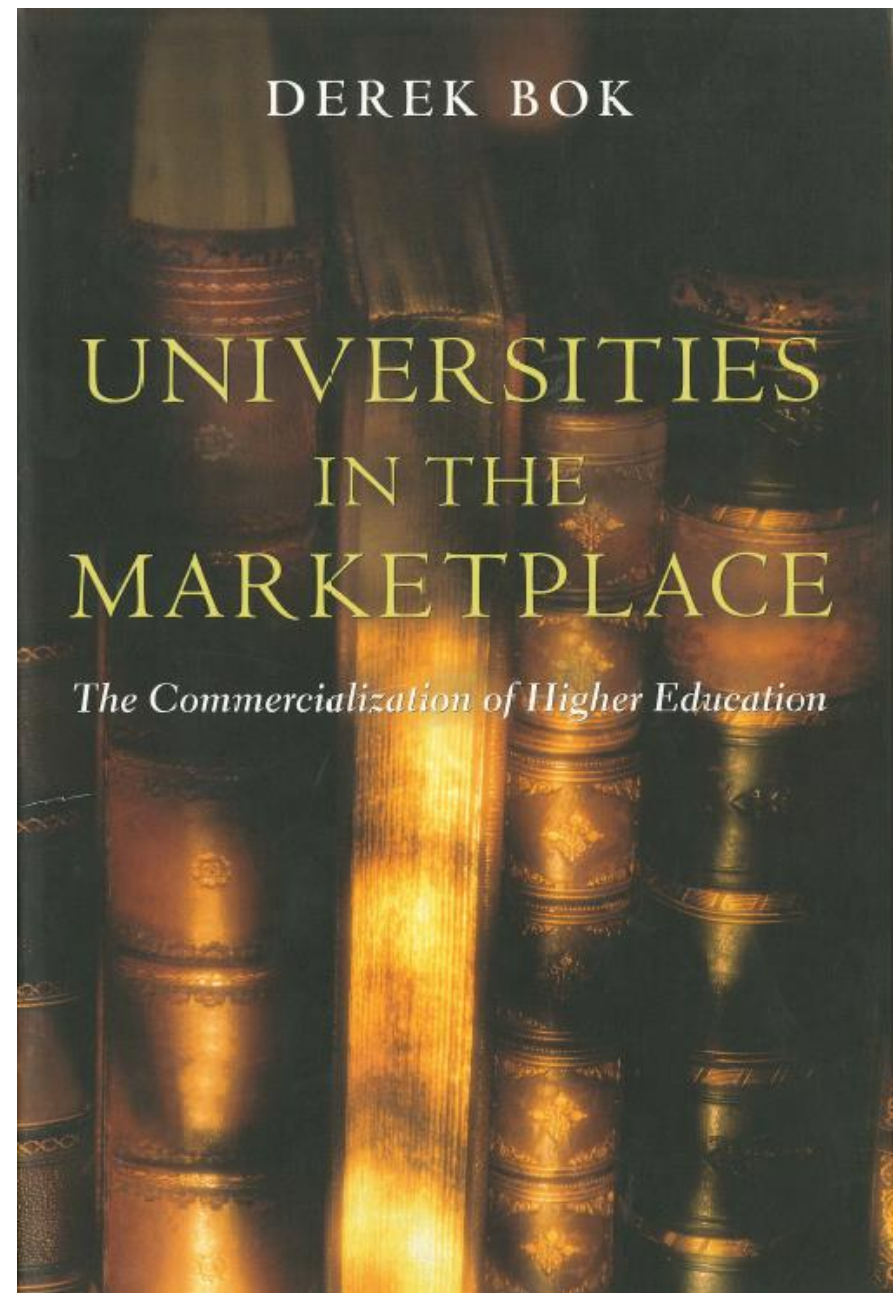


Inauguration of Asia Pacific Society for Immunodeficiencies in 2016





“Sold my soul to the devil, but held on to the intellectual property rights.”





Dr Maurice Leung Ping



Dr Cheong Kai Ning



Nurturing curiosity



學問 = Learning to ask questions

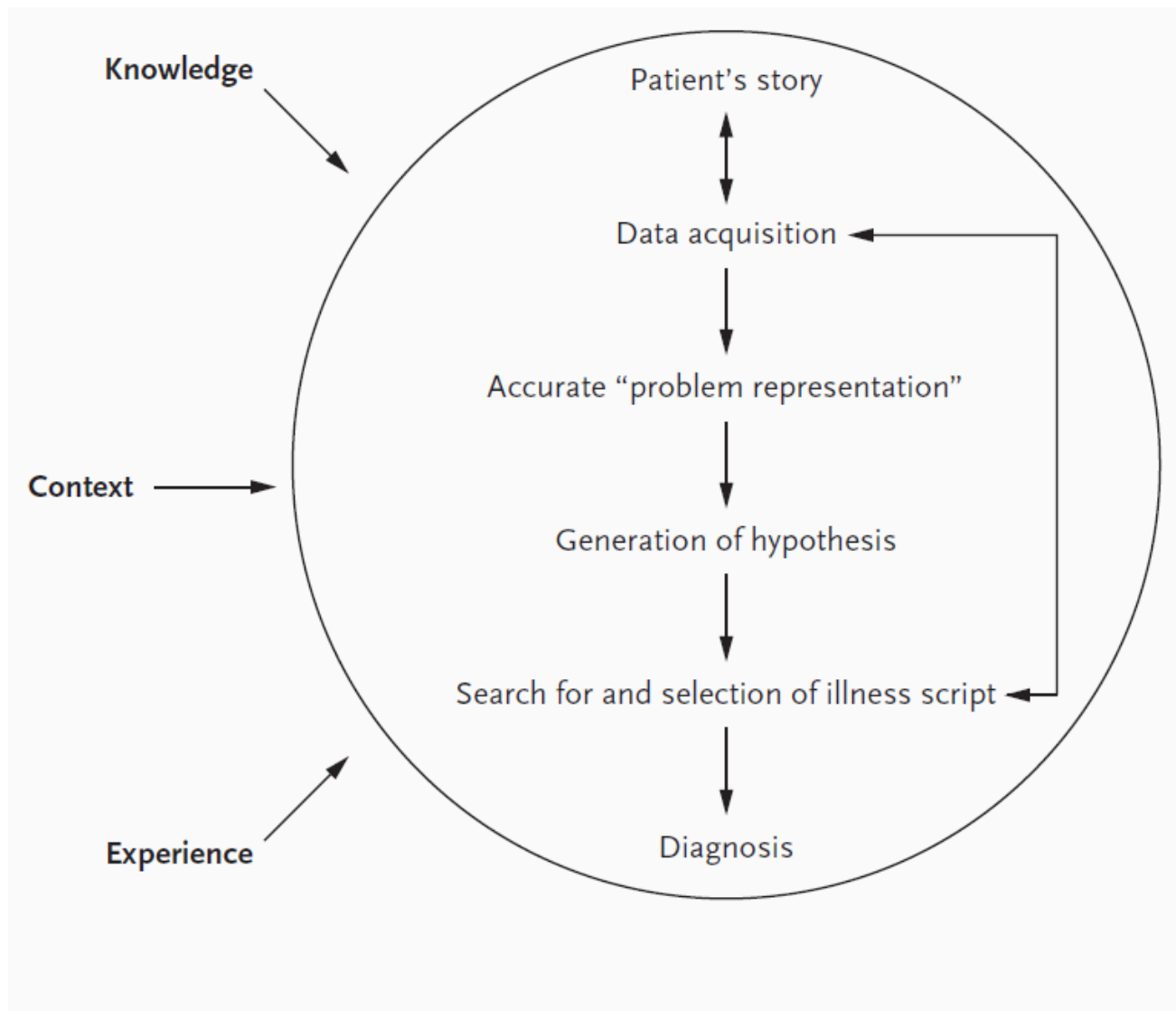


Figure 1. Key Elements of the Clinical Diagnostic Reasoning Process.

WHAT IS IT?

YOU SAID
TO DO AN
ABSTRACT



Definition of Scientific Misconduct

Scientific misconduct is fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.

(Federal Register, October, 1999)

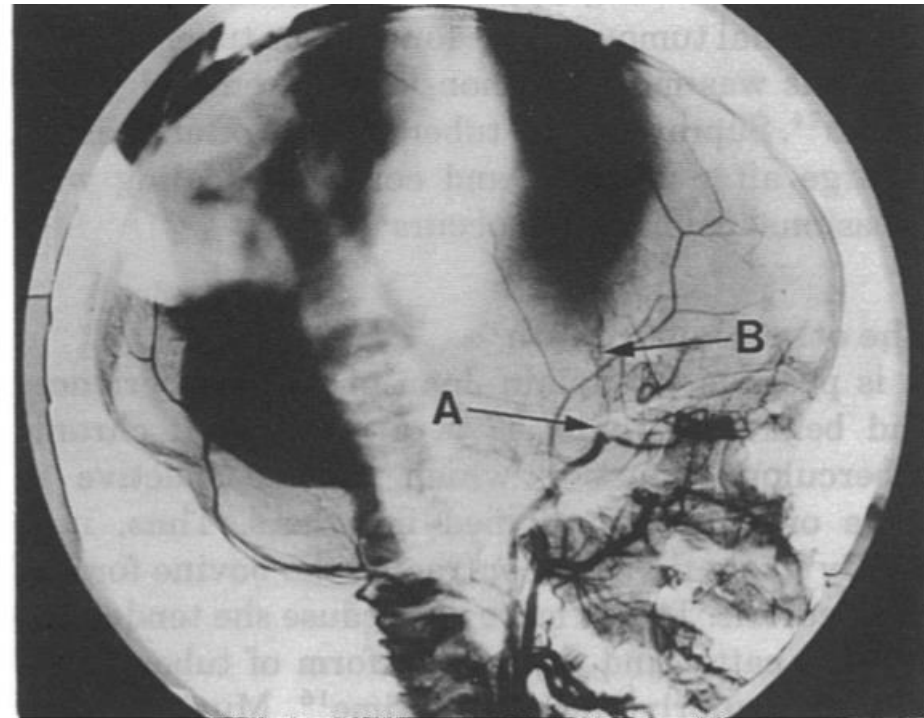


Case presented to
Clinical Section,
8 November 1985

**Atypical presentation of
craniopharyngioma associated
with Moyamoya disease**

Y L Lau MRCP D W A Milligan MRCP
Newcastle General Hospital, Newcastle upon Tyne

- A boy presented with focal seizure of left arm at 21 months, CT brain normal.
- Recurrent transient left hemiparesis from 3 years old, associated with crying during bath time
- CT showed a suprasellar mass
- Cerebral angiography showed occlusion of Rt ICA

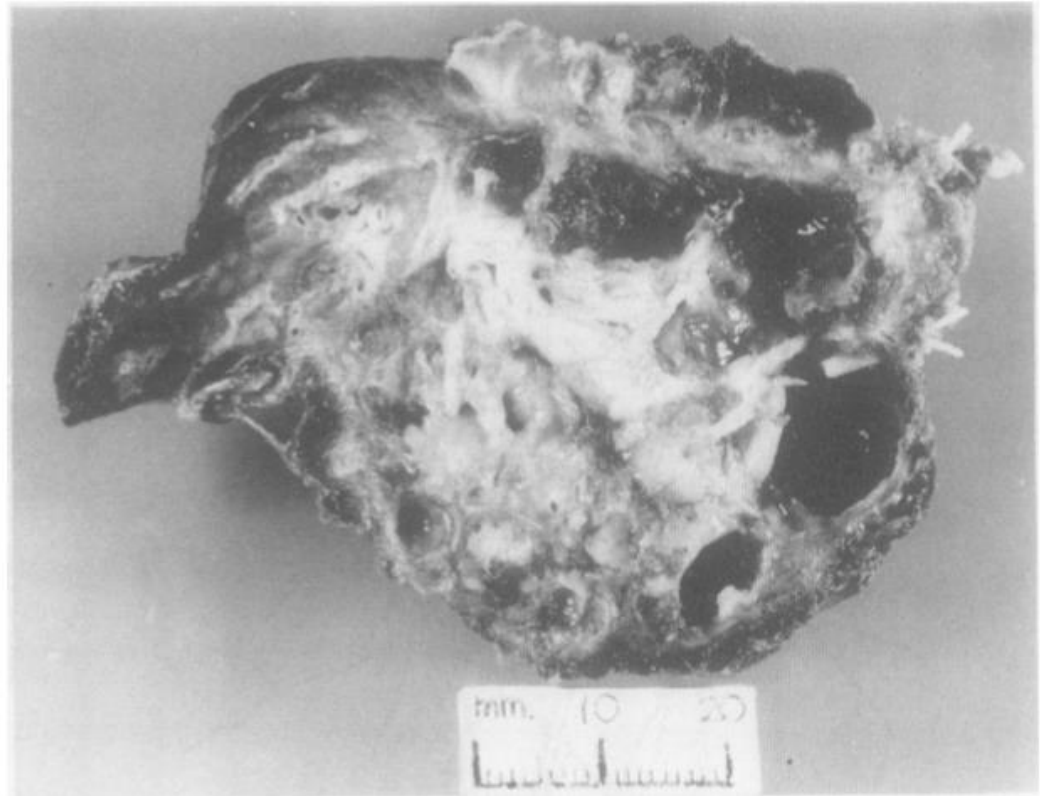


A case of middle lobe pulmonary sequestration

Y L LAU, J M RADHI, A BLESOVSKY, A S HUNTER

From the Departments of Paediatric Cardiology, Cardiothoracic Surgery, and Pathology, Freeman Hospital, Newcastle upon Tyne

- An 8-month old girl presented with **persistent right-sided pneumonia** and heart failure
- Intralobar sequestration in which the unusual location and anatomical features support the concept of a “sequestration spectrum”



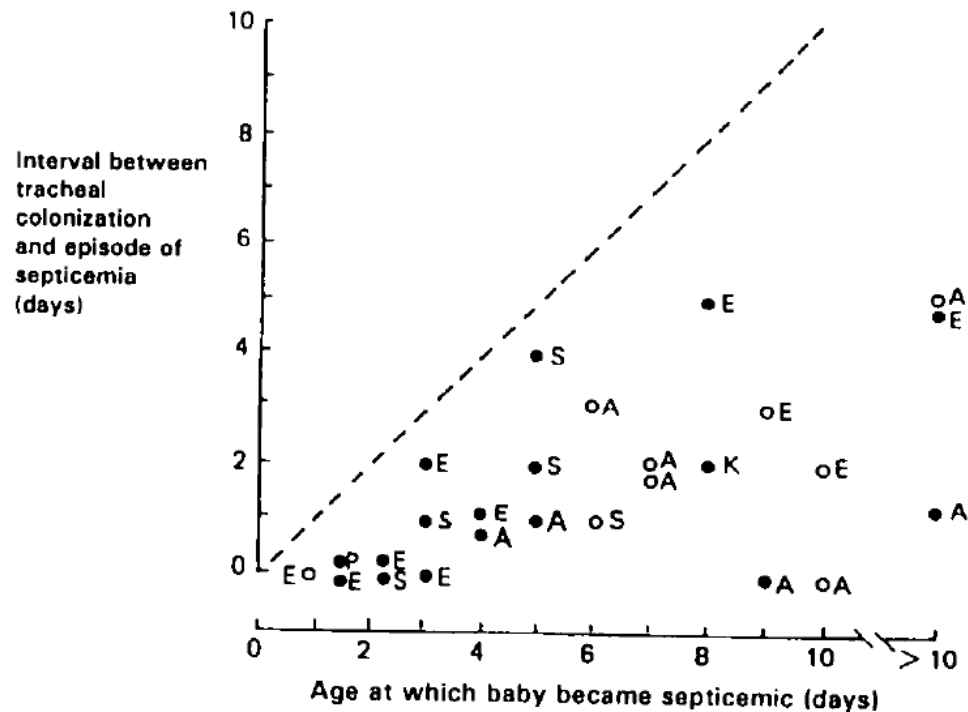
Sensitivity and specificity of daily tracheal aspirate cultures in predicting organisms causing bacteremia in ventilated neonates

YU LUNG LAU, MD AND EDMUND HEY, FRCP

Because of low positive predictive value (0.26) the role of daily tracheal aspirate culture is limited to providing early information regarding potential pathogens when sepsis occurs rather than to identify babies who are going to become septic.



**Edmund Hey
(1934 – 2009)**



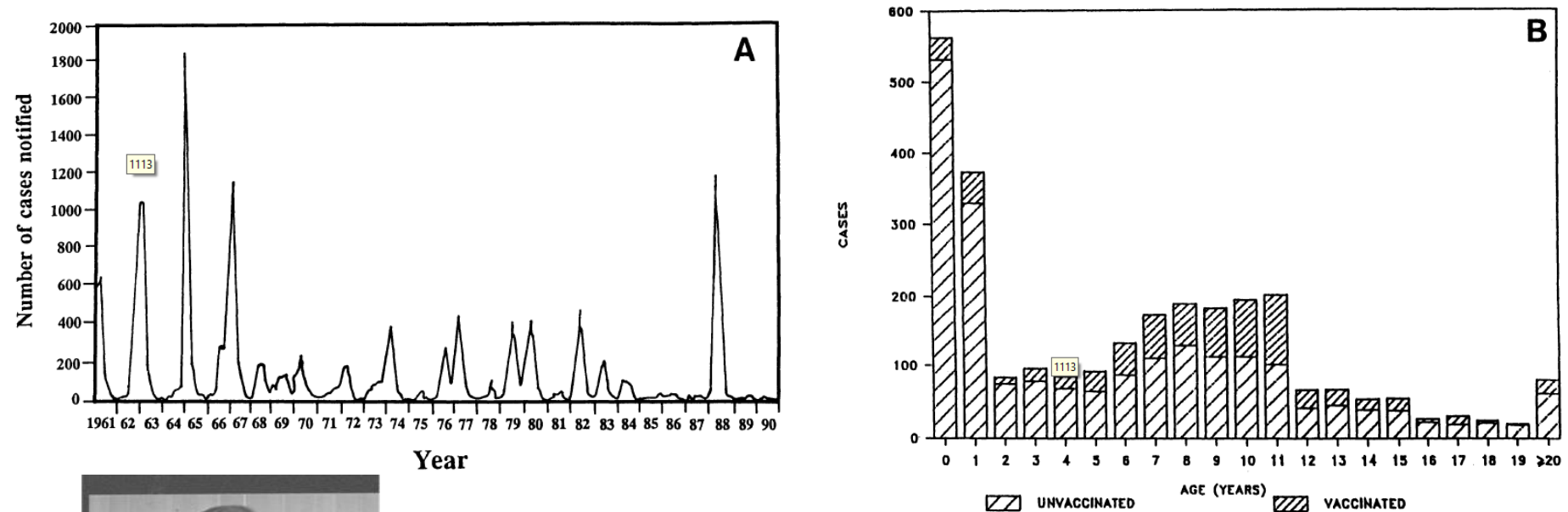
Response of preterm infants to hepatitis B vaccine

Yu-Lung Lau, MD, Alfred Y. C. Tam, FRCP, K. W. Ng, PhD, N. S. Tsoi, MRCP, Barbara Lam, MRCP, Paul Lam, MRCP, and C. Y. Yeung, FRCP

Ninety-nine preterm infants with birth weights <1750 gm had three doses of hepatitis B vaccine. Fifty-seven received the first dose when they weighed ≥ 1000 gm (group 1) and 42 when they weighed ≥ 2000 gm (group 2). The final seropositive rates and geometric mean titers of group 1 infants (79%, 61 mIU/ml) and group 2 infants (91%, 262 mIU/ml) were less than that of 43 normal term infants (100%, 679 mIU/ml). (J PEDIATR 1992;121:962-5)

Changing Epidemiology of Measles in Hong Kong from 1961 to 1990—Impact of a Measles Vaccination Program

Yu-Lung Lau, Chun-Bong Chow, and Ting-Hung Leung



Bill Marshall
(1929-1983)

Figure 1. A, Monthly measles notifications, Hong Kong, 1961–1990. B, Age distribution of measles cases, by immunization status, Hong Kong, 1988.

Invasive *Haemophilus influenzae* type b infections in children hospitalized in Hong Kong, 1986–1990

YL Lau¹, LCK Low¹, R Yung², KW Ng³, CW Leung⁴, WH Lee⁵, A Ho⁶, SJ Oppenheimer⁷ and the Hong Kong Hib Study Group

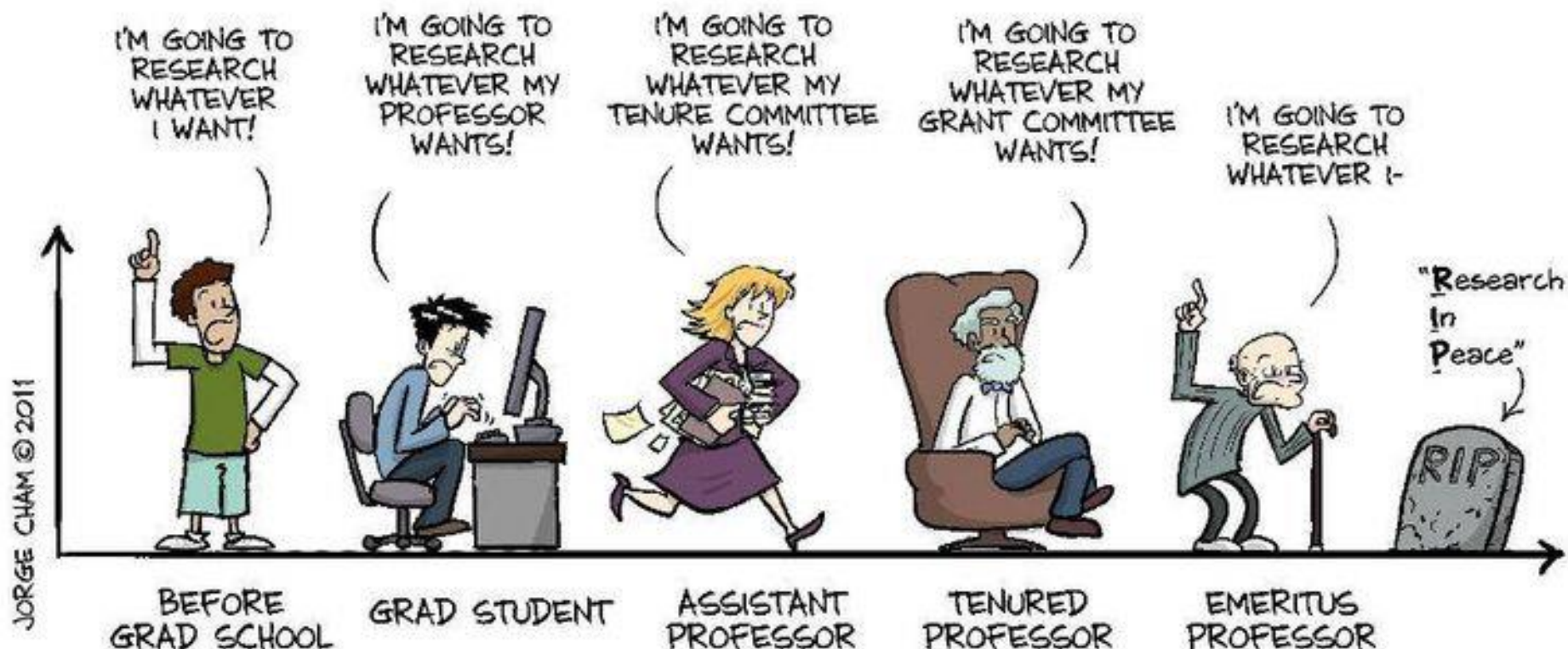
- **The annual incidence for children less than 5 years old was 2.7 per 100,000 (95% confidence interval (CI) 2.0-3.5). Of the 57 cases, 39 were Chinese and 18 non-Chinese (7 Vietnamese refugees, 6 Caucasians, 5 others)**
- **The annual incidence in Vietnamese refugees less than 5 years old was 42.7 per 100,000 (95% CI 17.2-87.9), giving a relative risk of 18.5 (95% CI 8.3-41.0).**

Confirmed and probable Hib meningitis in Korea & Vietnam

- **6 per 100,000 < 5 years in
Jeonbuk Province, Korea (1999 to 2001)**
- **12 per 100,000 <5 years in
Hanoi, Vietnam (2000 to 2002)**

Vaccine 2004; 3953-62
Am J Trop Med Hyg 2006; 508-515

THE EVOLUTION OF INTELLECTUAL FREEDOM

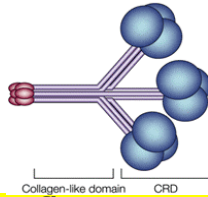


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Influenza Immunity

Innate

- **MBL:**



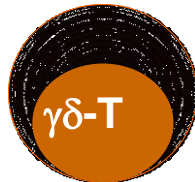
Deleterious inflammatory response in pandemic H1N1 infection

- **NK cells:**



Direct infection & suppression by influenza virus.

- **gdT cells:**



Kill virus-infected cells *in vitro* & protect humanized mice from infection *in vivo*

Activation by phosphoantigen

Adaptive

- **CTL:**



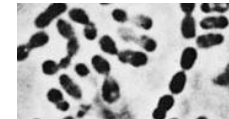
Cross reactivity against distinct viruses

Competent T cell responses to influenza in XLA patients

- **Vaccination:**

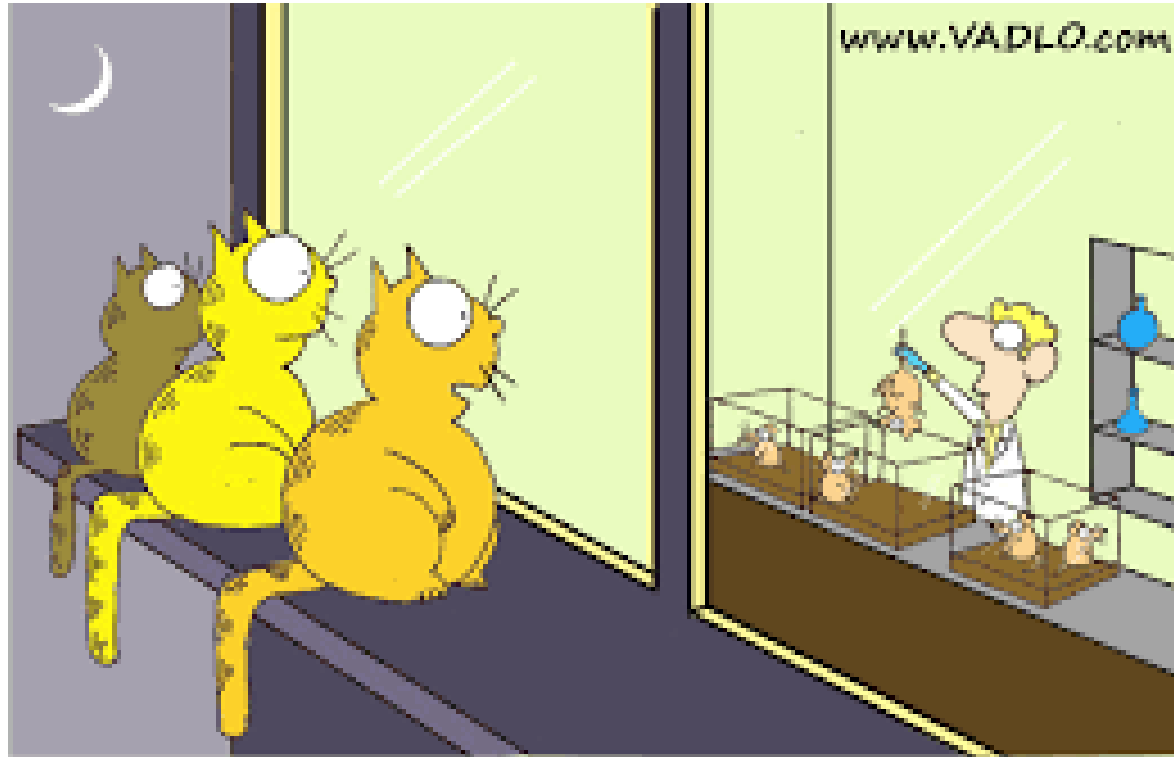


Intradermal < 6 months old immunogenic



- **Bacterial co-infection:**

Pneumococci reduce humoral response to influenza virus



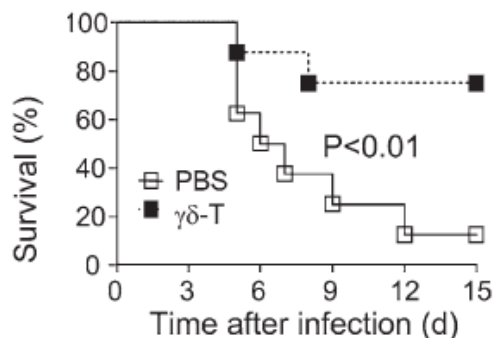
"Boy! I would love to be his pet cat."



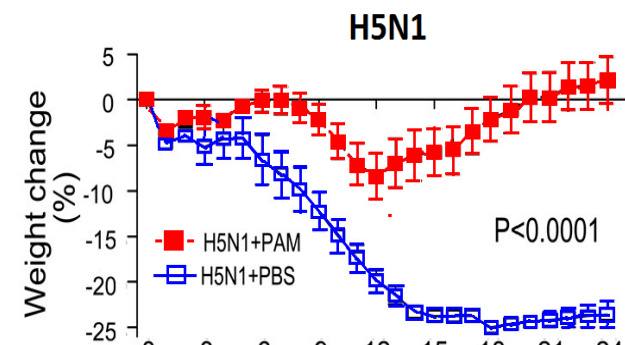
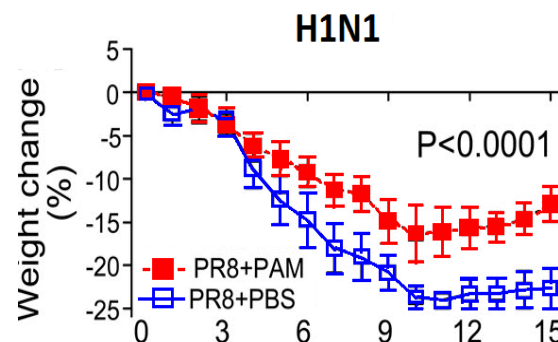
The aminobisphosphonate pamidronate controls influenza pathogenesis by expanding a $\gamma\delta$ T cell population in humanized mice

Wenwei Tu,^{1,3} Jian Zheng,¹ Yinping Liu,¹ Sin Fun Sia,² Ming Liu,⁴ Gang Qin,¹ Iris H.Y. Ng,^{1,2} Zheng Xiang,¹ Kwok-Tai Lam,¹ J.S. Malik Peiris,² and Yu-Lung Lau¹

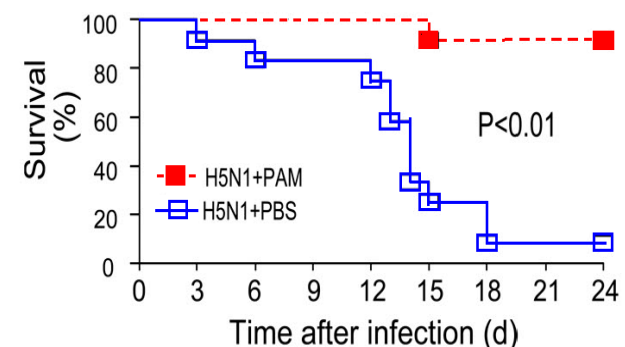
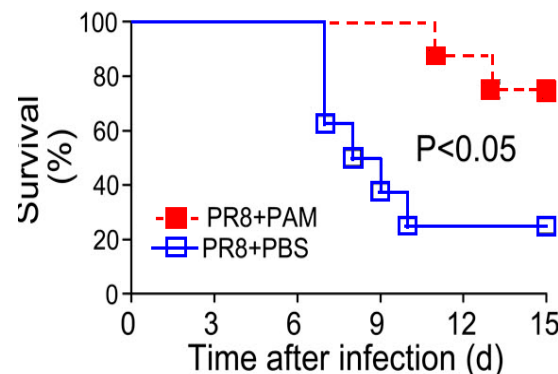
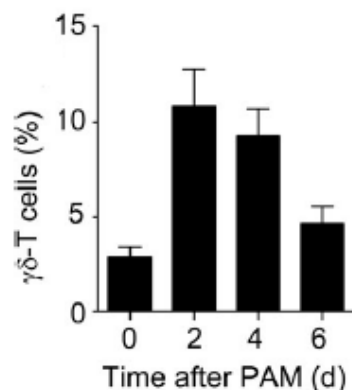
Adoptive transfer of $\gamma\delta$ T improved survival after influenza infection



PAM treatment improved survival after influenza infection



PAM expanded the % of $\gamma\delta$ T





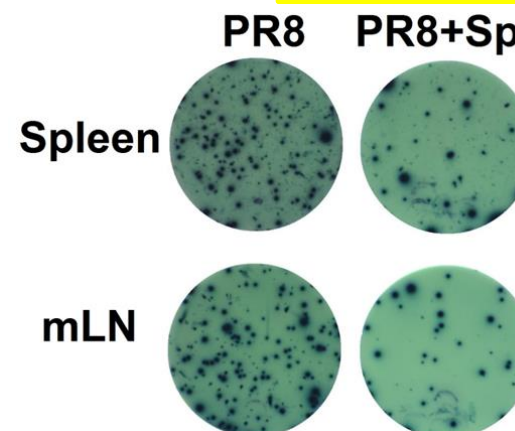
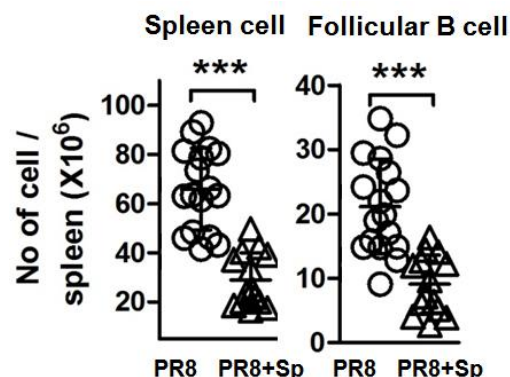
Lethal Coinfection of Influenza Virus and *Streptococcus pneumoniae* Lowers Antibody Response to Influenza Virus in Lung and Reduces Numbers of Germinal Center B Cells, T Follicular Helper Cells, and Plasma Cells in Mediastinal Lymph Node

Yuet Wu,^a Wenwei Tu,^a Kwok-Tai Lam,^a Kin-Hung Chow,^b Pak-Leung Ho,^b Yi Guan,^c Joseph S. Malik Peiris,^c Yu-Lung Lau^a

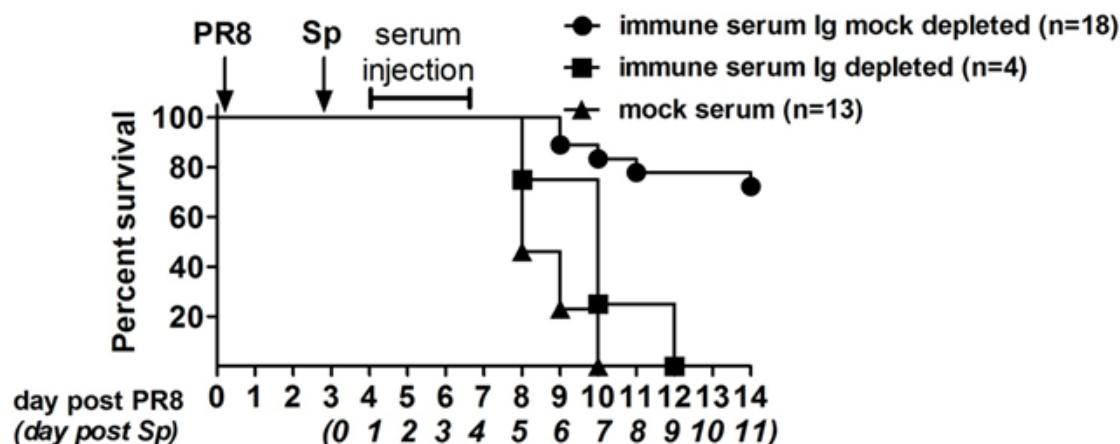
Co-infection reduces **B cells** in spleen

Co-infection reduces **IgG secreting cells**

PR8 **PR8+Sp**



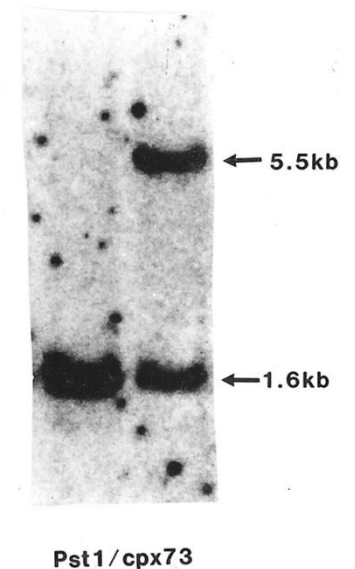
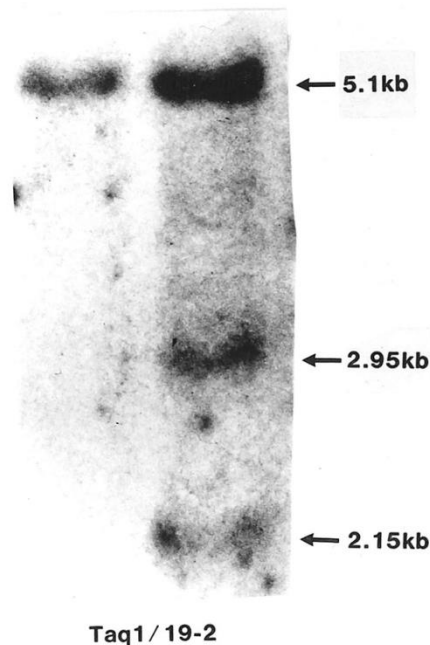
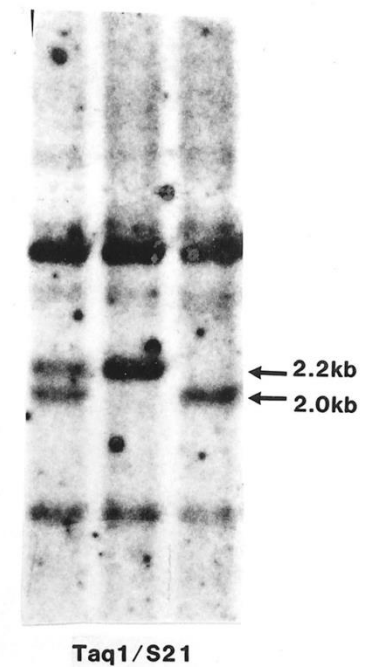
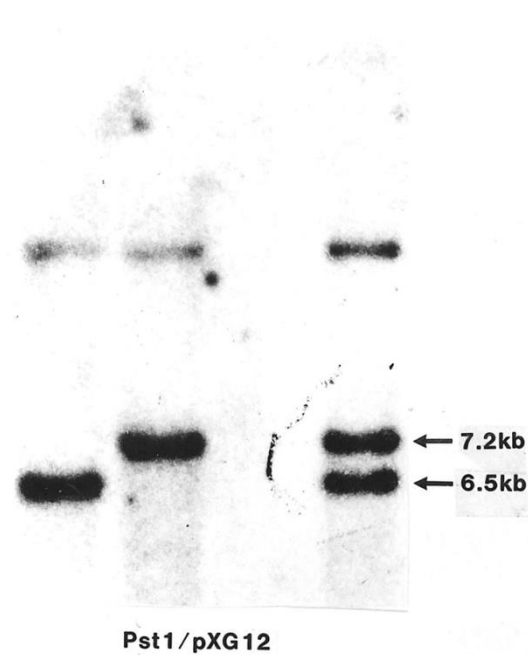
Adoptive transfer of **immune serum rescue co-infected mice**



Using Restriction Fragment Length Polymorphism to map XLA and X-SCID genes



**Roland Levinsky
(1943-2007)**



Family 1

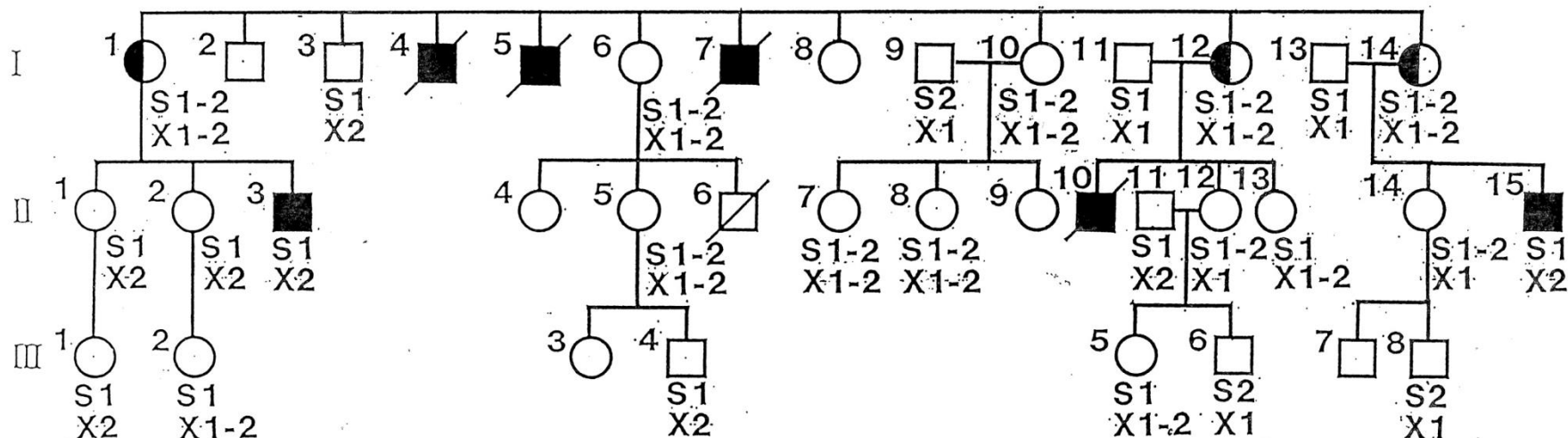


Figure 4-1 Pedigrees with RFLP data of the 15 families with X-linked agammaglobulinaemia. S21 Taq 1 polymorphism (S1 is 2.2kb, S2 is 2.0kb). pXG12 Pst 1 polymorphism (X1 is 7.2kb, X2 is 6.5kb). 19.2 Taq 1 polymorphism (P1 is 5.1kb, P2 is 2.95/2.15kb).



PREVALENCE AND GENOTYPES OF α - AND β -THALASSEMIA CARRIERS IN HONG KONG — IMPLICATIONS FOR POPULATION SCREENING

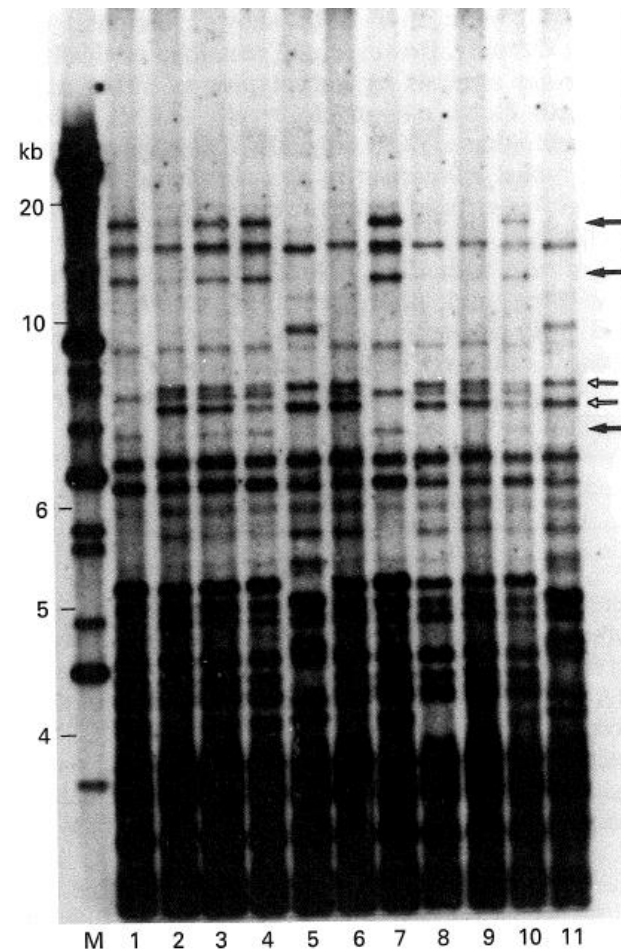
YU-LUNG LAU, M.D., LI-CHONG CHAN, M.D., YUK-YIN A. CHAN, B.S., SHAU-YIN HA, M.B., CHAP-YUNG YEUNG, M.B.,
JOHN S. WAYE, PH.D., AND DAVID H.K. CHUI, M.D.

Methods An educational and screening program for the thalassemias was carried out in three high schools with a total of 2420 students. Seventy-five percent of the students agreed to undergo screening, which consisted of blood counts, hemoglobin electrophoresis, serum ferritin measurements, and DNA analyses.

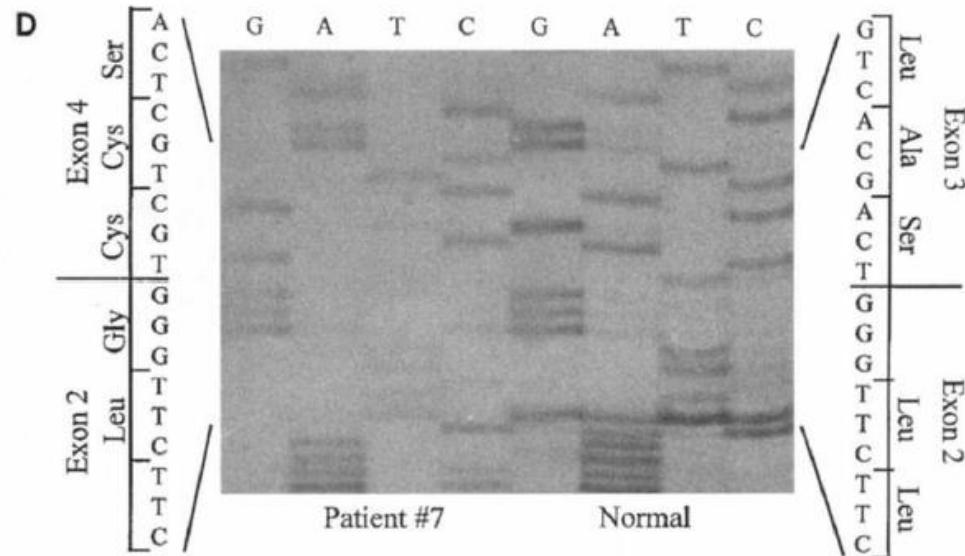
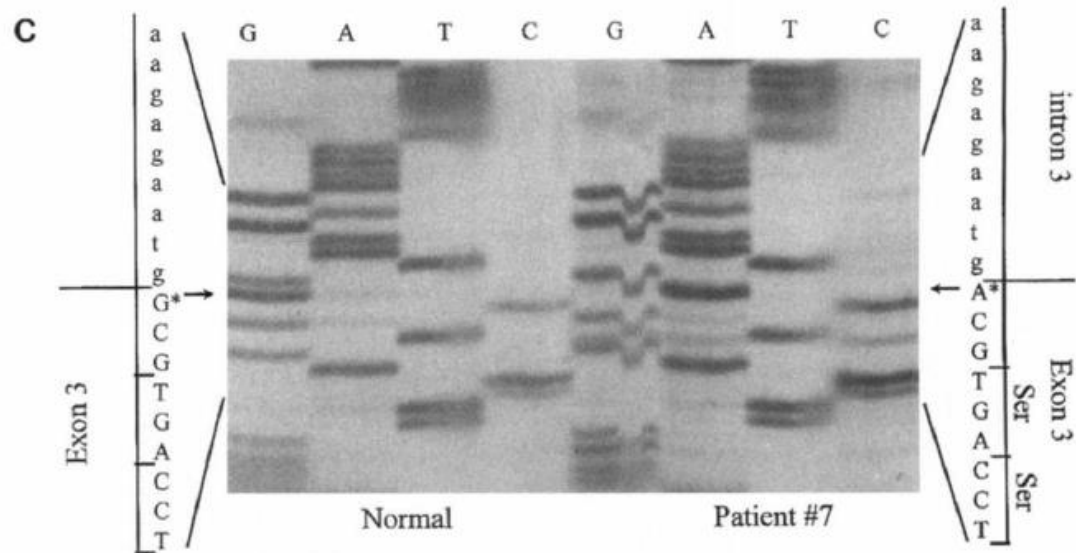
Conclusions Despite the availability of hospital-based screening and prenatal diagnosis for many years in Hong Kong, many women carrying fetuses at risk for thalassemia are not referred for genetic counseling. A community-based program of education, screening, and counseling is needed in Hong Kong and southern China. (N Engl J Med 1997;336:1298-301.)

Mixed chimerism following bone marrow transplantation for severe combined immunodeficiency: a study by DNA fingerprinting and simultaneous immunophenotyping and fluorescence *in situ* hybridisation

YL Lau¹, YL Kwong², ACW Lee¹, EKW Chiu², SY Ha¹, CF Chan¹, V Chan² and TK Chan²



Identification of Mutations in Seven Chinese Patients With X-Linked Chronic Granulomatous Disease



Need to understand local infections to help PID diagnosis

Susceptibility to Mycobacterial Infections in Children With X-Linked Chronic Granulomatous Disease

A Review of 17 Patients Living in a Region Endemic For Tuberculosis

Pamela P. W. Lee, MBBS, Koon-Wing Chan, MPhil,* Liping Jiang, MD,† Tongxin Chen, MD,‡
Chengrong Li, MD,§ Tsz-Leung Lee, MBBS,* Priscilla H. S. Mak, MPhil,* Susanna F. S. Fok, MPhil,*
Xiqiang Yang, MD,† and Yu-Lung Lau, MD**

- Incidence of TB in Hong Kong:

- All ages: 89.9/100,000
- Age < 4yr: 5.3/100,000
- Age 5-9yr: 2.7/100,000

- CGD: 10/28 (35.7%)

BCG complications

11/28 (39.3%)

- Abnormal BCG scar / abscess
- Ipsilateral axillary lymphadenopathy / abscess
- Disseminated disease



**Need to understand local infections
to help PID diagnosis**

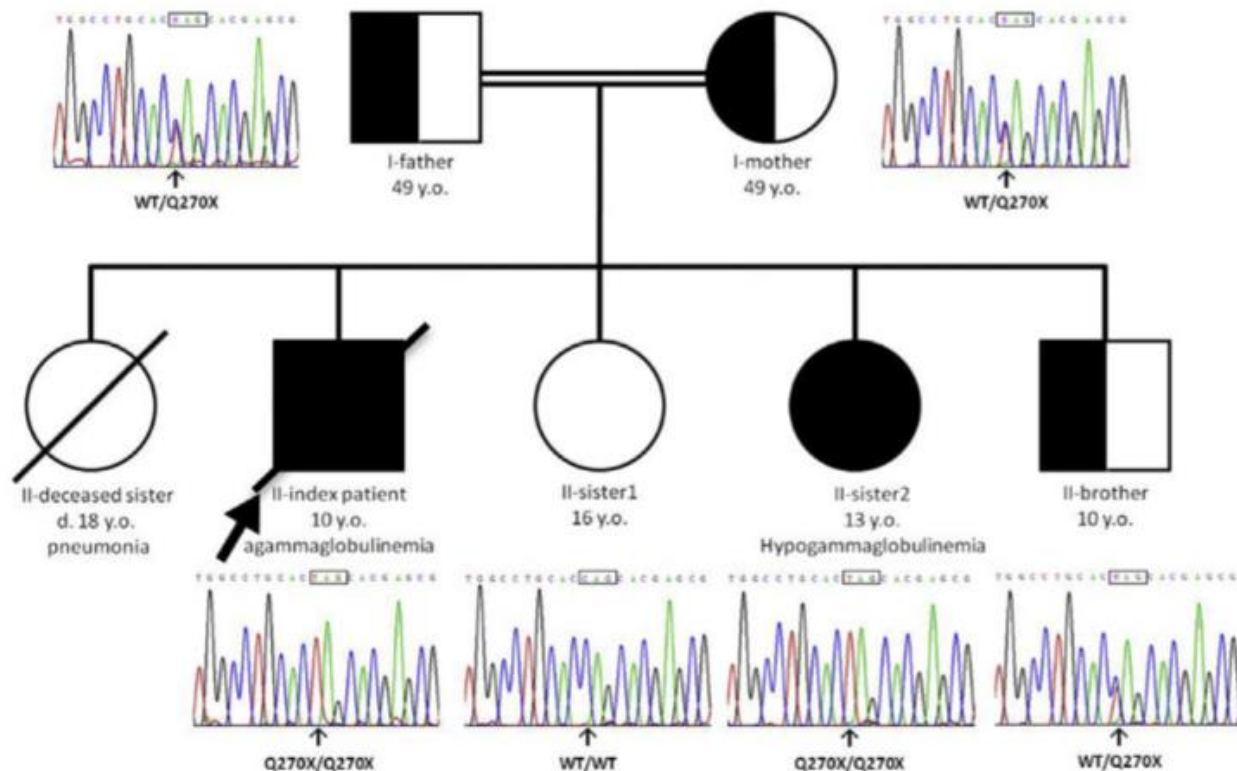
***Penicillium marneffe* infection and impaired
IFN- γ immunity in humans with autosomal-
dominant gain-of-phosphorylation STAT1
mutations**

THE JOURNAL OF
**Allergy AND Clinical
Immunology**

2014 Mar;133(3):894-896



Homozygous transcription factor 3 gene (*TCF3*) mutation is associated with severe hypogammaglobulinemia and B-cell acute lymphoblastic leukemia

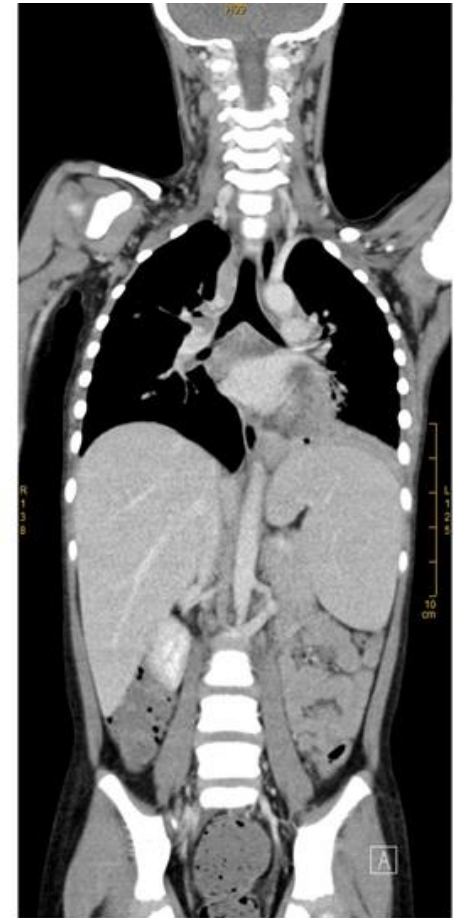
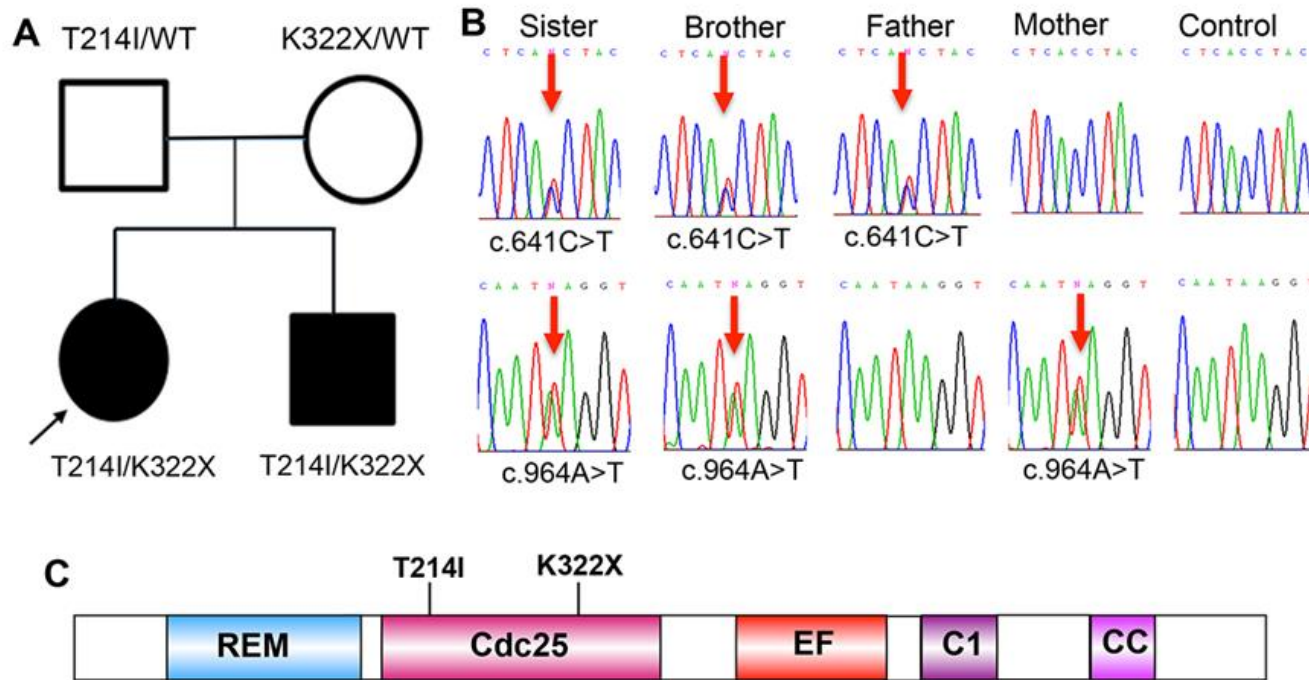


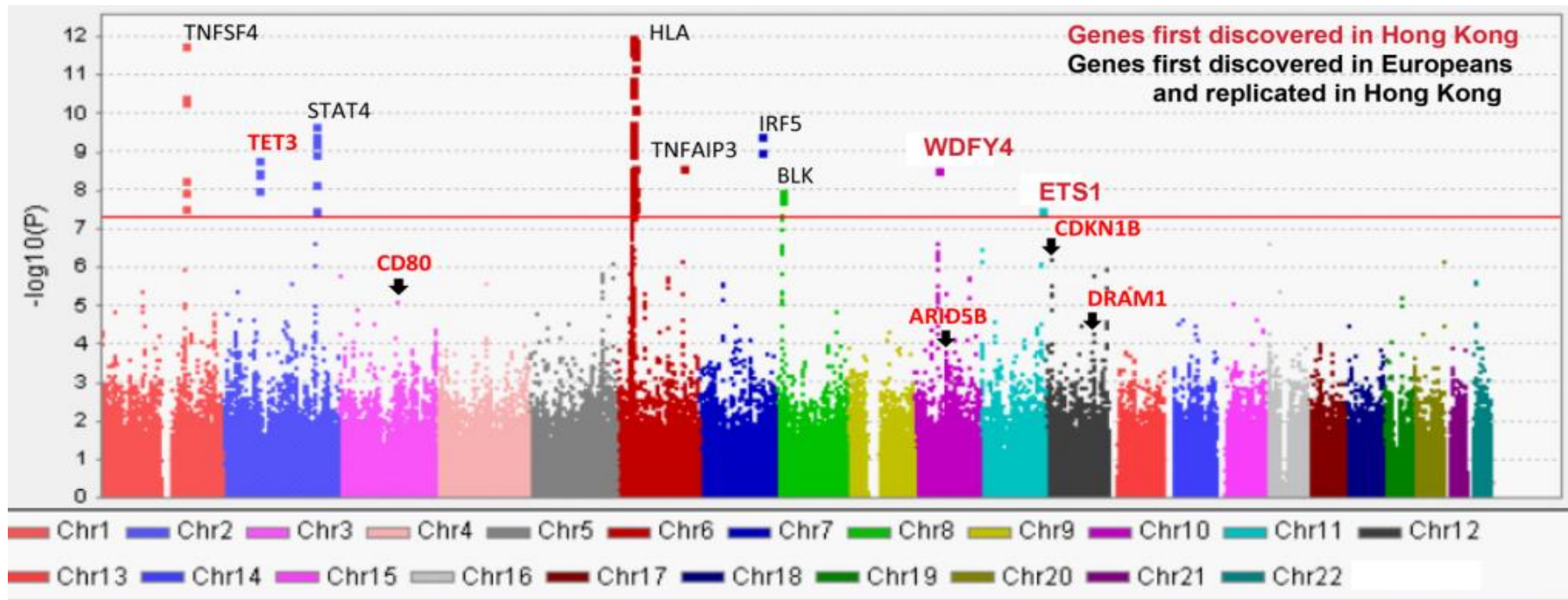


Family History of Early Infant Death Correlates with Earlier Age at Diagnosis But Not Shorter Time to Diagnosis for Severe Combined Immunodeficiency

Anderson Dik Wai Luk¹, Pamela P. Lee¹, Huawei Mao^{1,2}, Koon-Wing Chan¹, Xiang Yuan Chen³, Tong-Xin Chen⁴, Jian Xin He⁵, Nadia Kechout⁶, Deepti Suri⁷, Yin Bo Tao³, Yong Bin Xu⁸, Li Ping Jiang⁹, Woei Kang Liew¹⁰, Orathai Jirapongsananuruk¹¹, Tassalapa Daengsuwan¹², Anju Gupta⁷, Surjit Singh⁷, Amit Rawat⁷, Amir Hamzah Abdul Latiff¹³, Anselm Chi Wai Lee¹⁴, Lynette P. Shek¹⁵, Thi Van Anh Nguyen¹⁶, Tek Jee Chin¹⁷, Yin Hsiu Chien¹⁸, Zarina Abdul Latiff¹⁹, Thi Minh Huong Le¹⁶, Nguyen Ngoc Quynh Le¹⁶, Bee Wah Lee¹⁵, Qiang Li²⁰, Dinesh Raj²¹, Mohamed-Ridha Barbouche²², Meow-Keong Thong²³, Maria Carmen D. Ang²⁴, Xiao Chuan Wang²⁵, Chen Guang Xu²⁶, Hai Guo Yu²⁷, Hsin-Hui Yu¹⁸, Tsz Leung Lee¹, Felix Yat Sun Yau²⁸, Wilfred Hing-Sang Wong¹, Wenwei Tu^{1,2}, Wangling Yang^{1,2}, Patrick Chun Yin Chong¹, Marco Hok Kung Ho¹ and Yu Lung Lau^{1,2*}

RASGRP1 mutation in autoimmune lymphoproliferative like syndrome





ARTICLE

Collaboration and
Meta-analysis allowed
Discovery of 8 variants
In 5 genes associated
With SLE

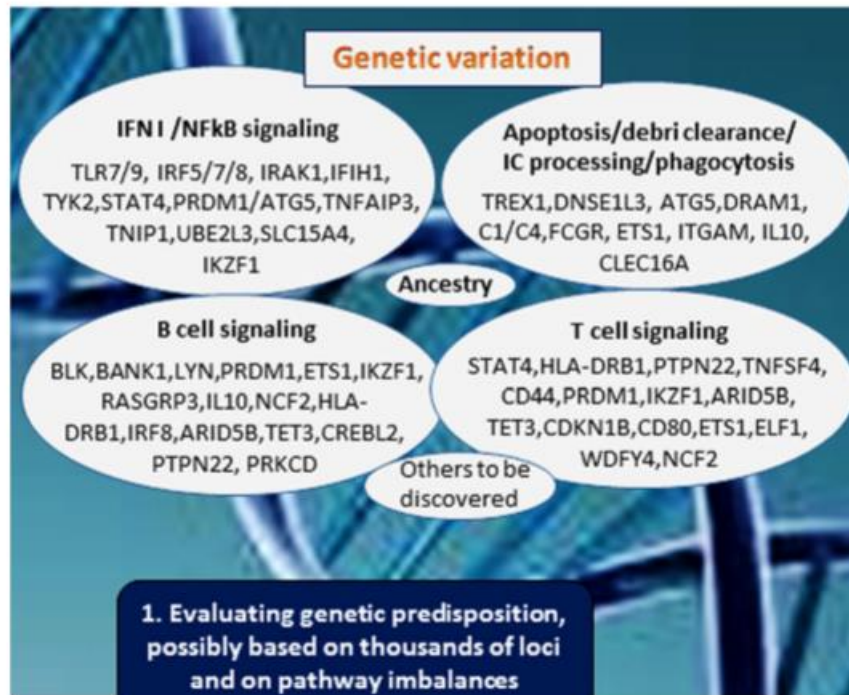


Meta-analysis Followed by Replication Identifies Loci
in or near *CDKN1B*, *TET3*, *CD80*, *DRAM1*, and *ARID5B*
as Associated with Systemic Lupus Erythematosus in Asians

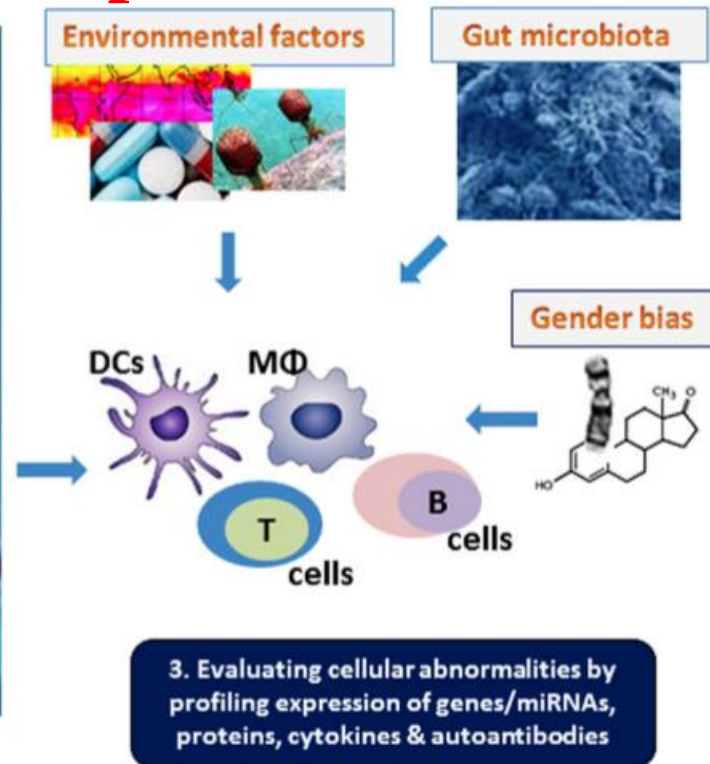
Wanling Yang,^{1,29} Huayang Tang,^{2,29} Yan Zhang,^{1,29} Xianfa Tang,^{2,29} Jing Zhang,^{1,29} Liangdan Sun,² Jing Yang,¹ Yong Cui,² Lu Zhang,¹ Nattiya Hirankarn,³ Hui Cheng,² Hai-Feng Pan,⁴ Jinping Gao,² Tsz Leung Lee,¹ Yujun Sheng,² Chak Sing Lau,⁶ Yang Li,² Tak Mao Chan,⁶ Xianyong Yin,² Dingge Ying,¹ Qianjin Lu,⁷ Alexander Moon Ho Leung,¹⁰ Xianbo Zuo,² Xiang Chen,¹¹ Kwok Lung Tong,¹² Fusheng Zhou,² Qingchun Diao,¹³ Niko Kei Chiu Tse,¹⁴ Hongfu Xie,¹¹ Chi Chiu Mok,⁵ Fei Hao,¹⁵ Sik Nin Wong,⁹ Bingjun Shi,¹³ Ka Wing Lee,⁸ Yan Hui,¹⁶ Marco Hok Kung Ho,¹ Bo Liang,² Pamela Pui Wah Lee,¹ Hongzhou Cui,² Qing Guo,¹⁷ Brian Hon-Yin Chung,¹ Xiongming Pu,¹⁸ Qiji Liu,¹⁹ Xiaoguang Zhang,² Change Zhang,² Chun Yin Chong,¹ Hong Fang,²⁰ Raymond Woon Sing Wong,⁶ Yonghu Sun,² Mo Yin Mok,⁶ Xiang-Pei Li,²¹ Yingyos Avihingsanon,²² Zhifang Zhai,¹⁵ Pornpimol Rianthavorn,²³ Thavatchai Deekajorndej,²³ Kanya Suphapeetiporn,^{23,24} Fei Gao,⁷ Vorasuk Shotelersuk,^{23,24} Xiaojing Kang,¹⁸ Shirley King Yee Ying,¹² Lijuan Zhang,¹⁶ Wilfred Hing Sang Wong,¹ Dingxian Zhu,²⁰ Samuel Ka Shun Fung,¹² Fanqin Zeng,¹⁷ Wai Ming Lai,¹⁴ Chun-Ming Wong,²⁵ Irene Oi Lin Ng,²⁵ Maria-Mercè Garcia-Barceló,²⁶ Stacey S. Cherny,²⁷ Nan Shen,²⁸ Paul Kwong-Hang Tam,²⁶ Pak Chung Sham,²⁷ Dong-Qing Ye,⁴ Sen Yang,² Xuejun Zhang,^{2,*} and Yu Lung Lau^{1,*}

Comprehensive analysis of the joint impact of **genetic**, **epigenetic**, and **environmental** factors in SLE

To translate to better patient care



2. Evaluating clinical manifestations and disease activities



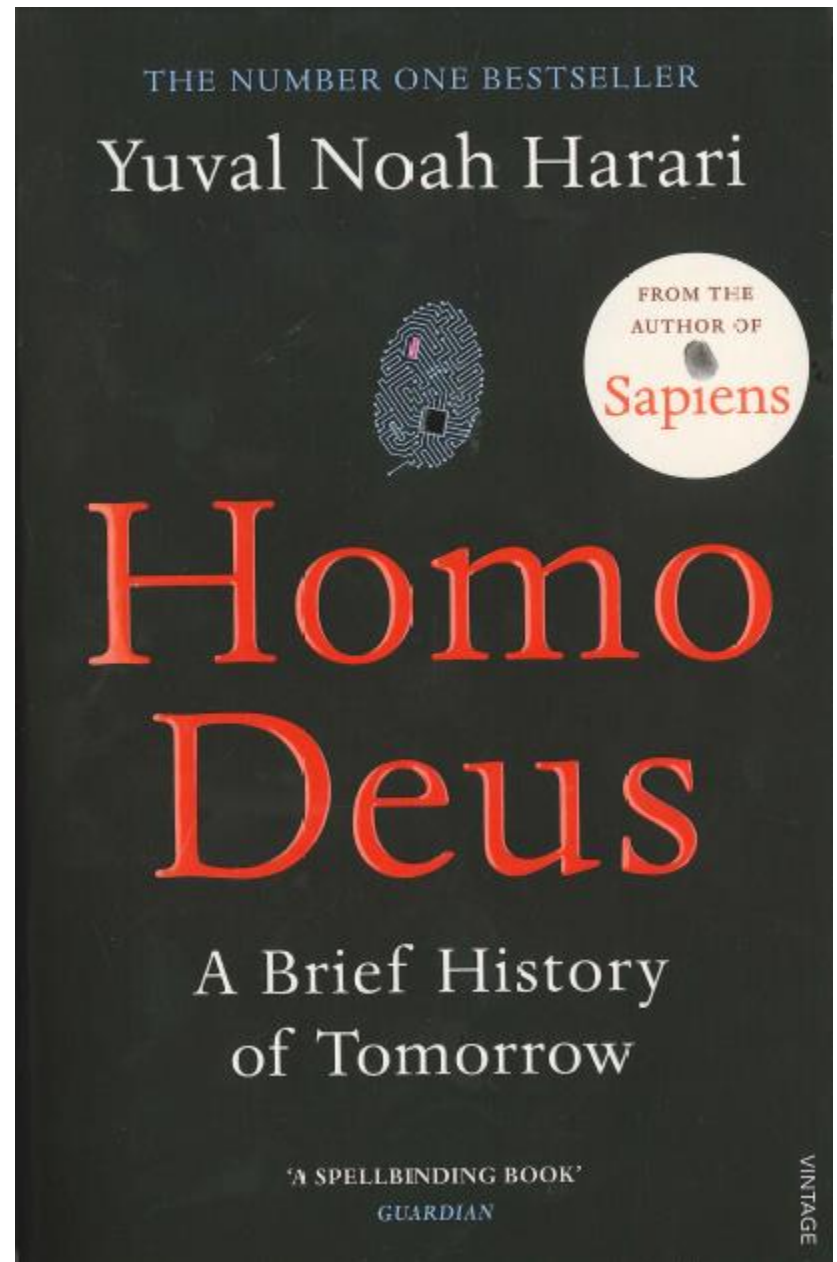
Evaluating cellular and pathway disturbances and designing targeted therapies



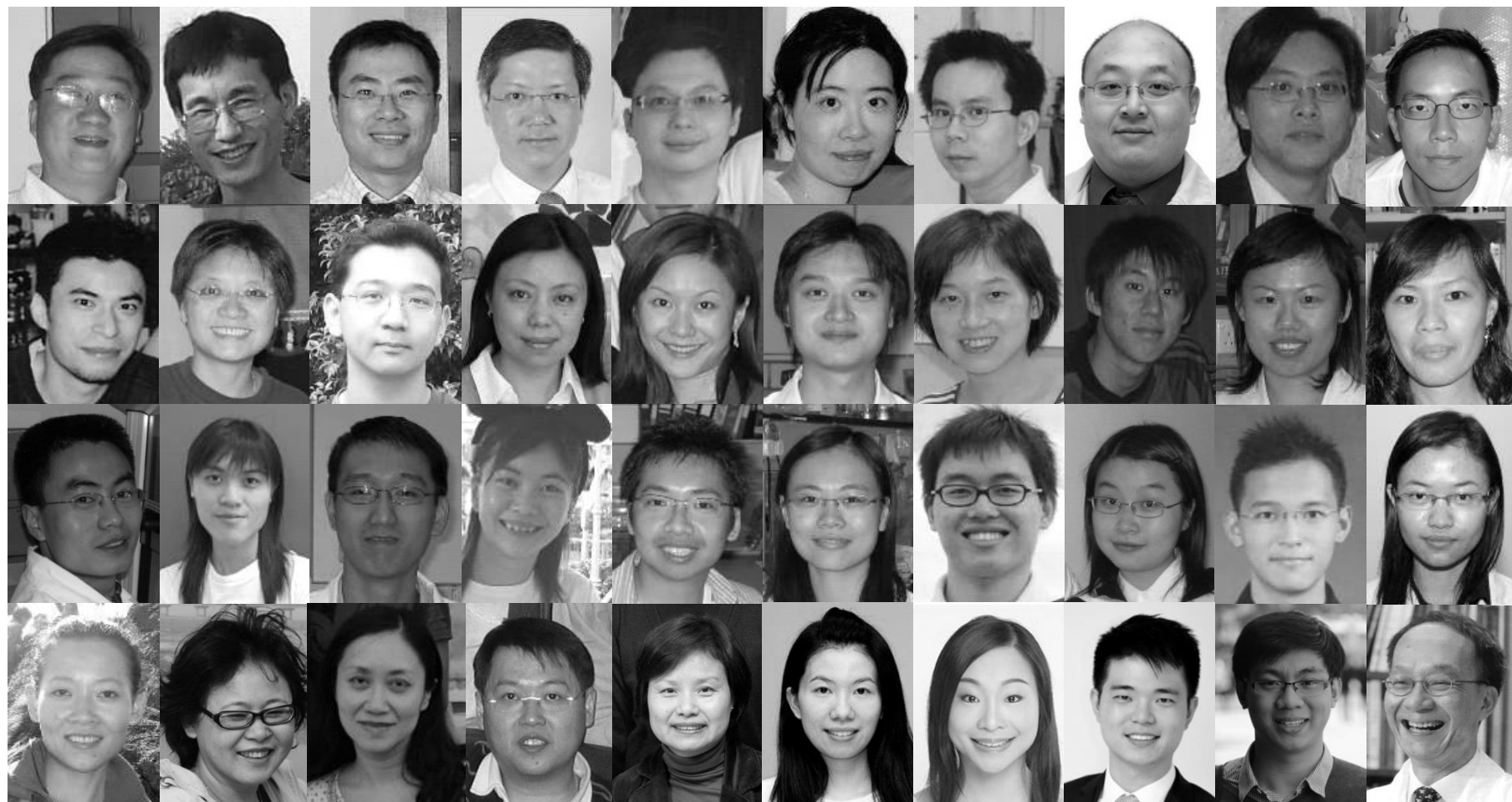
Lost in Thought — The Limits of the Human Mind and the Future of Medicine

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Thomas H. Lee , M.D.**

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Learning with my students & fellows



I would like to end this dissertation with a quote from Robert A. Good in his presidential address to the American Association of Immunologists on April 13, 1976:

"the very great strengths of immunology, from its very beginning....., is that this discipline originated and has been maintained by the interaction between the clinic and effective scientific investigation."