Novel H1N1 2009 HSI Pandemic Implication to Children of China

Influenza Encephalopathy

Potential Role of High Dose
N-Acetylcysteine Anti-oxidant Therapy

Would Epidemic Encephalitis Lethargica
Re-emerge After Novel 2009 H1N1
Human Swine Influenza Pandemic ?

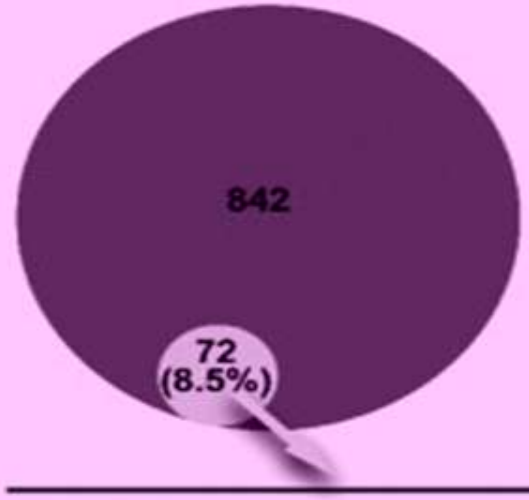
Dr. Lai Kang Yiu
Intensive Care Unit
Queen Elizabeth Hospital

Spectrum of CNS Complication of Influenza Virus Infection

- Encephalitis lethargica
- Reye's syndrome
- Acute necrotizing encephalopathy (ANE)
- Influenza encephalopathy and encephalitis
  - Sudden onset of high fever, early development of unconsciousness, recurrent convulsions and death within 2 or 3 days.
- Acute encephalopathy with biphasic seizures and late reduced diffusion
- Febrile convulsion (most common)

Disease burden to U.S.A and Hong Kong

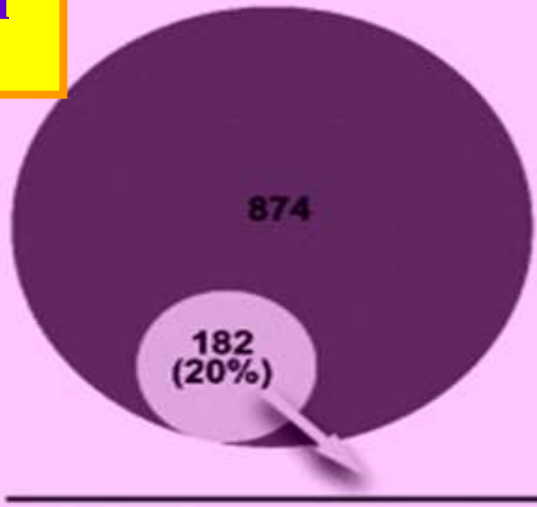
Study by Newland et al.



Neurologic complications	N= 72
Seizure	56
Febrile seizure	27
Seizure with fever	8
Other seizure	21
Encephalopathy	8
Post-infectious encephalopathy	2
Other	6
Stroke secondary to hypotension	4
Aseptic meningitis	2

4-year retrospective cohort in USA 2000-2004: no mortality, 1 with neuologic sequelae

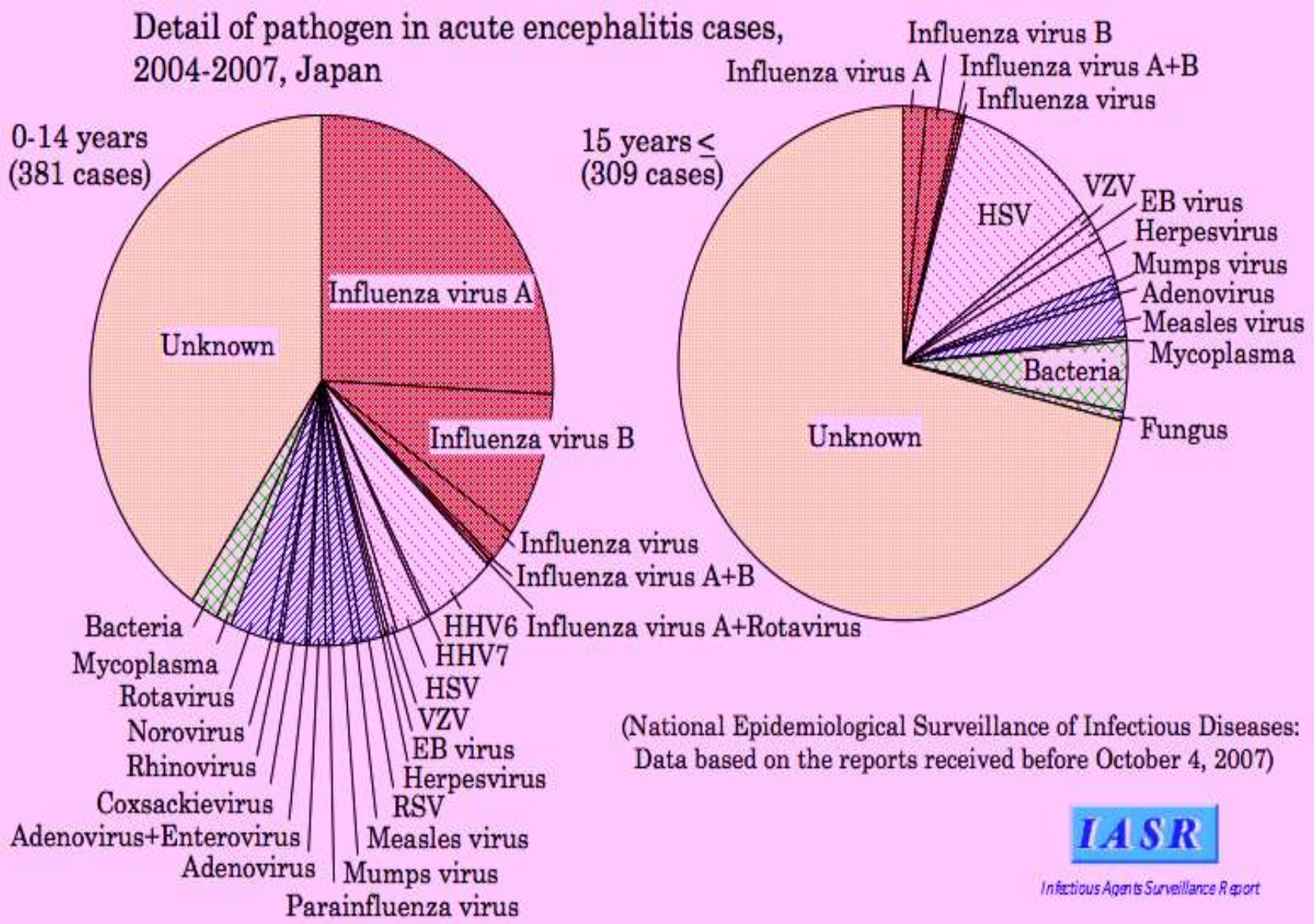
y in Hong Kong



Neurologic complications	N= 182
Encephalopathy	5
Encephalitis	1
Aseptic meningitis	1
Febrile seizure	165
Other seizures	8
Myositis	2

5-year retrospective cohort in Hong Kong 1998-2003: 2 mortality, 1 with neuologic sequelae

- Neurologic complications in children hospitalized with influenza: comparison between USA and Hong Kong. Chung BH. Tsang AM. Wong VC Journal of Pediatrics. 151(5):e17-8; author reply e18-9, 2007 Nov.

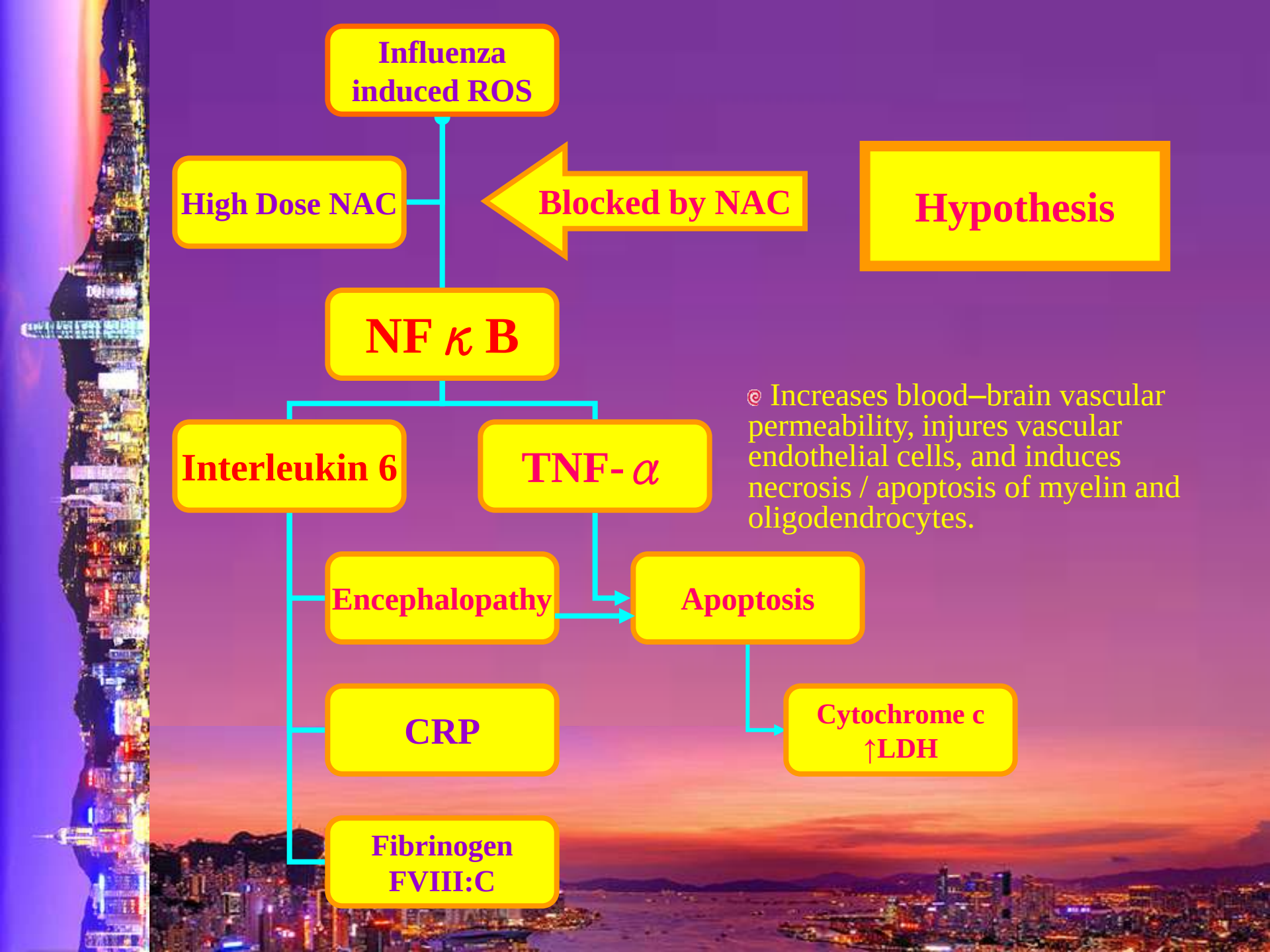


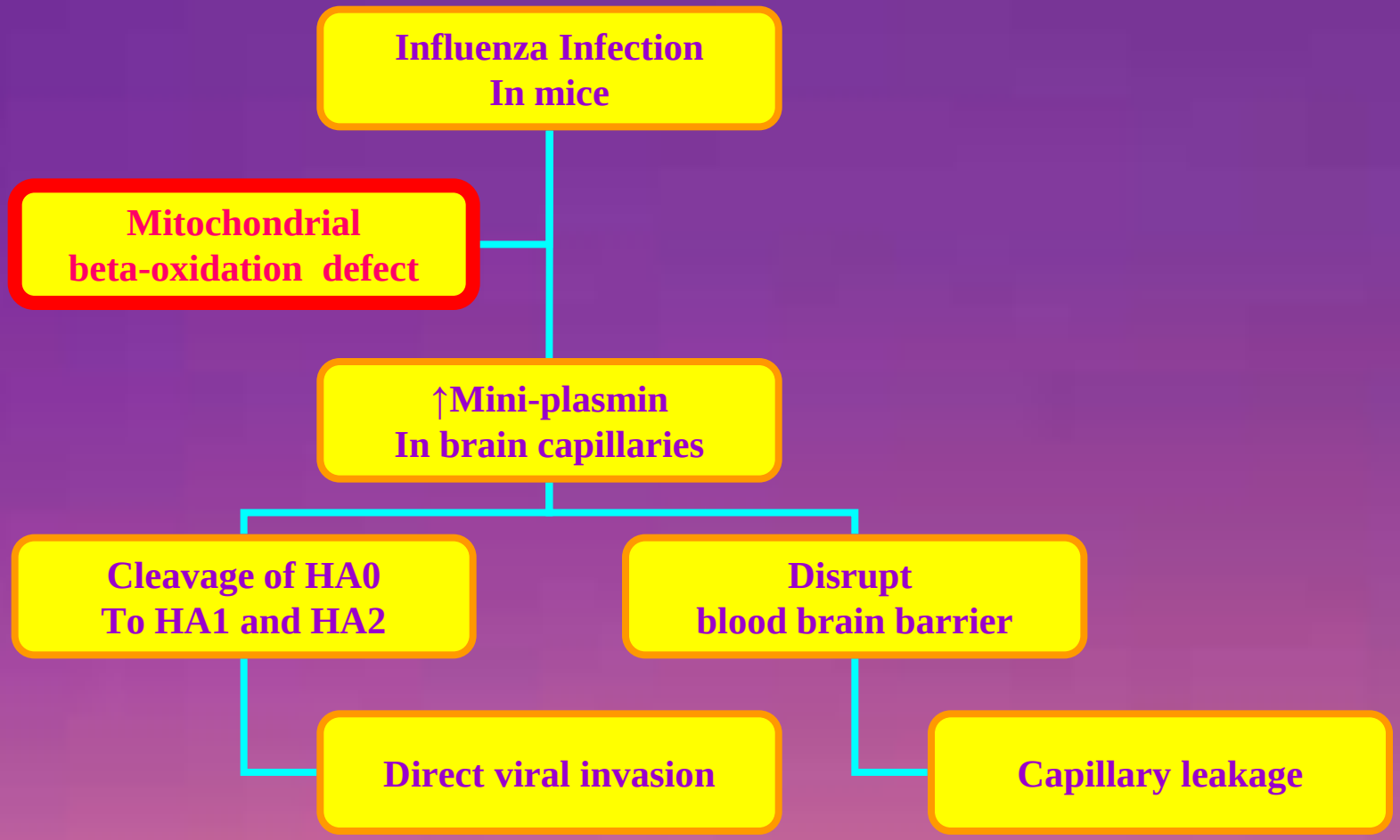
Details of pathogen in acute encephalitis cases 2004-2007 Japan

Predictive value of serum interleukin-6 level in influenza virus–associated encephalopathy

[Hideo Aiba, MD, Mika Mochizuki, MD, Mitsuaki Kimura, MD and Hiroatsu Hojo, MD *Neurology* 2001;57:295-299]

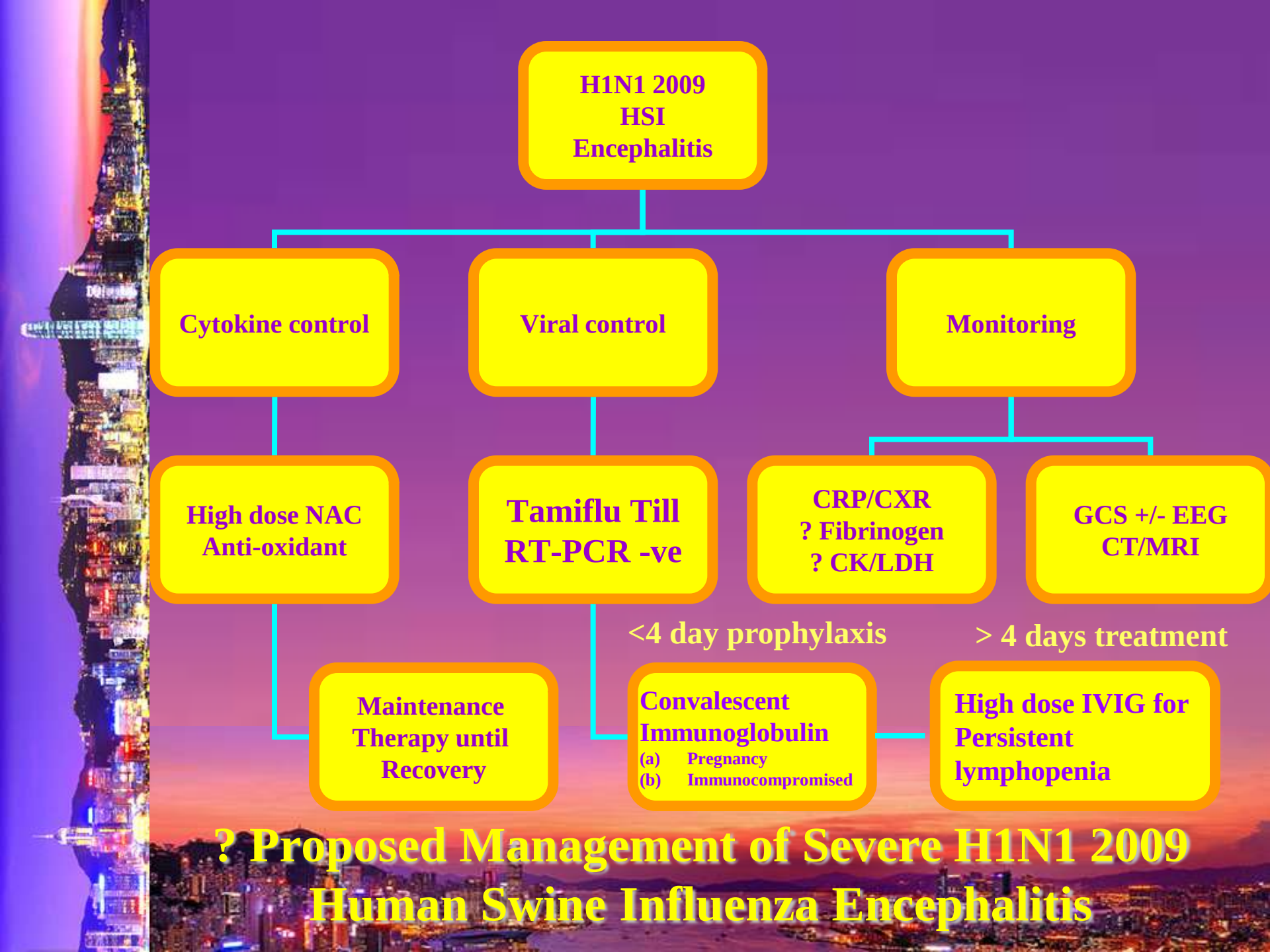
- The serum IL-6 levels were >6,000 pg/mL in children with brain stem dysfunction, about 150 pg/mL in children without brain stem dysfunction, and <80 pg/mL in controls.
- The time course of the serum IL-6 level also reflected the clinical condition. Once the serum IL-6 level was increased to >15,000 pg/mL, none of the children survived. The lower the maximal serum IL-6 level, the milder the CNS sequelae.


Influenza induced ROS
High Dose NAC
Blocked by NAC
Hypothesis
NF κ B
Interleukin 6
TNF- α
Encephalopathy
Apoptosis
CRP
Cytochrome c
↑LDH
Fibrinogen
FVIII:C
Increases blood–brain vascular permeability, injures vascular endothelial cells, and induces necrosis / apoptosis of myelin and oligodendrocytes.

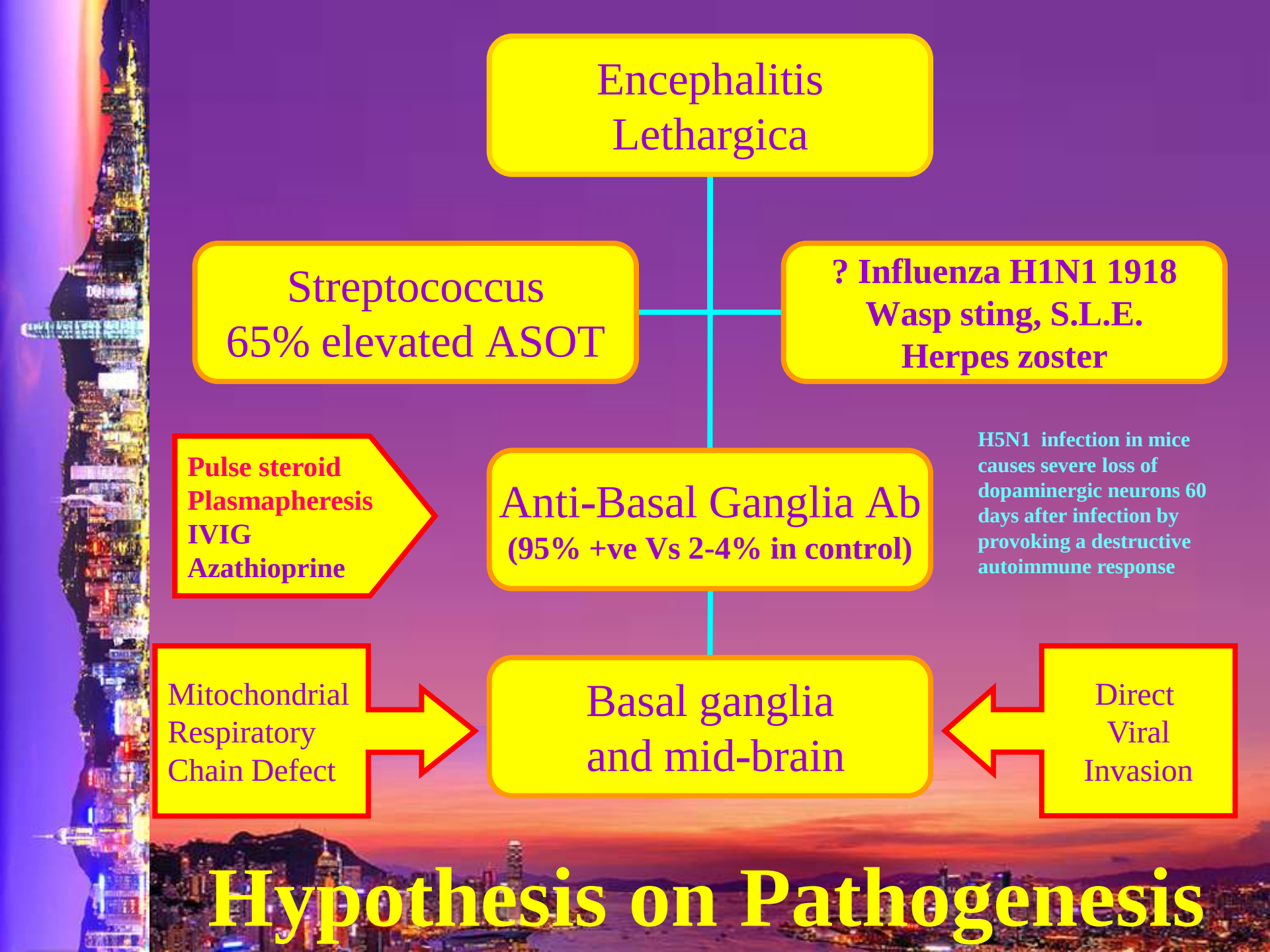


Accumulation of mini-plasmin in the cerebral capillaries causes vascular invasion of the murine brain by a pneumotropic influenza A virus: implications for influenza-associated encephalopathy.

Yao D. Chen Y. Kuwajima M. Shiota M. Kido H. Biological Chemistry. 385(6):487-92, 2004 Jun.



? Proposed Management of Severe H1N1 2009 Human Swine Influenza Encephalitis


Encephalitis Lethargica
Streptococcus 65% elevated ASOT
? Influenza H1N1 1918 Wasp sting, S.L.E. Herpes zoster
Pulse steroid Plasmapheresis IVIG Azathioprine
Anti-Basal Ganglia Ab (95% +ve Vs 2-4% in control)
H5N1 infection in mice causes severe loss of dopaminergic neurons 60 days after infection by provoking a destructive autoimmune response
Mitochondrial Respiratory Chain Defect
Basal ganglia and mid-brain
Direct Viral Invasion
Hypothesis on Pathogenesis

Encephalitis Lethargica
First Report 1917 in central Europe.

Epidemic in the winter of 1918/1919
Spread to Russia and North America

In epidemic form in winter seasons
Spread to rest of world (1918- 1927)

- **65000 reported case with mortality**
  30% in the acute stage and during relapse
- **50% survivors had persistent or recurrent neuro-psychiatric illness/Parkinsonism**
- **Recurrent or chronic illness with downhill course**
  Prone to sudden death
  60/300 young patient healthy after 2 years

Was encephalitis lethargica a post-influenzal or some other phenomenon? Time to re-examine the problem.

Mortimer PP. Epidemiology & Infection. 137(4):449-55, 2009 Apr.

Temporal Relationship of 1918 Influenza Encephalitis lethargica, Parkinsonism

Successful quarantining of American Samoa from influenza in 1919 spared those islands from Encephalitis lethargica in subsequent years.

Epidemic influenza years in Seattle after 1919 were followed by peaks of cases of encephalitis lethargica

1918 Influenza, encephalitis lethargica, Parkinsonism

Ravenholt RT, Foege WH. Lancet 1982; ii : 860–864.

Clinical Features and Laboratory Findings

Encephalitis Lethargica
(55% has preceding pharyngitis)

Sleep disorders
Iomnolence, Sleep inversion, Insomnia

Lethargy

Extrapyramidal symptoms
(Parkinsonism, dyskinesias)

Oculogyric crisis
Ocular palsy and ptosis

Neuropsychiatric Diorders
Catatonia, obsessive±compulsive disorder and mutism
apathy and conduct disorders

Central cardiorespiratory Features (e.g. hiccup)

LP: Lymphocyrosis, elevated proteins,
Intrathecal oligoclonal band
Human anti-basal ganglia neuronal Ab

MRI: 60% normal and 40%
deep grey matter inflammation

墨西哥的疫情對中國兒童的啟示

黎鏡堯醫生

伊利沙伯醫院

墨西哥的疫情對中國的啟示

- 從基因測試 2009 H1N1 豬流感是綜合病毒，含有四種不同的流感病毒基因，其中包括：北美洲的豬流感、歐亞型的豬流感、北美洲型的禽流感、及人類流感。其中 HA, NS1 and NP 則是於1918年傳入北美豬隻 。因此**我們現今第一波時實已處身於1918年的第二波。**
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墨西哥的疫情對中國的啟示

中國的嬰兒死亡率與孕婦死亡率與墨西哥基本相近。墨西哥的疫情可於中國重演。但中國小童並沒b型嗜血桿菌和肺炎鏈球菌疫苗保障及中國成年人煙民數目及比例為世界之冠。因此疫情可能比墨西哥嚴峻。

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- 但常用的PCV-7 肺炎鏈球菌疫苗並不能為中國小童提供足夠保障, 因為PCV-7只能有效防止38%於中國流行的肺炎鏈球菌。
- 除肺炎併發症，中國須要防禦豬流感引發的兩類腦部併發症
  - 流感腦炎/腦病*(Influenza-associated encephalopathy/encephalitis).*
  - *昏睡性腦炎* (*encephalitis lethargica*)
    - 40% 死亡率
    - 人格變化後的少年犯罪問題。

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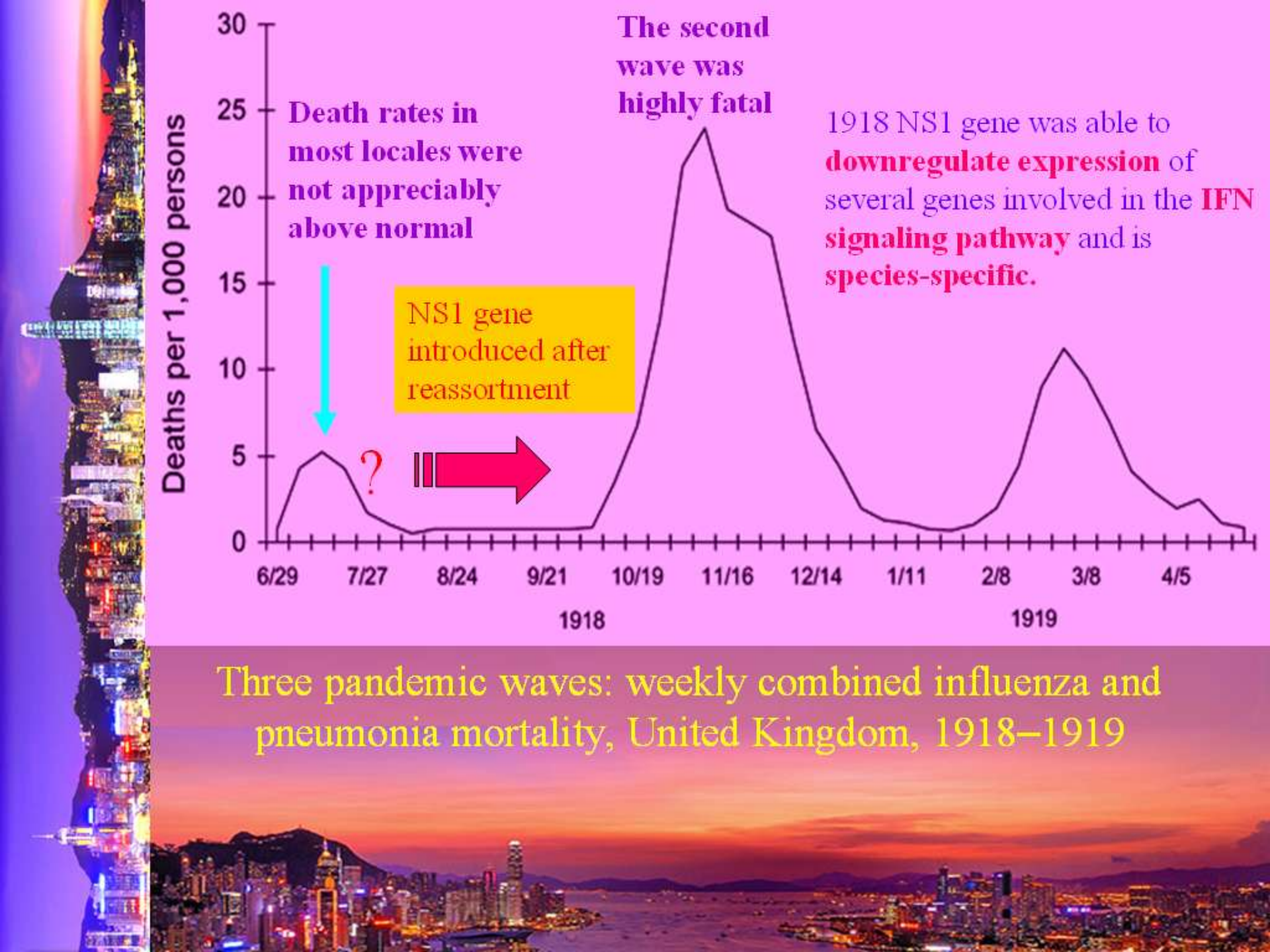
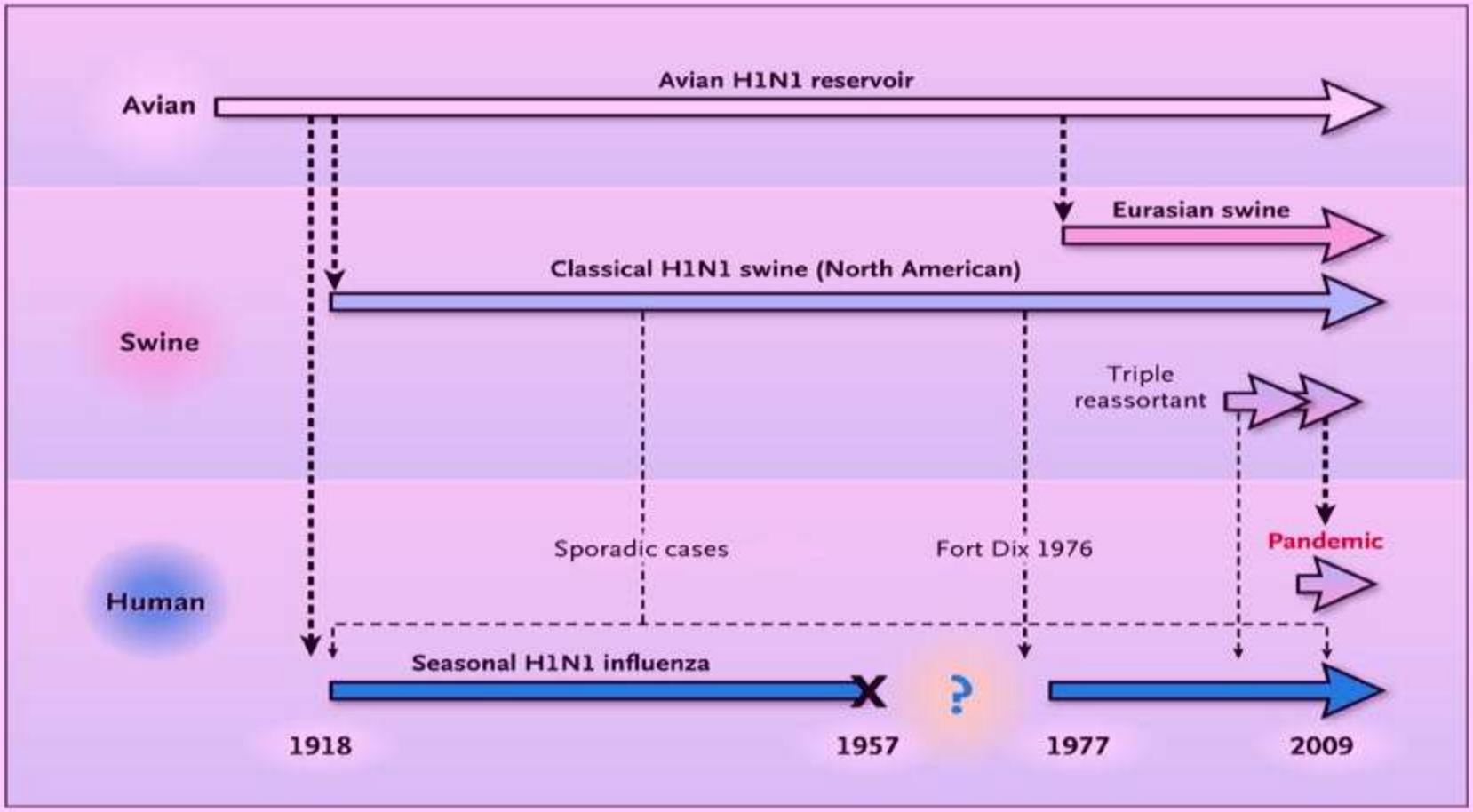


Three pandemic waves: weekly combined influenza and pneumonia mortality, United Kingdom, 1918–1919



Sporadic cases of Post-encephalitis Parkinsonism and Post encephalitis lethargica have been reported recently after H1N1 was reintroduced in 1977 although no viral etiology has been documented. (Rail et al., 1981; Clough et al., 1983; Howard and Lees, 1987; Geddes et al., 1993; Barletta et al., 1995).

Historical Perspective — Emergence of Influenza A (H1N1) Viruses
Shanta M. Zimmer, M.D., and Donald S. Burke, M.D. **Volume 361:279-285 July 16, 2009 Number 3**

In Nov. 1977, the Soviet Union reported to W.H.O. the occurrence of widespread outbreaks of influenza due to viruses antigenically related to the H1N1 viruses that has circulated in the human population during the period 1947-1956.

By late Dec 1977, the Soviet Union reported that A/USSR/77(H1N1) virus has caused disease in nearly 2/3 of the cities and has displaced the prevalent H3N2 viruses.

Summary of Clinical Trials of Inactivated Influenza Vaccine – 1978

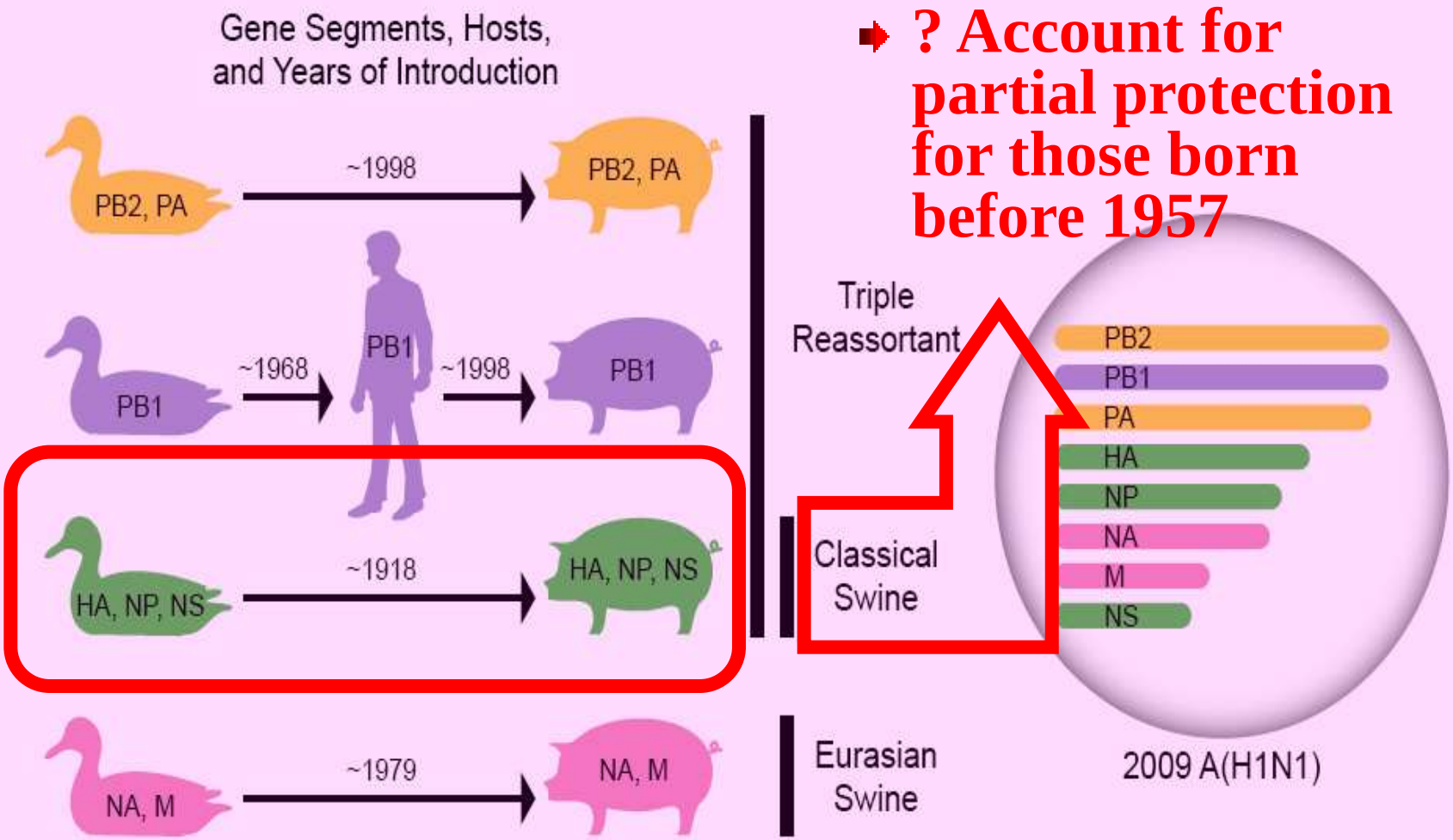
John. R et al. Reviews of infectious dieases Vol 5 No 4 July- August

Since the spring of 1977, two subtypes of influenza A virus (H3N2 and H1N1) have been seasonally infecting the human population.

Data from 1995 to 2008 has shown that the symptomatic flu due to H1N1 is distributed mainly in a younger population relative to H3N2. (The median age of the H3N2 patients is 23 years while H1N1 patients are 9 years old.) These distinct characteristic spectra of age groups may indicate partial protection possibly carried over from previous pandemics in the older population.

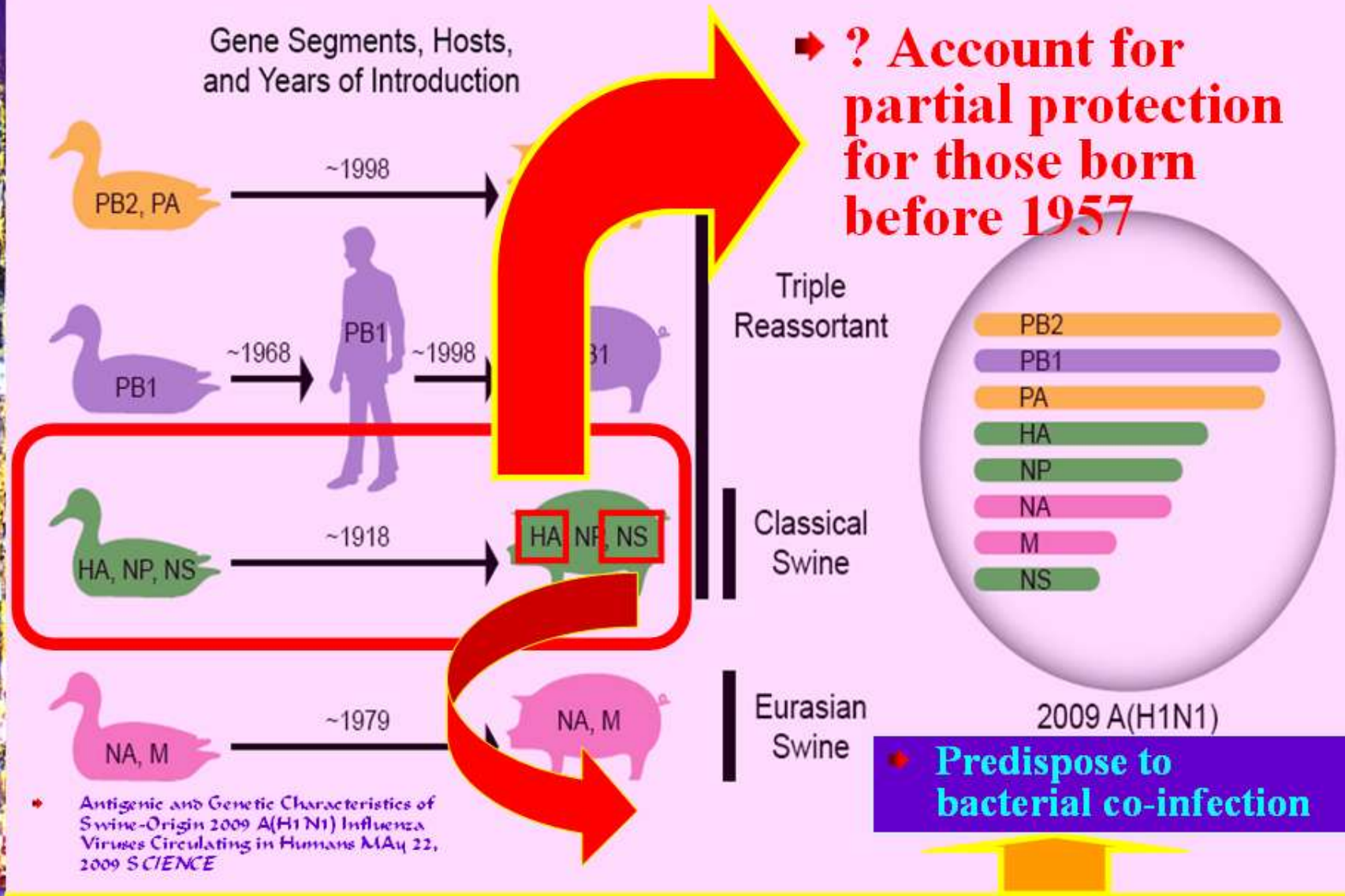
Differences in Patient Age Distribution between Influenza A Subtypes

Hossein Khiabanian, Gregory M. Farrell, Kirsten St. George, Raul Rabadan PLOS One August 2009 | Volume 4 | Issue 8 | e6832



- **? Account for partial protection for those born before 1957**

- Antigenic and Genetic Characteristics of Swine-Origin 2009 A(H1N1) Influenza Viruses Circulating in Humans MAy 22, 2009 S*CIENCE*



- **Suppression of innate immune response leading to initial rapid proliferation of influenza virus and severe mucosal damage**

Mexican Flu, Swine Flu, H1N1 Pandemic Pandemonium Origin

- It is believed that a five year old boy in La Gloria, Mexico was the very first person that tested positive for the Mexican Flu.
- The outbreak may started as early as 15/2/2009

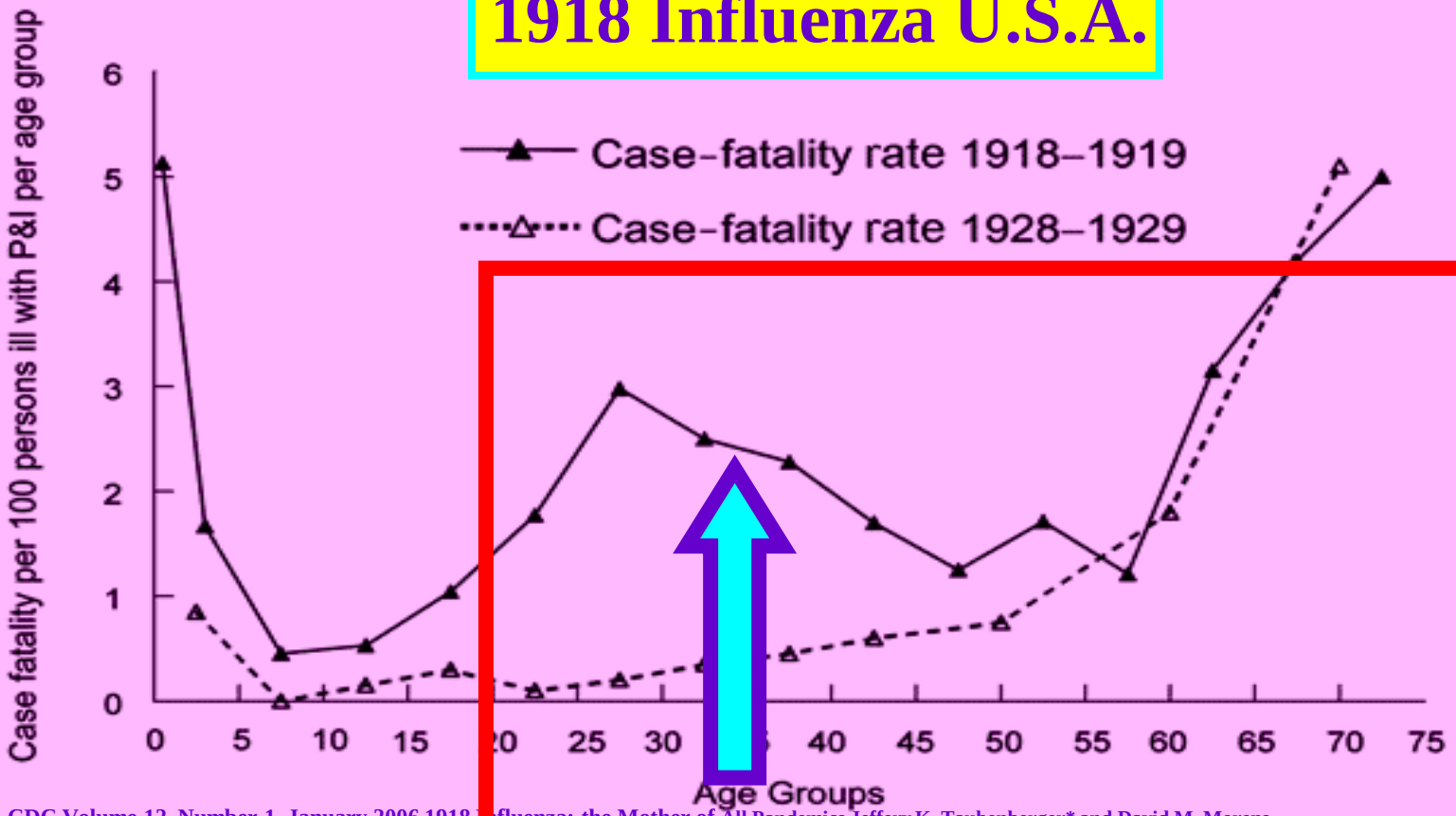
W.H.O. has raised pandemic alert from phase 5 to phase 6 on 11/6/2009

La Gloria clinical attack rates by age and gender

Age Group	Male (%)	Female(%)	Total(%)
<1	91.2	73.7	**83.9**
1-4	66.2	66.1	**58.1**
5-14	49.7	66.3	**57.7**
15-24	25.6	28.2	27.0
25-44	22.8	39.4	31.6
45-64	18.4	42.7	29.6
65+	17.5	25.7	22.0
Total	33.5	44.6	39.1

High Clinical Attack Rate Among Children especially those < 1 year of age

1918 Influenza U.S.A.

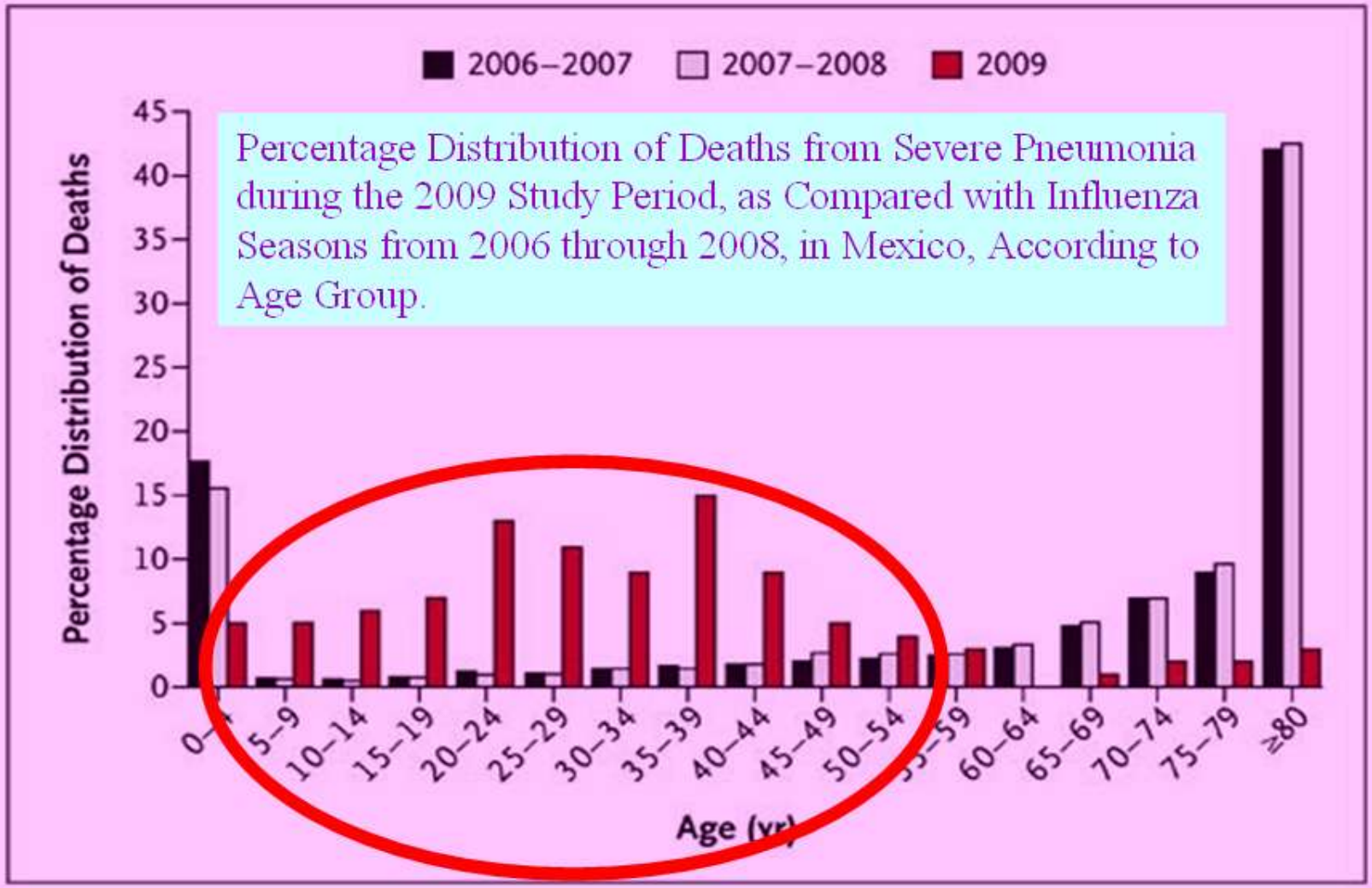


CDC Volume 12, Number 1, January 2006 1918 Influenza: the Mother of All Pandemics Jeffery K. Taubenberger* and David M. Morens

Mexico	0.6%	0.38%	2.74%	4.06%	3.8%	5.0%	5.1%
Age	0-9	10-19	20-29	30-39	40-49	50-59	60+

Very similar Mortality Rate

? Protected by Immunization Program with major reduction in mortality



March 24 to April 29, 2009, a total of 2155 cases of severe pneumonia, involving 821 hospitalizations and 100 deaths

Severe Respiratory Disease Concurrent with the Circulation of H1N1 Influenza Gerardo Chowell, Ph.D., Stefano M. Bertozzi, NEJM June 29 2009

Implication to Hong Kong & China

Age	Mexico	U.S.A.	U.S.A. (1918)	HKSAR	China
< 15	31.3%	20.6%	32%	13.8%	21.4%
> 65	5.8%	12.5%	4.68%	12.8%	7.7%
IMR	19.01	6.3	111.2	***2.93***	21.16
MMR	55	8	22.3	***2.5*** *(2008DH)*	55

IMR = Infant mortality rate (death per 1000 live birth) 2008
MMR = Maternal mortality rate (death per 100,000 delivery)

This may partially explained why Mexico is more affected than U.S.A. apart from immunization program. This has strong implication to China.

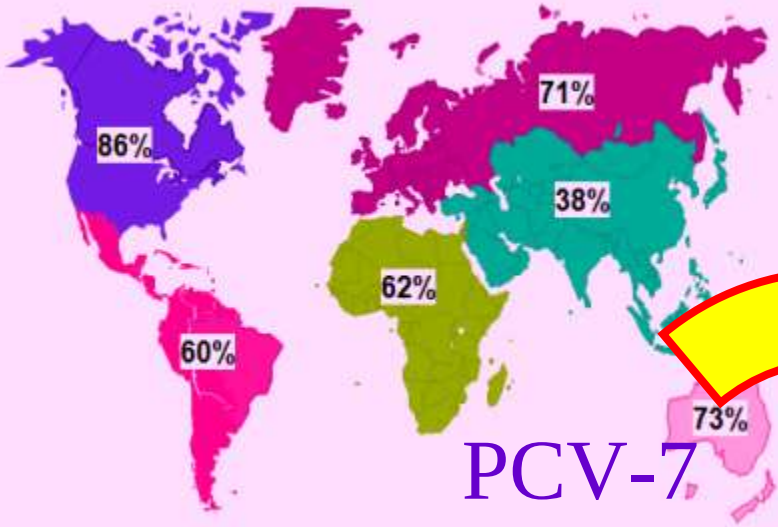
H Haemophilus Influenza B Immunization program

P Pneumococcus Immunization program

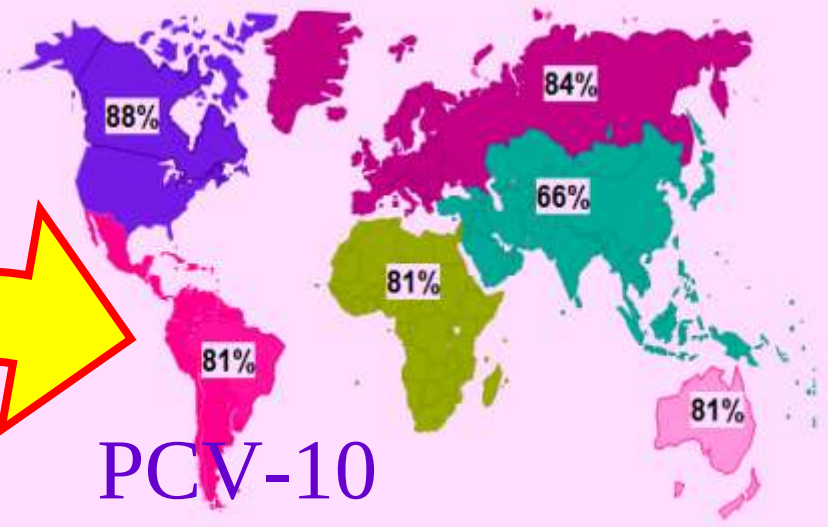
La Gloria clinical attack rates

Age Group	Attack Rate	U.S.A.	Mexico	China
<1	83.9	H P	H P	
1-4	58.1	H P	H P	
5-14	57.7	H P	H	
15-24	27.0			
25-44	31.6			
45-64	29.6			
65+	22.0	P		
Total	39.1			

Immunization Status of U.S.A. Mexico and China



PCV-7

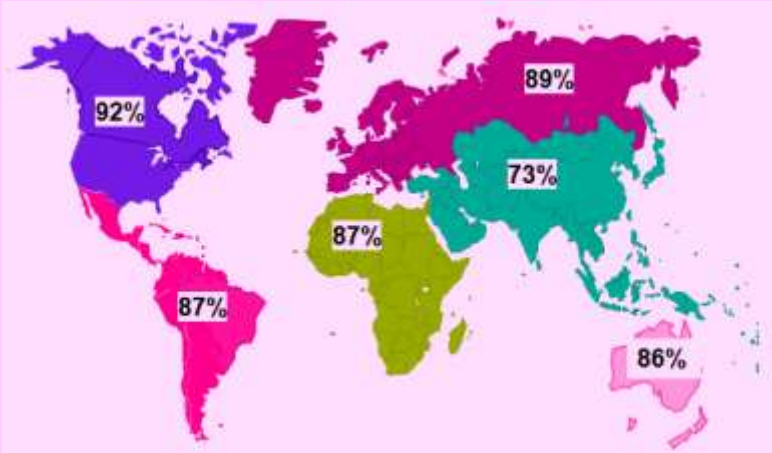


PCV-10

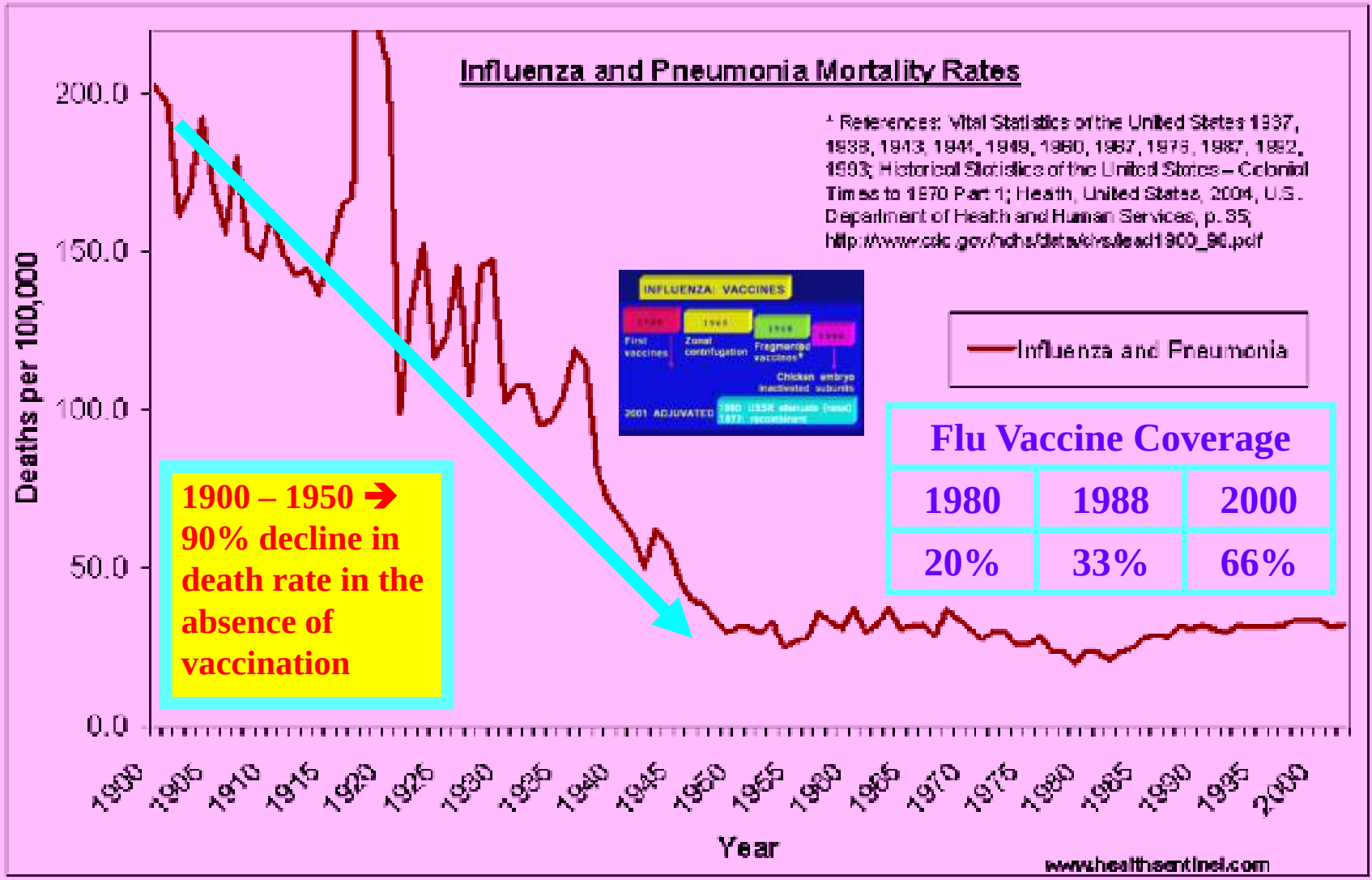
- **Proportion of pediatric pneumococcal disease prevented by PCV**

- **There are 90 serotypes of the pneumococcus each of which has a different polysaccharide capsule. Even though there are a total of 90 serotypes, 88% of global disease is caused by 23 serotypes, and only 11 serotypes account for greater than 80% of disease in children under five.**

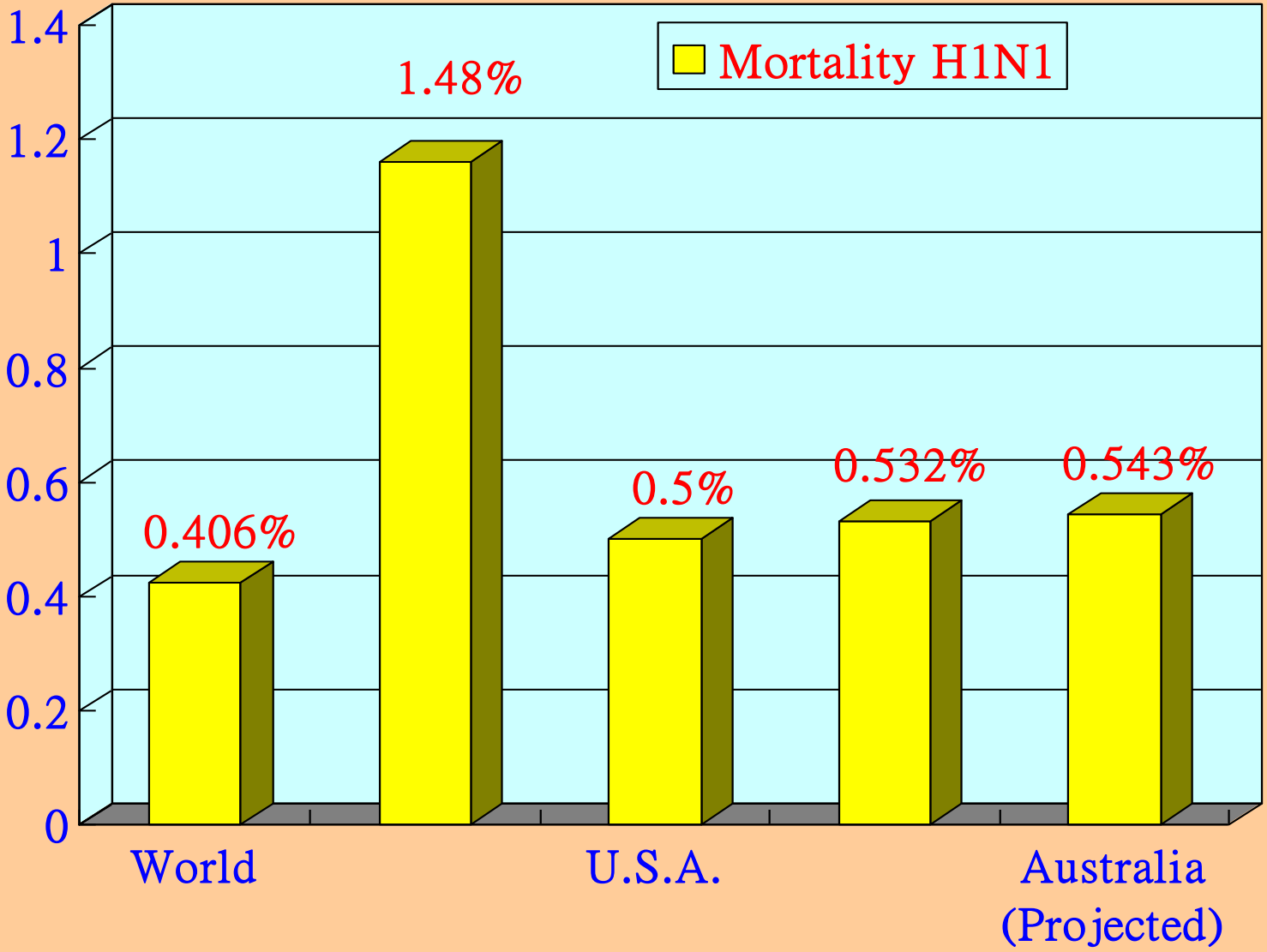
PCV -13



- **Different serotypes of pneumococcus have different global distributions. The 7-valent PCV7 vaccine is in wide use around the world in developed countries because this vaccine contains seven of the most common disease causing serotypes (4, 6B, 9V, 14, 18C, 19F, 23F) in the U.S., Canada, Australia, and Europe**



Major reduction in flu deaths depends on sanitation, nutrition and basic healthcare



- The current mortality rate in Australia is 0.486 but 53 patient is still in ICU.
- On the projected mortality of 30-40% for ARDS patient, the estimated mortality rate is 0.532% - 0.543 %which is very similar to that of the United States and the world figure.

Implication To Children in China (I)

- China and Mexico has similar maternal and neonatal mortality. What happened in Mexico would be repeated in China in the absence of mitigation and influenza vaccination.
- When there is bacterial co-infection, the mortality rate if children would increase ten times. 30 to 60% of co-infection is due to pneumococcus and Haemophilus influenza. Unlike Mexico, children in China has no Haemophilus influenza b and pneumococcal vaccination. Therefore China would be expected to have higher mortality rate in children then Mexico.. This would be disastrous to affected families because of current one child policy.

Implication To Children in China (II)

- However, the current pneumococcal vaccine PCV7 is not suitable for China because it can only cover 38% of the circulating pneumococcal strains in China.
- Because of the expected high attack rate among children in China, China should also prepare for two potential complications
  - Influenza encephalopathy/encephalitis
  - Encephalitis lethargica
    - Implication on mortality and morbidity
    - Implication for subsequent personality change with juvenile delinquency

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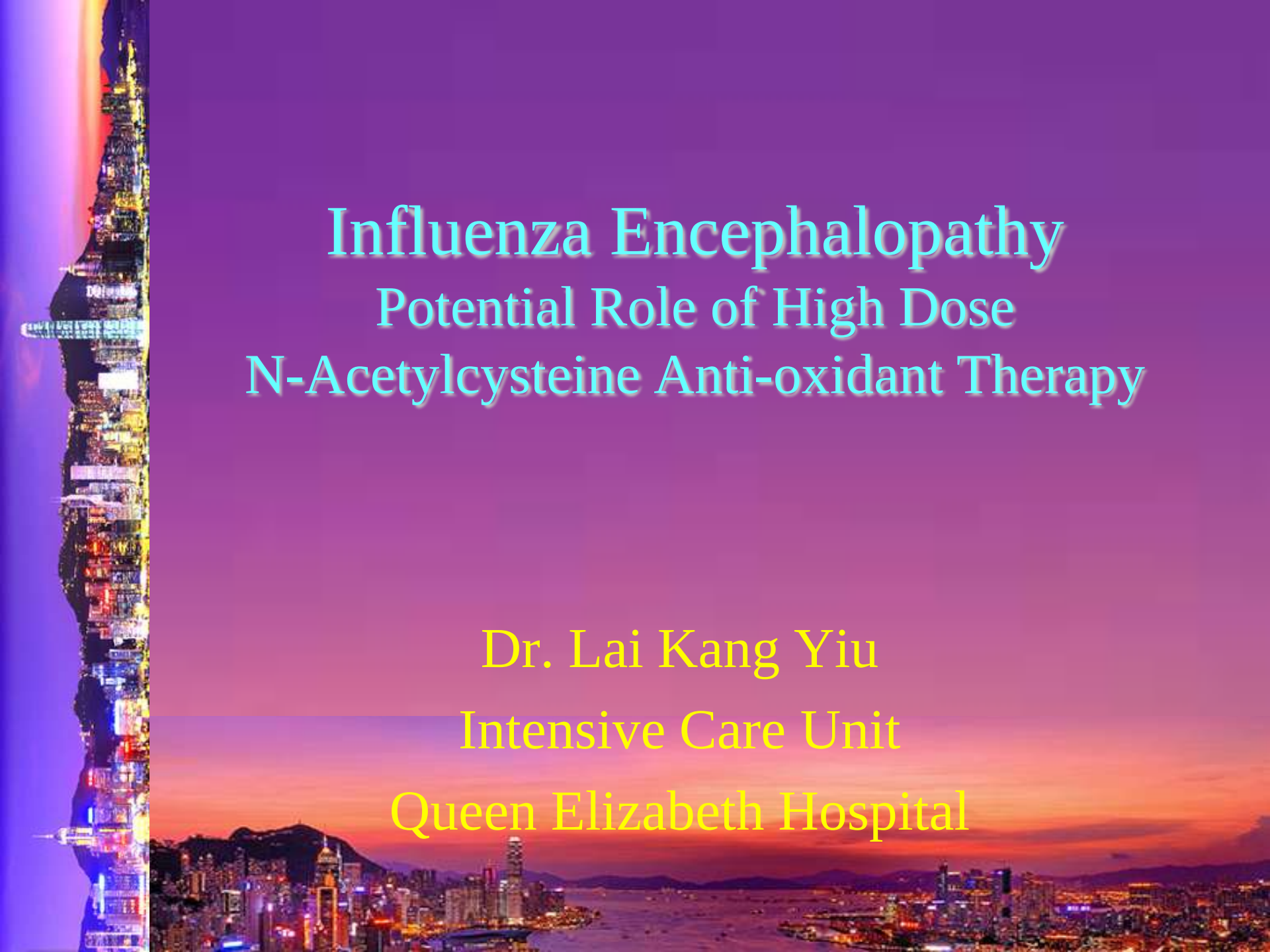
    - 40% 死亡率
    - 人格變化後的少年犯罪問題。

Any Questions ?



Influenza Encephalopathy
Potential Role of High Dose N-Acetylcysteine Anti-oxidant Therapy

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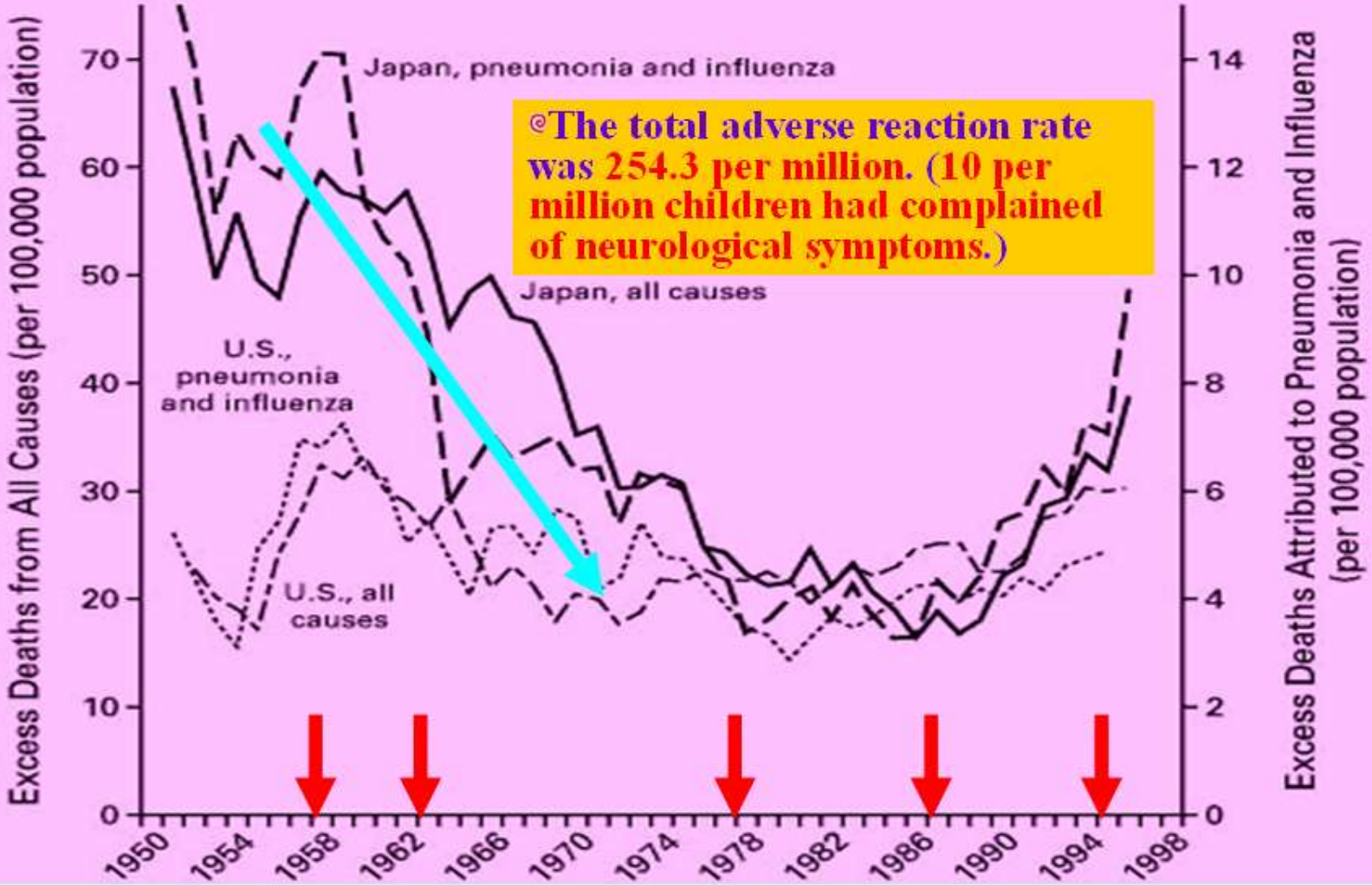
Intensive Care Unit
Queen Elizabeth Hospital



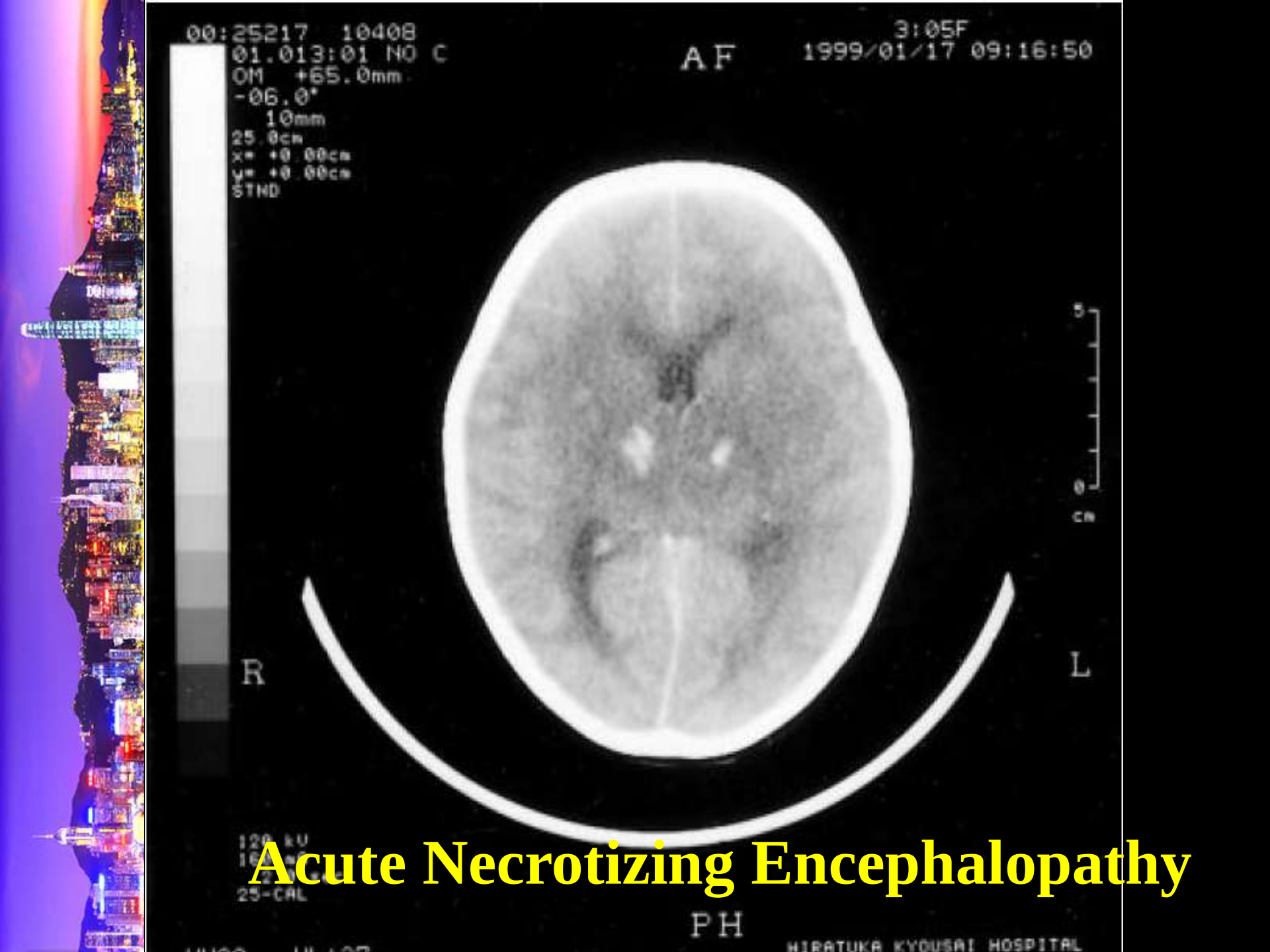
The Japanese Experience with Vaccinating Schoolchildren against Influenza N Engl J Med 344:889, March 22, 2001

1957 Asian Influenza Epidemic claimed 8,000 lives	Program to vaccinate children begins in 1962	Influenza vaccination mandatory 1977	Parents allow to refuse vaccination 1987	The government lost the case in the court 1992	Program terminated in 1994

Increasing Incidence of Influenza-encephalopathy reported in Japan after termination of mandatory influenza vaccination program

- 100 cases of fatal influenza encephalopathy in Japan reported annually over past 4 years, most following A/H3N2/Hong Kong:
  - Associated with early sudden onset of high fever, early severe seizures, rapidly progressive coma, death within 2-3 days
  - Acute necrotizing encephalopathy in >90%
  - > 25% of patients with bilateral thalamic necrosis

Influenza-associated encephalopathy in Japan
Sugaya N. Sem in Pediatr Infect Dis 2002; 13(2):79-84.



Acute Necrotizing Encephalopathy

Spectrum of CNS Complication of Influenza Virus Infection

- Encephalitis lethargica
- Reye's syndrome
- Acute necrotizing encephalopathy (ANE)
- Influenza encephalopathy and encephalitis
  - Sudden onset of high fever, early development of unconsciousness, recurrent convulsions and death within 2 or 3 days.
- Acute encephalopathy with biphasic seizures and late reduced diffusion
- Febrile convulsion (most common)

Pathological Finding

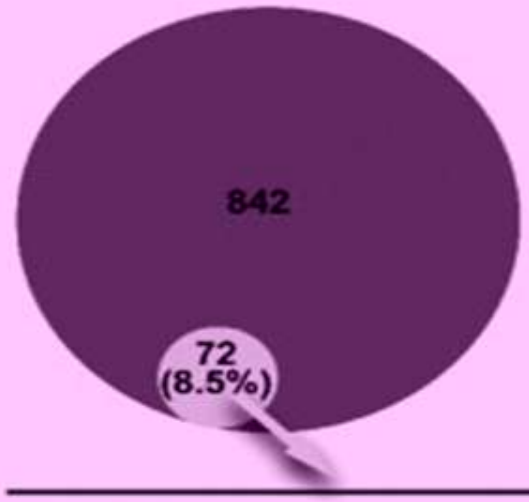
Influenza encephalopathy	Intense congestion, occasional small hemorrhage and extravasation of plasma-like fluid into the perivascular space in all CNS regions
Influenza encephalitis	Perivascular mononuclear cell infiltration + other features of encephalopathy
Acute necrotizing encephalitis	Necrosis with many petechiae in the thalamus and tegmentum of the pons, and myelin pallor in the cerebral and cerebellar deep white matter

Influenza-associated Acute Encephalopathy

- The most serious complication of influenza infection.
- Occur worldwide, but is most prevalent in East Asia, and every year several hundreds of Japanese children are affected by influenza-associated encephalopathy.
- Mortality has recently declined, but is still high. Many survivors are left with motor and intellectual disabilities, and some with epilepsy.

Disease burden to U.S.A and Hong Kong

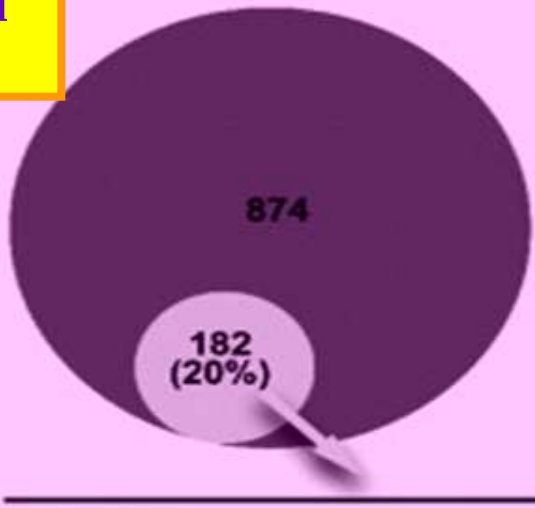
Study by Newland et al.



Neurologic complications	N= 72
Seizure	56
Febrile seizure	27
Seizure with fever	8
Other seizure	21
Encephalopathy	8
Post-infectious encephalopathy	2
Other	6
Stroke secondary to hypotension	4
Aseptic meningitis	2

4-year retrospective cohort in USA 2000-2004: no mortality, 1 with neuologic sequelae

y in Hong Kong



Neurologic complications	N= 182
Encephalopathy	5
Encephalitis	1
Aseptic meningitis	1
Febrile seizure	165
Other seizures	8
Myositis	2

5-year retrospective cohort in Hong Kong 1998-2003: 2 mortality, 1 with neuologic sequelae

- Neurologic complications in children hospitalized with influenza: comparison between USA and Hong Kong. Chung BH. Tsang AM. Wong VC Journal of Pediatrics. 151(5):e17-8; author reply e18-9, 2007 Nov.

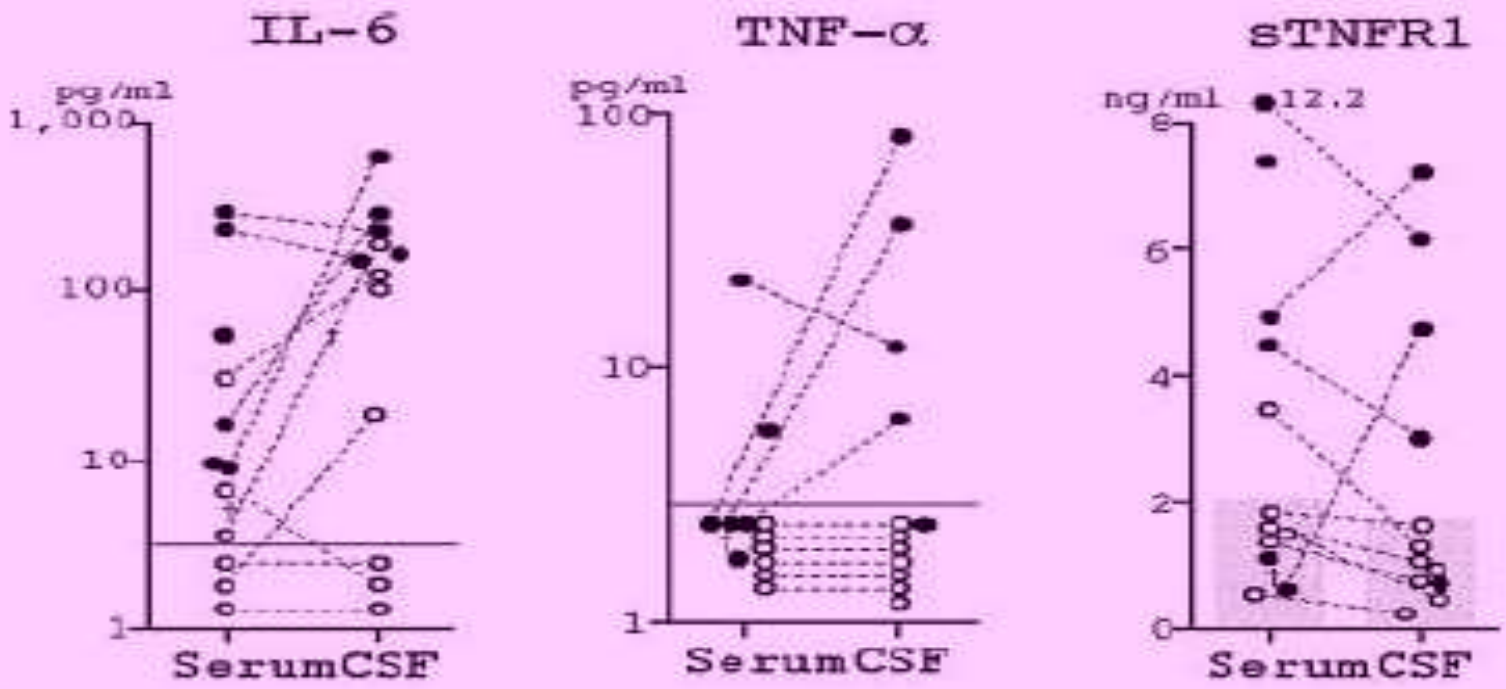
Cytokines and Influenza Encephalopathy

- Cytokines are considered to play an important role in the pathogenesis of influenza encephalopathy. The levels of IL-6, IL10, TNF-α and soluble TNF receptors 1 (sTNFR1) were significantly increased in both serum and CSF in influenza encephalopathy.
- The IL-6 serum level could be used as a predictive value in the prognosis of influenza encephalopathy.
- CSF TNF-α and sTNFR1 levels are potentially important for predicting neurological sequelae, however they were not elevated in several severe cases.
- Apoptosis under hypercytokinemia is a possible pathogenesis in influenza-associated encephalopathy

Predictive value of serum interleukin-6 level in influenza virus–associated encephalopathy

[Hideo Aiba, MD, Mika Mochizuki, MD, Mitsuaki Kimura, MD and Hiroatsu Hojo, MD *Neurology* 2001;57:295-299]

- The serum IL-6 levels were >6,000 pg/mL in children with brain stem dysfunction, about 150 pg/mL in children without brain stem dysfunction, and <80 pg/mL in controls.
- The time course of the serum IL-6 level also reflected the clinical condition. Once the serum IL-6 level was increased to >15,000 pg/mL, none of the children survived. The lower the maximal serum IL-6 level, the milder the CNS sequelae.



Serum and cerebrospinal fluid (CSF) concentrations of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and soluble TNF receptor 1 (sTNFR1) in children with influenza virus-associated encephalopathy. Horizontal lines denote detection limits. The shaded areas show the values for control subjects (mean ± 2 SD). Dotted lines indicate samples from the same children on the same days. Closed circles: group 1; †: deceased case; open circles: group 2.

Cerebrospinal fluid and serum levels of cytokines and soluble tumor necrosis factor receptor in influenza virus-associated encephalopathy

T. Ichiyama, H. Isumi, H. Ozawa, T. Matsubara, T. Morishima and S. Furukawa,, *Scand J Infect Dis* 35 (2003), pp. 59–61

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- The present study revealed elevated cytokine levels not only in serum but also in CSF of children with influenza virus-associated encephalopathy.
- The children with a poor outcome tended to have highly elevated levels of IL-6, TNF- α and sTNFR1 in serum and/or CSF. In particular, the 4 children with elevated TNF- α and sTNFR1 levels in CSF had neurological sequelae.
- A high level or overexpression of IL-6 may be neurotoxic under pathological conditions.
- TNF- α increases blood–brain vascular permeability, injures vascular endothelial cells, and induces necrosis of myelin and oligodendrocytes.
- Previous studies showed that sTNFR is the natural homeostatic regulator of the action of TNF- α, and that its level, rather than that ofTNF- α, reflects the true biological activity of TNF- α.

Statistical analysis of various markers in sera from patients with and without influenza-associated encephalopathy

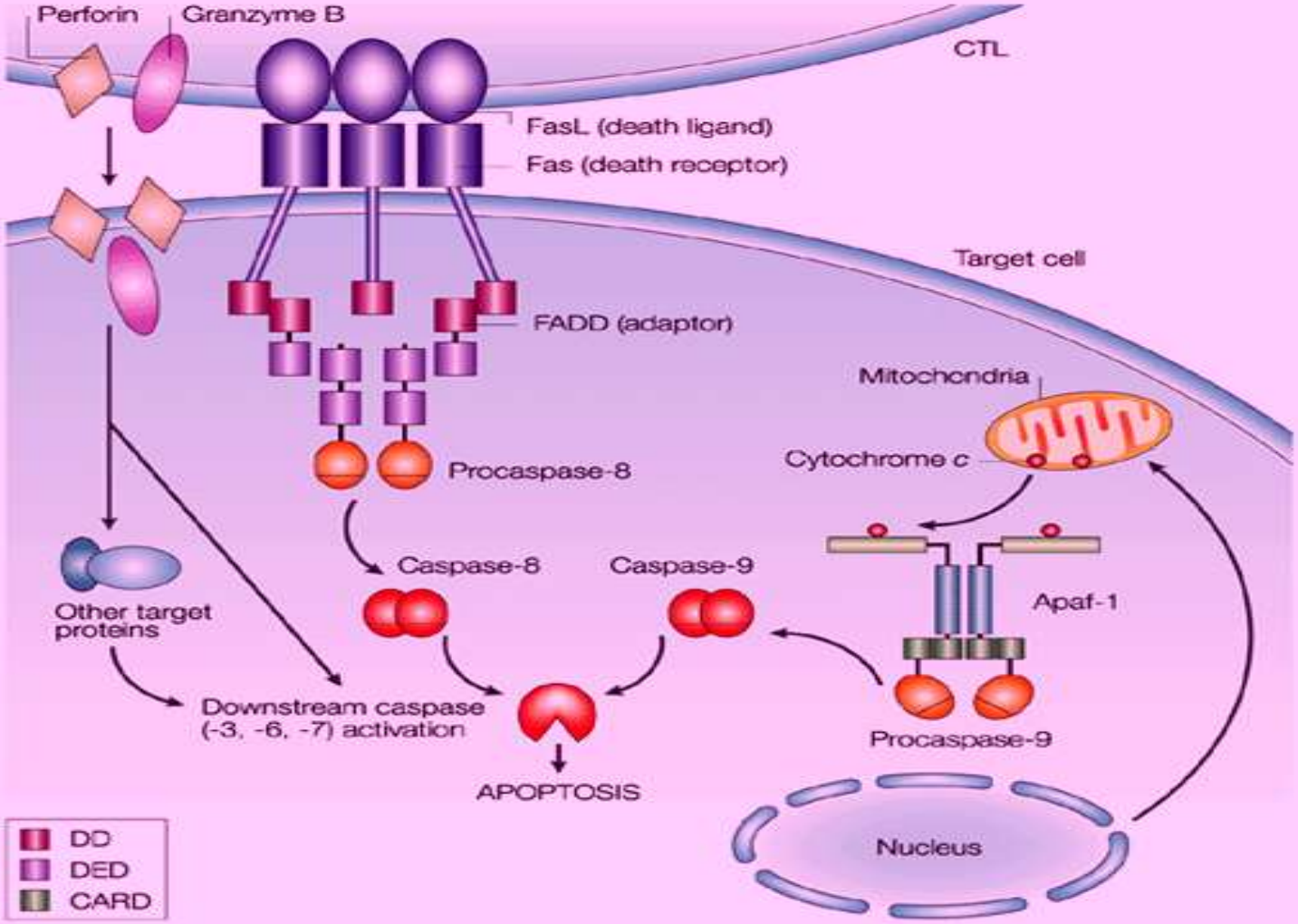
Markers	Normal	without IE	with IE	*P*-value
Cytochrome c	< 0.05 ng/mL	0.3 ± 0.7 (42)	26.8 ± 19.5 (11)	< 0.001
TNF-α	0 pg/mL	0.9 ± 3.7 (17)	11.6 ± 17.1 (5)	0.003
IL-8	1.2–16.7 pg/mL	17.3 ± 16.1 (16)	339.8 ± 400.2 (8)	0.016
IL-6	0–149 pg/mL	49.8 ± 156.7 (17)	55.5 ± 125.7 (6)	0.35
Soluble TM	11–20 ng/mL	1.4 ± 0.8 (27)	17.4 ± 19.8 (6)	0.39
Soluble Fas	1–3.9 ng/mL	1.4 ± 0.8 (29)	1.7 ± 0.5 (6)	0.52
Soluble E-selectin	20–60 ng/mL	76.6 ± 43.7 (42)	133.7 ± 0.5 (6)	0.99

The Mann-whitney *U*-test was used to determine significant differences in each marker between the patients with or without encephalopathy ($P < 0.05$).

IE, influenza-associated encephalopathy; IL, interleukin; Patients, number of patients examined; TNF-α, tumor necrosis factor-α.

Apoptosis under hypercytokinemia is a possible pathogenesis in influenza-associated encephalopathy

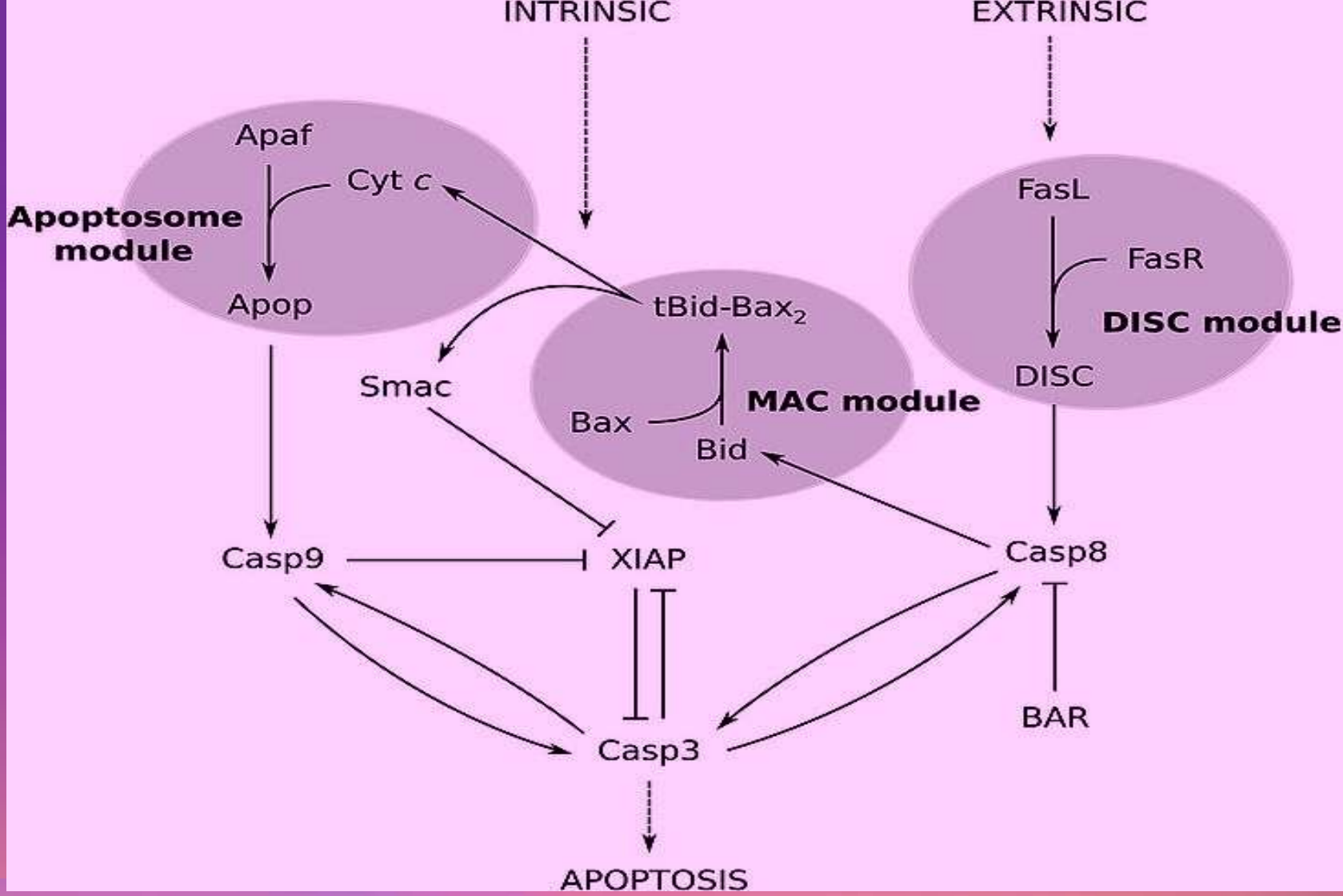
H. Nunoi, M.R. Mercado, T. Mizukami, K. Okajima, T. Morishima and H. Sakata *et al.*, *Pediatr Int* **47** (2005), pp. 175–179.



Apoptosis can occur via cell-surface-death-receptor- or mitochondrial-dependent pathways.

SIV-mediated apoptosis might be regulated by both receptor- and mitochondrial-mediated cell death.

Activation of the intrinsic mitochondrial apoptotic pathway in swine influenza virus-mediated cell death
Young Ki Choi EXPERIMENTAL and MOLECULAR MEDICINE, Vol. 38, No. 1, 11-17, February 2006


INTRINSIC
EXTRINSIC
Apaf
Cyt c
Apoptosome module
Apop
FasL
FasR
DISC module
DISC
tBid-Bax2
Smac
MAC module
Bax
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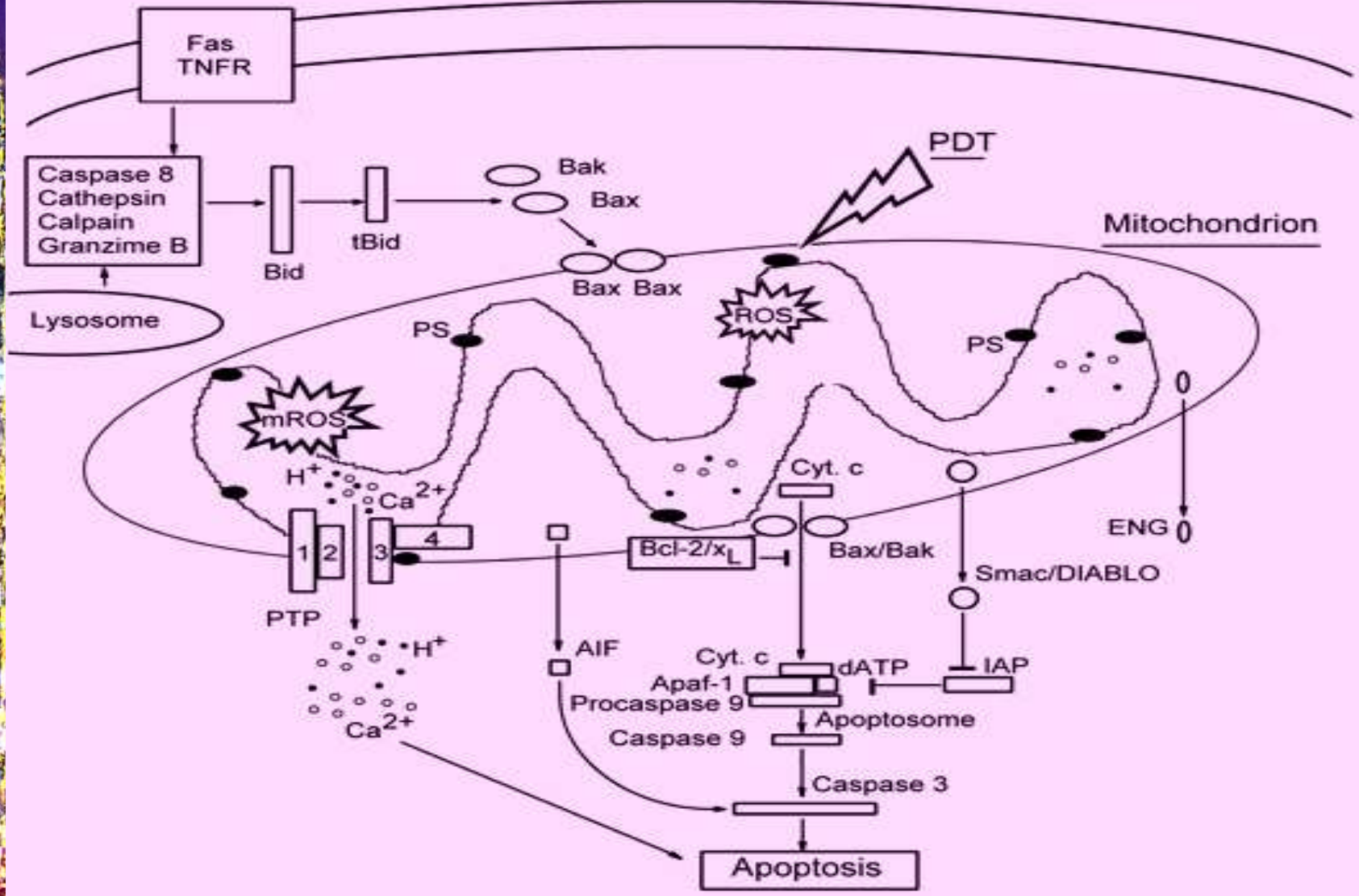
Casp9
XIAP
Casp8
BAR
Casp3
APOPTOSIS



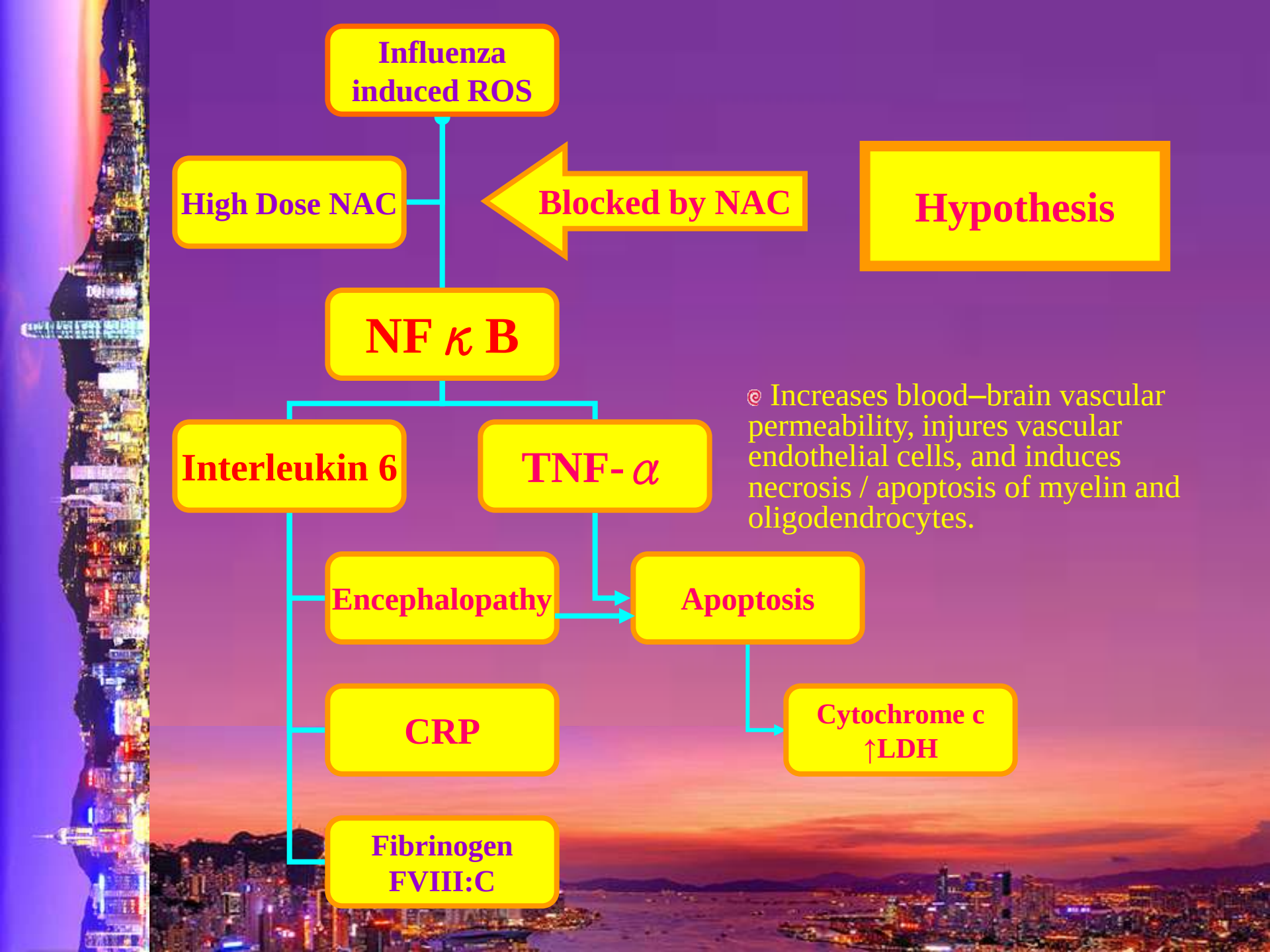
FAS and TNFR induced mitochondrial apoptosis pathway

? LDH can serve as a marker of influenza virus induced apoptotic cell degradation

Lactate Dehydrogenase Leakage as a Marker for Apoptotic Cell Degradation Induced by Influenza Virus Infection in Human Fetal Membrane Cells

Noboru Uchide, Kunio Ohyama, Toshio Bessho, Hiroo Toyoda

Intervirology 2009;52:164-173

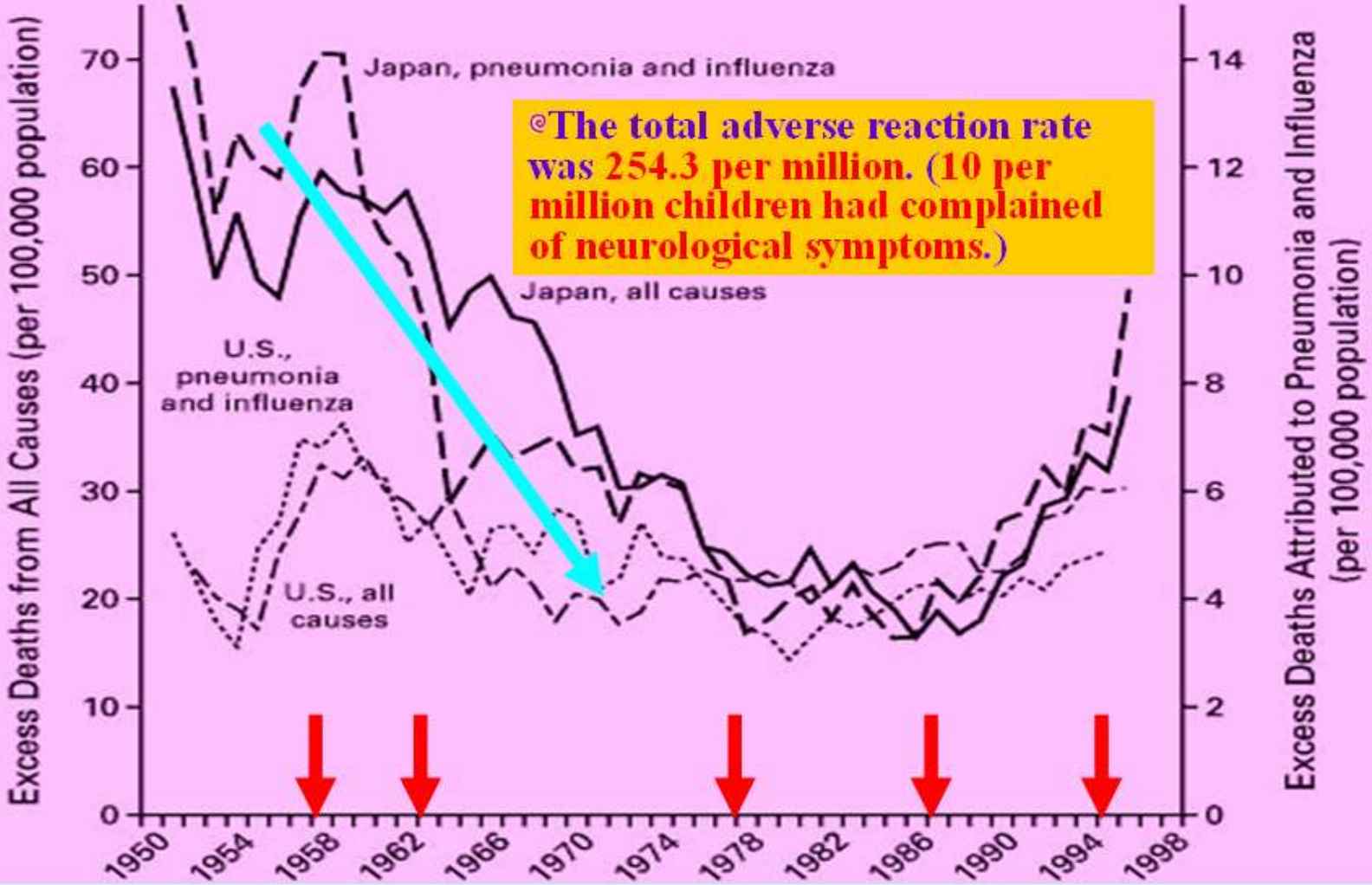

Influenza induced ROS
High Dose NAC
Blocked by NAC
Hypothesis
NF κ B
Interleukin 6
TNF- α
Encephalopathy
Apoptosis
CRP
Cytochrome c
↑LDH
Fibrinogen
FVIII:C
Increases blood–brain vascular permeability, injures vascular endothelial cells, and induces necrosis / apoptosis of myelin and oligodendrocytes.

Influenza Encephalopathy
A bitter experience from Japan

Mandatory mass influenza vaccination program in children was aborted because of neurological complications

Discontinuation of Vaccination Program results in more death and disability due to influenza encephlopathy, encephalitis and acute necrotizing encephalopathy

Mass immunization of school-aged children reduced the mortality rate from influenza-associated acute encephalopathy/encephalitis in children less than 9 years of Age !!!



The Japanese Experience with Vaccinating Schoolchildren against Influenza N Engl J Med 344:889, March 22, 2001

1957 Asian Influenza Epidemic claimed 8,000 lives	Program to vaccinate children begins in 1962	Influenza vaccination mandatory 1977	Parents allow to refuse vaccination 1987	The government lost the case in the court 1992	Program terminated in 1994

Influenza Vaccination Program for School children In Japan

- A mass study of adverse reactions against the influenza vaccine was conducted in 1987 involving about 400,000 children.
- The total adverse reaction rate was 254.3 per million. (10 per million children had complained of neurological symptoms.)
- This study was revealing, since from 1971 the government had changed the flu vaccine from a whole body type to a split particle type announcing that adverse reactions were almost nothing with the new one. The previous type , used in the 1960s had resulted in between 5-9 deaths occurring every year.
- In 1987 the government changed the vaccine from compulsory to free choice.
- From 1972 to 1979 , a total number of 142 children and families sued the government for damages. The total number of deaths were 50, severe developmental retardation were 65, and intractable epilepsy were 35.
- In 1992, the government lost the case in the court after about 20 years of legal proceedings.

The Japanese Experience with Vaccinating Schoolchildren against Influenza

N Engl J Med 344:889, March 22, 2001

- Vaccinating schoolchildren against influenza provides protection and reduces mortality from influenza among older persons.
- The vaccination of Japanese children prevented about 37,000 to 49,000 deaths per year, or about 1 death for every 420 children vaccinated.
- As the vaccination of schoolchildren was discontinued, the excess mortality rates in Japan increased.

Influenza-associated encephalitis and encephalopathy in children

- Increased reports of influenza-associated encephalitis and encephalopathy from Japan beginning in 1990s
- Prompted nationwide surveillance efforts in Japan with medical community and public education of CNS complications of influenza
- It become a notifiable disease since Nov 2003 and physicians must notify within 7 days after diagnosis. [IASR Vol. 28, No. 12 (No. 334)]
  - http://idsc.nih.go.jp/iasr/28/334/tpc334.html

Encephalitis and encephalopathy associated with an influenza epidemic in Japan.

Morishima T et al. Clin Infect Dis 2002; 35:512-7.

- Retrospective study of 1998-99 flu season,
  - National survey of every local health care center in Japan
  - Definition of encephalitis/encephalopathy clinical (altered consciousness or loss of consciousness), diagnosis of influenza based on positive culture, antigen test, PCR, or increased HAI titers
  - 148 cases met their definition of encephalopathy with documented influenza

Encephalitis and encephalopathy associated with an influenza epidemic in Japan.

Morishima T et al. Clin Infect Dis 2002; 35:512-7.

- Typical course
  - Onset of high fever, seizures, and altered consciousness, rapid progression to comatose state within 1-2 days of flu symptoms
  - Few patients with Reye's syndrome (4%)
  - Associated with influenza A (88%)
  - CSF findings frequently normal, brain imaging suggestive of cerebral edema and localized areas of low density, some with bilateral symmetric thalamic low densities (acute necrotizing encephalopathy, ANE)
  - Very high mortality (32%) and "disability" (28% total, 9% with severe sequelae)

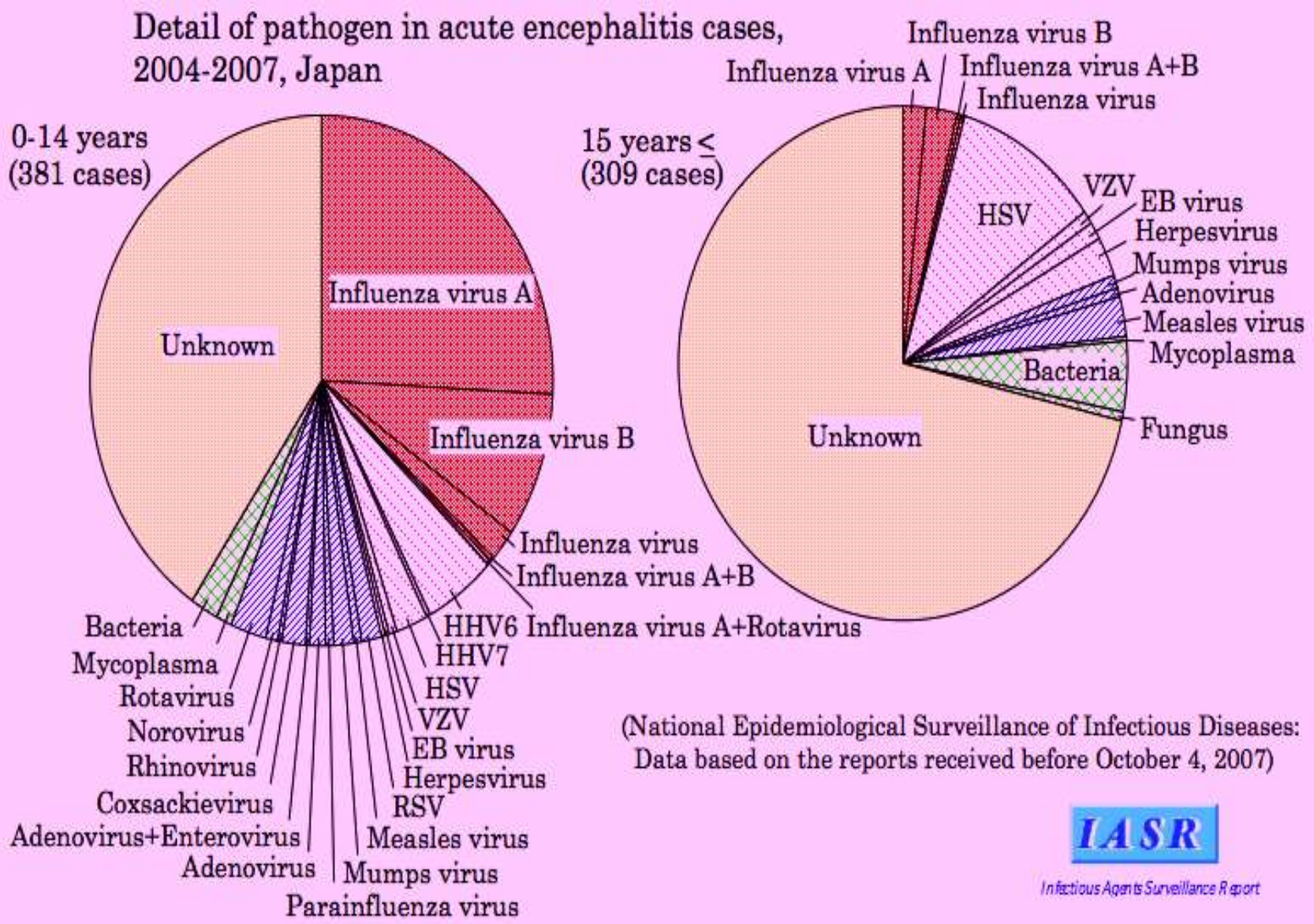
Influenza-associated encephalopathy in Japan

Sugaya N. Sem in Pediatr Infect Dis 2002; 13(2):79-84.

- 100 cases of fatal influenza encephalopathy in Japan reported annually over past 4 years, most following A/H3N2/Hong Kong:
  - Associated with early sudden onset of high fever, early severe seizures, rapidly progressive coma, death within 2-3 days
  - Acute necrotizing encephalopathy in >90%
  - > 25% of patients with bilateral thalamic necrosis

Influenza-associated encephalitis and encephalopathy in children

- No accepted explanation for difference in rate/pattern of CNS complications in Japan compared to other countries
- Japanese report continued high rates of influenza-related encephalitis and encephalopathy in recent flu seasons but mortality rates have decreased
- Some suggest decreased mortality due to increased awareness and rapid diagnosis and treatment of influenza among children



Details of pathogen in acute encephalitis cases 2004-2007 Japan

Influenza encephalopathy in Japan 2004 – 2007 (after Nov. 2003)

- It is estimated that annually 100-300 cases of acute encephalopathy accompanying influenza occur according to the study group of MHLW on influenza encephalopathy headed by Dr. T. Morishima.
- According to NESID, 53 cases (type A 19 cases, type B 29 cases, types A+B 3 cases, and type unknown 2 cases) in 2004/05 season, 53 cases (type A 48 cases, type B 4 cases, and type A+rotavirus 1 case) in 2005/06 season, and, 42 cases (type A 30 cases, type B 7 cases and type unknown 5 cases) in 2006/07season were reported, reflecting the prevalent type of each season.

Mass immunization of school-aged children reduced the mortality rate from influenza-associated acute encephalopathy/encephalitis in children less than 9 years of Age !!!

- Total influenza mortality among children aged <19 years has increased since 1990, with children aged <4 years after 1994 being the worst affected. The mean values of mortality rates of influenza associated with central nervous system signs during 1963–1978 and the estimated mortality of children aged <9 years during 1979–1994 were significantly lower than in some years before 1962, and after 1995 ($P < 0.05$).
- The annual mortality rates of influenza-associated acute encephalopathy/encephalitis during 1995–2000 were significantly higher than the expected mortality of influenza associated with central nervous system signs in children aged <14 years ($P < 0.05$).

Effect of mass immunization against influenza encephalopathy on mortality rates in children

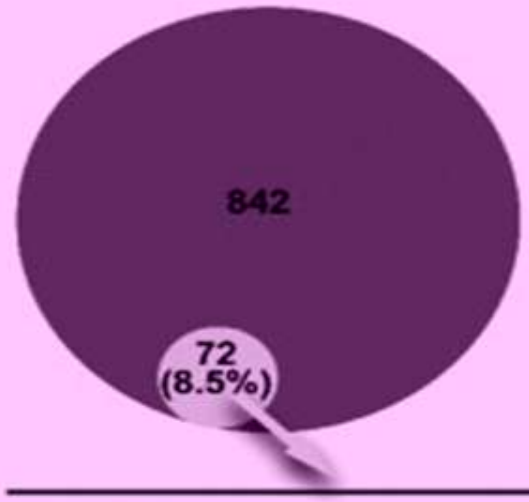
SHIGETOO ONO, MASANOBU KUDO, KAZUO AOKI, FUSAKO EZAKI AND JUNICHI MISUMI *Pediatrics International* (2003) 45 , 680–687

Influenza-associated encephalitis and encephalopathy in children

- Isolated case reports and small series of encephalitis and encephalopathy from U.S.
- Largest series from Houston during 2003-04 flu season (Maricich S et al. Neurologic complications associated with influenza A in children during the 2003-2004 influenza season in Houston, Texas. Pediatr 2004; 114:e626-33.)
  - 478 laboratory-confirmed cases of influenza A at Texas Children's Hospital
  - 8 patients hospitalized with neurologic symptoms
  - Antiviral use after admission – 4 received rimantidine and one received Tamiflu
  - One with significant neurologic sequelae (ANE)

Disease burden to U.S.A and Hong Kong

Study by Newland et al.



Neurologic complications	N= 72
Seizure	56
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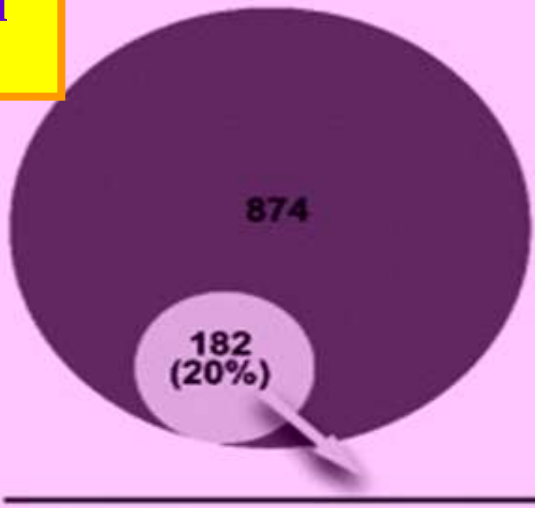
Seizure with fever	8
Other seizure	21
Encephalopathy	8
Post-infectious encephalopathy	2
Other	6
Stroke secondary to hypotension	4
Aseptic meningitis	2

4-year retrospective cohort in USA 2000-2004: no mortality, 1 with neuologic sequelae

y in Hong Kong



Neurologic complications	N= 182
Encephalopathy	5
Encephalitis	1
Aseptic meningitis	1
Febrile seizure	165
Other seizures	8
Myositis	2

5-year retrospective cohort in Hong Kong 1998-2003: 2 mortality, 1 with neuologic sequelae

- Neurologic complications in children hospitalized with influenza: comparison between USA and Hong Kong. Chung BH. Tsang AM. Wong VC Journal of Pediatrics. 151(5):e17-8; author reply e18-9, 2007 Nov.

Neurologic complications in children hospitalized with influenza: characteristics, incidence, and risk factors

Newland JG. Laurich VM. Rosenquist AW. Heydon K. Licht DJ. Keren R. Zaoutis TE. Watson B. Hodinka RL. Coffin SE. Journal of Pediatrics. 150(3):306-10, 2007 Mar.

- The incidence of influenza related neurological complications (INC) was approximately 4 cases per 100,000 child-years.
- Patients between the ages of 2 and 4 years and patients with a pre-existing NNMD were at greatest risk for developing an INC.
- Seizures were the most common INC.
- Influenza encephalopathy occurred in a small proportion of patients hospitalized with laboratory confirmed influenza (LCI) infections.

Febrile convulsion Vs AESD

- Influenza A is associated with a high incidence (6 to 40%) of FS, especially in older children and.
- Most of these persist for less than 15 min (45/47, 95.7%), and neurological prognosis is good. Therefore, no clinical follow-up is generally recommended for patients with a brief FS associated with influenza A infections.
- However, the parents should be informed about the possible secondary progression around day 5. This may herald the condition acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) that is associated with significant mortality and morbidity.

- Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD)
  - Biphasic seizures on days 1, and 4 to 6;
  - Radiologically by no acute abnormality is visible during the first two days, while reduced diffusion in the subcortical white matter is seen during days 3 to 9, finally resulting in cerebral atrophy.
  - The subcortical abnormalities do not result from the initial seizure as patient with status epilepticus has no subcortical abnormalities.

Severe form of acute influenza encephalopathy with biphasic seizures and late reduced diffusion.
Tada H. Takanashi JI. Terada H. Tajima K. Neuropediatrics. 39(2):134-6, 2008 Apr.

Mild influenza encephalopathy with biphasic seizures and late reduced diffusion.
Takanashi J. Tsuji M. Amemiya K. Tada H. Barkovich AJ Journal of the Neurological Sciences. 256(1-2):86-9, 2007 May 15.

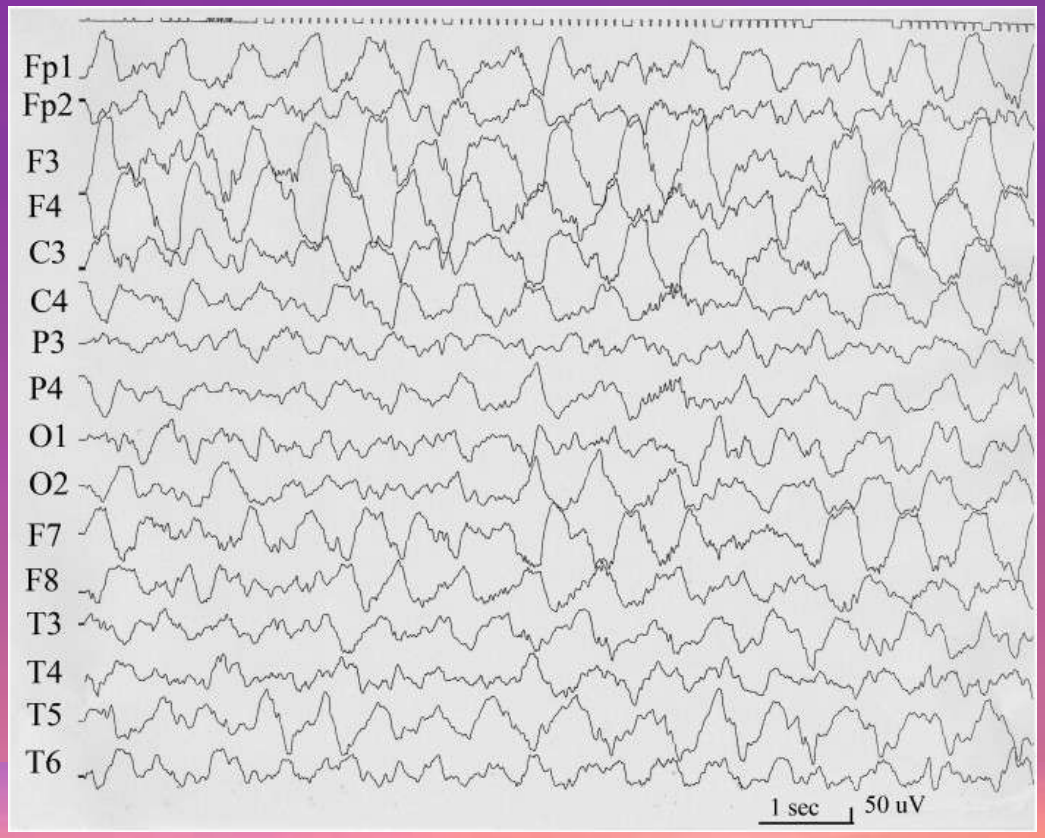
Acute encephalopathy with biphasic seizures and late reduced diffusion

- MR spectroscopy study revealed transient increased glutamate/glutamine complex along with imaging findings of reduced subcortical diffusion.
- Glutamate, an excitatory neurotransmitter, is taken up by surrounding astrocytes and metabolized into a relatively harmless compound, glutamine. Excess of glutamine in astrocytes creates an osmotic gradient, resulting in astrocytic swelling or edema, which may play a part in the reduced diffusion seen in AESD.
- In patients with influenza associated encephalopathy, CSF studies have shown increased glutamine and nitrite/nitrate (NO*x*) levels together with decreased glutamate levels, suggesting increased activity of the glutamate uptake transporter and glutamine synthetase in astrocytes.
- Some authors have speculated that the astrocytes may be activated by high NO*x*, some (unknown) viral factors and cytokines in CSF

Mild influenza encephalopathy with biphasic seizures and late reduced diffusion.

Takanashi J. Tsuji M. Amemiya K. Tada H. Barkovich AJ Journal of the Neurological Sciences. 256(1-2):86-9, 2007 May 15.

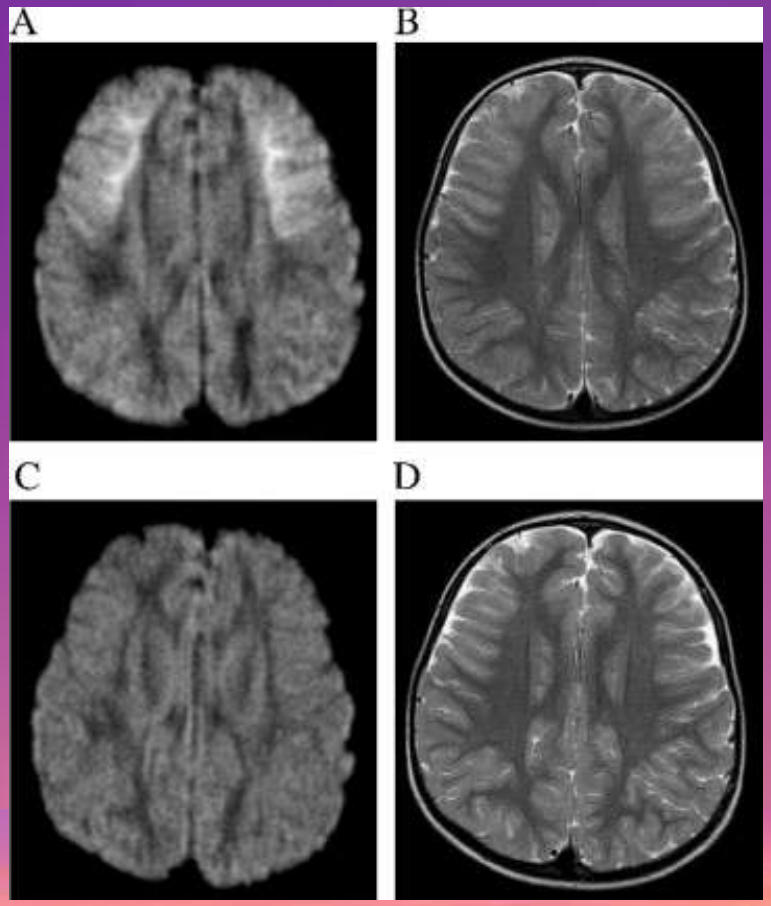
EEG on day 5 shows high voltage slow waves in the frontal region.



Mild influenza encephalopathy with biphasic seizures and late reduced diffusion.

Takanashi J. Tsuji M. Ameniya K. Tada H. Barkovich AJ Journal of the Neurological Sciences. 256(1-2):86-9, 2007 May 15

Reduced diffusion in the subcortical white matter

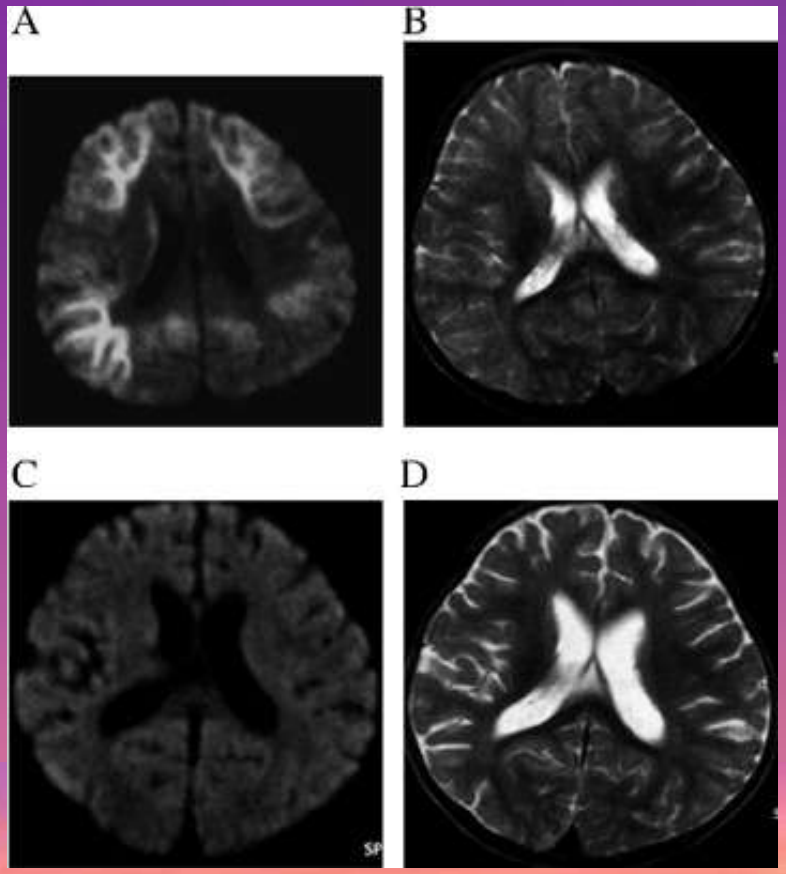


- Diffusion weighted image (A, spin-echo EPI: TE = 103; *b* = 1000; MPG with *y* axis) on day 6 reveals symmetric high signal lesion in the frontal subcortical white matter. T2-weighted image (B, FSE: TR/TE = 4000/100) shows no signal abnormality. These observations suggest reduced subcortical diffusion. Follow-up MRI after 6 months showed disappearance of the signal abnormalities and mild cerebral atrophy

Mild influenza encephalopathy with biphasic seizures and late reduced diffusion.

Takanashi J. Tsuji M. Amemiya K. Tada H. Barkovich AJ Journal of the Neurological Sciences. 256(1-2):86-9, 2007 May 15.

Reduced Subcortical Diffusion



- Diffusion weighted image (A, spin-echo EPI: TR, 4000; TE = 100; *b* = 1000) on day 5 reveals asymmetric high signal lesion in the fronto-parietal subcortical and deep white matter with sparing of peri-Rolandic region. T2-weighted image (B, FSE: TR/TE = 3400/90) shows subtle T2 abnormality in the cortex and blurring of the cortical-white matter junction in the same area that shows the diffusion abnormality. These observations suggest reduced subcortical diffusion. Follow-up MRI at day 40 shows mild cerebral atrophy with no signal abnormalities (C, D).

Mild influenza encephalopathy with biphasic seizures and late reduced diffusion.

Takanashi J. Tsuji M. Amemiya K. Tada H. Barkovich AJ Journal of the Neurological Sciences. 256(1-2):86-9, 2007 May 15

Cytokine regulation of interleukin-6 gene expression in astrocytes involves activation of an NF-κB-like nuclear protein

SPARACIO S. M. ; YIHONG ZHANG (1) ; VILCEK J. ; BENVENISTE E. N. Journal of neuroimmunology 1992, vol. 39, no3, pp. 231-242 (1 p.)

- The cytokines interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) induce interleukin-6 (IL-6) gene expression in astrocytes.
- The molecular mechanism(s) by which these cytokines activate IL-6 expression was examined by transient transfection of the human IL-6 promoter linked to the reporter gene CAT (IL-6-CAT) in primary rat astrocytes. Both IL-1β and TNF-α exert their effects through the IL-6 promoter to increase CAT activity, indicating that the cytokines act at the transcriptional level. Use of deletion mutants revealed that the **NF-KB-like binding site is required for cytokine induction of IL-6 promoter activity**.

There is an increase of microglia and apoptosis of neurons and glial cells in fatal cases of influenza encephalopathy and encephalitis. In particular activated microglia and apoptosis may play an important role in their pathogenesis.

Apoptosis and microglial activation in influenza encephalopathy

Yoshiko Nakai Acta Neuropathologica 2002

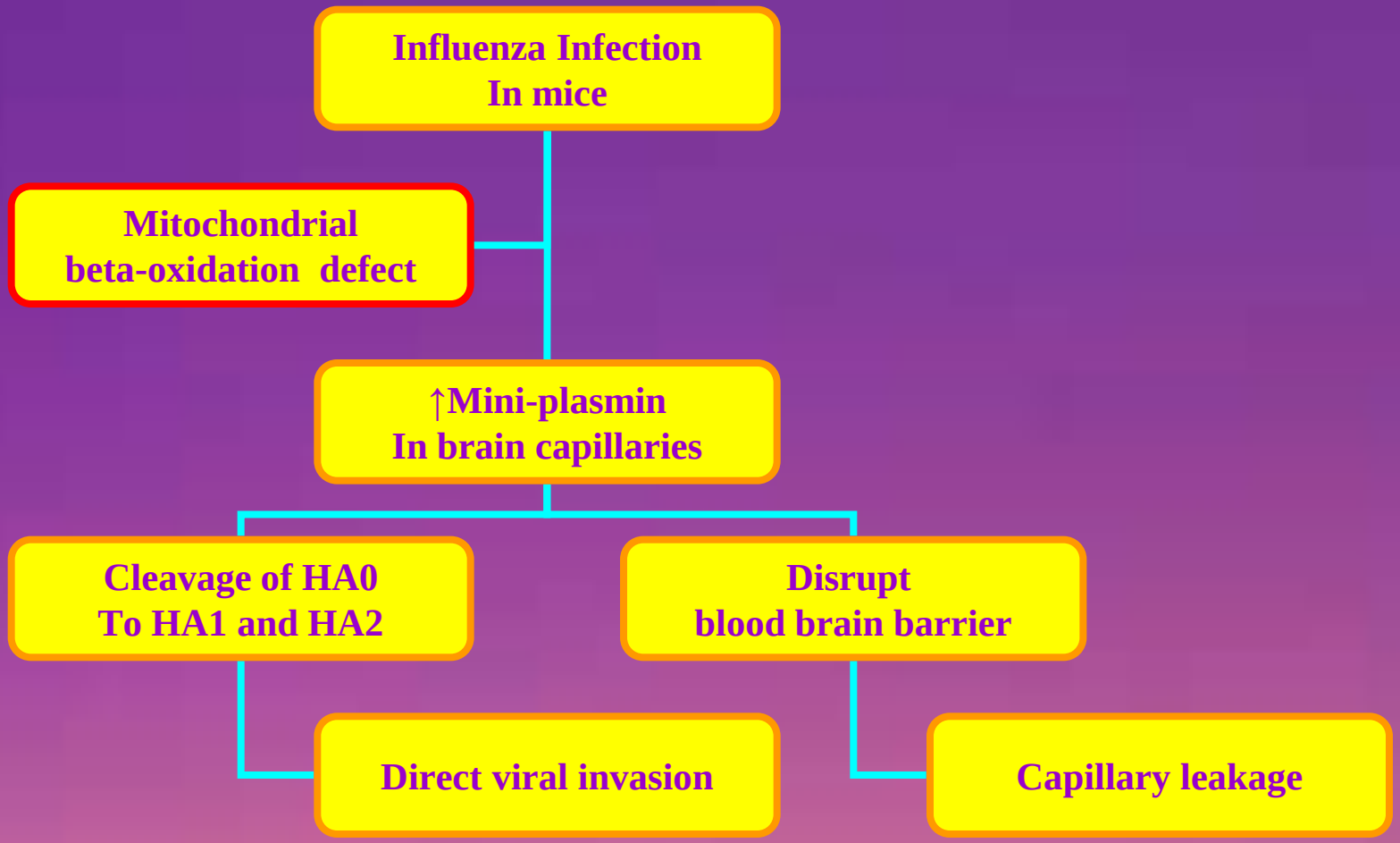
Possible Role of Direct Viral Invasion

Dr. Lai Kang Yiu
Intensive Care Unit
Queen Elizabeth Hospital

An adult autopsy case of acute encephalopathy associated with influenza A virus.

Ishigami A. Kubo S. Ikematsu K. Kitamura O. Tokunaga I. Gotohda T. Nakasono I.
Legal Medicine. 6(4):252-5, 2004 Oct.

- 35 year old male die of pneumonia and cerebral edema.
- Influenza A virus antigen was detected in both the lungs and brain.
- Brain edema was also observed, and proliferation of lymphocytes was observed around the capillary vessels of the **hippocampus.**



Accumulation of mini-plasmin in the cerebral capillaries causes vascular invasion of the murine brain by a pneumotropic influenza A virus: implications for influenza-associated encephalopathy.

Yao D. Chen Y. Kuwajima M. Shiota M. Kido H. Biological Chemistry. 385(6):487-92, 2004 Jun.

MRI Finding in Mitochondrial Respiratory Chain Defect

Magnetic resonance imaging (MRI) showed diffuse cortical atrophy in 34 cases (70.8%), basal ganglia signal changes in 18 cases (37.5%) and thalamus signal changes in 12 cases (25.0%).

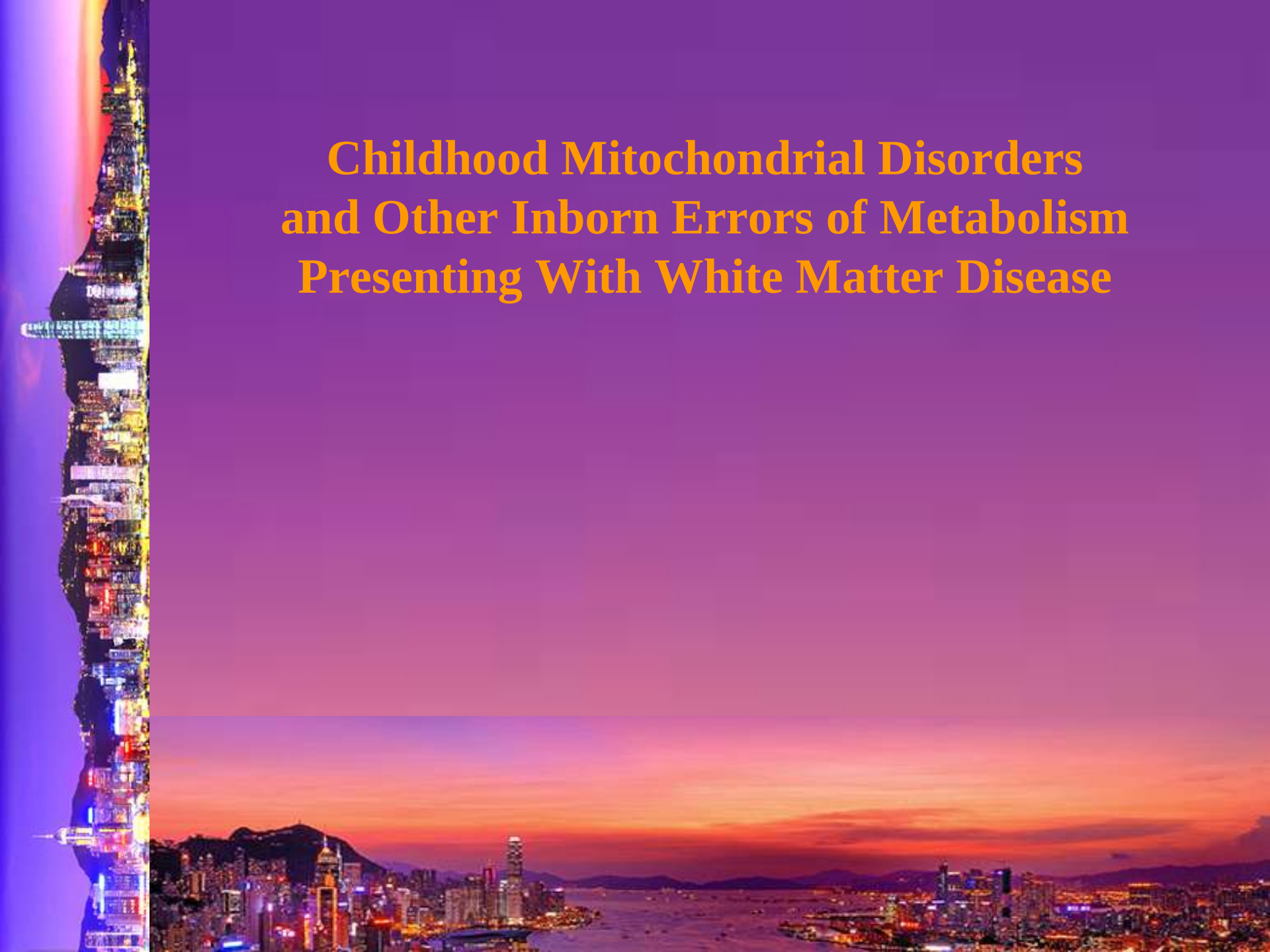
Mitochondrial respiratory chain defects:

Underlying etiology in various epileptic conditions

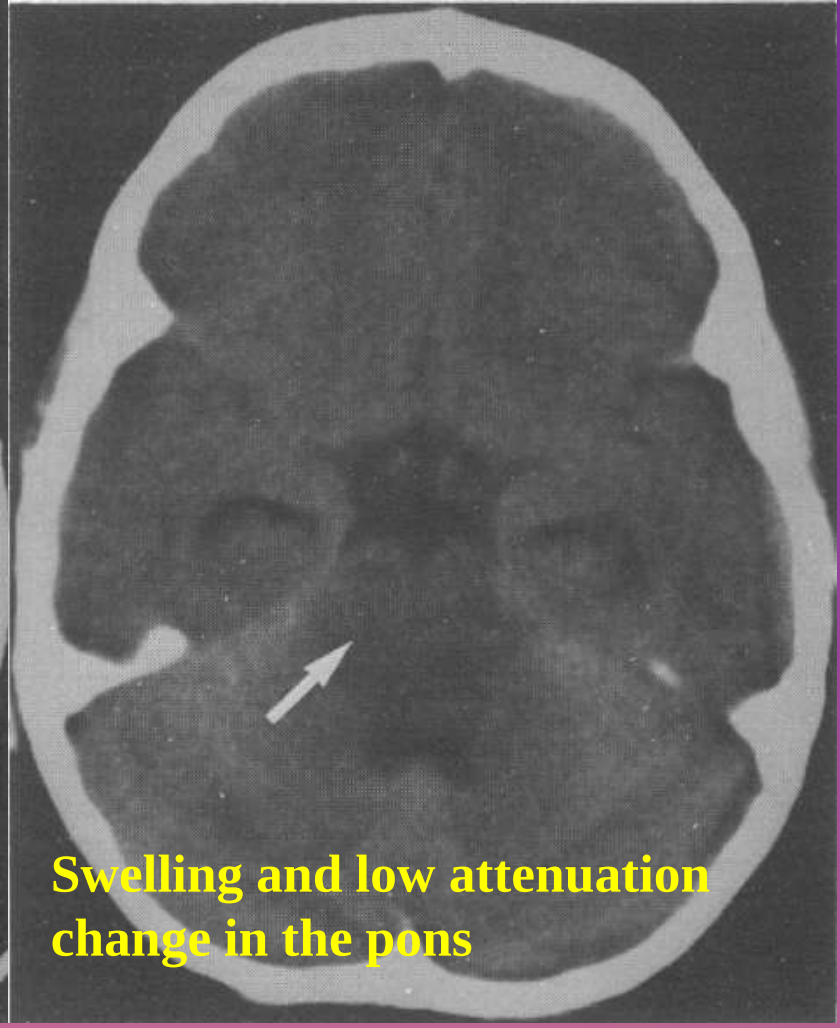
***Young Mock Lee, †Hoon Chul Kang, *Joon Soo Lee, ‡Se Hoon Kim, §Eung Yeop Kim, §Seung Koo Lee, ¶Abdelhamid Slama, and *Heung Dong Kim**

Epilepsia Volume 49 Issue 4, Pages 685 - 690

Childhood Mitochondrial Disorders and Other Inborn Errors of Metabolism Presenting With White Matter Disease



Low attenuation lesions in both thalami



Swelling and low attenuation change in the pons

MRI of Influenza Encephalopathy in Children: Value of Diffusion-Weighted Imaging

Tsuchiya, Kazuhiro; Katase, Shichiro; Yoshino, Ayako; Hachiya, Junichi
Volume 24(2), March/April 2000, pp 303-307

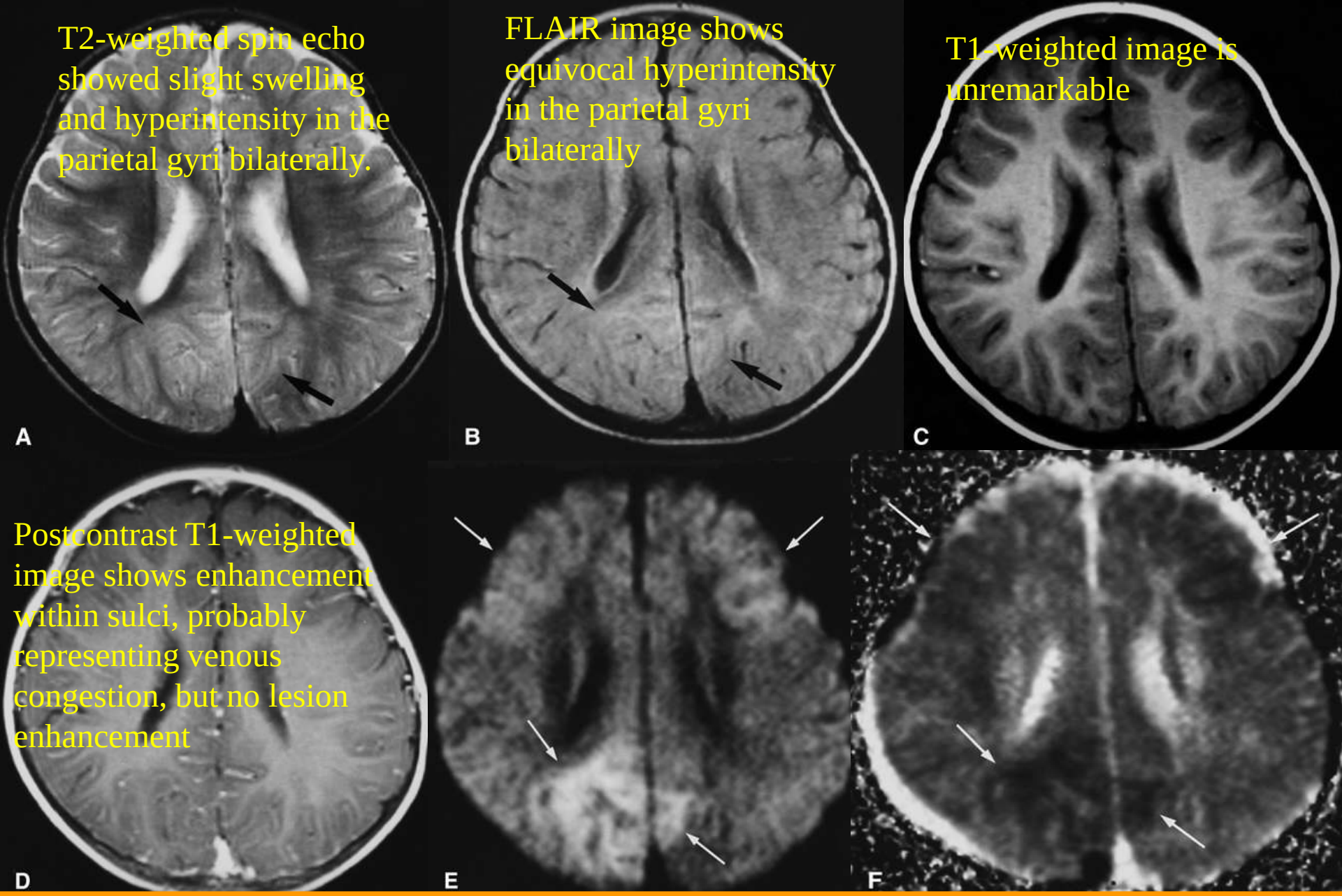
Influenza encephalopathy is visualized on MRI as areas of elongated T2, and sometimes T1, in the cerebral cortex and adjacent white matter. The lesion distribution is rather nonspecific. **Diffusion-weighted MRI** appears to depict the lesions as areas of restricted diffusion more sensitively than conventional imaging techniques.

Case no.	Lesion location	Signal intensity			Contrast enhancement	Comparison of conventional imaging and DWI	
		T2WI and FLAIR	T1WI	DWI		Lesion extent	Lesion conspicuity
1	Bilateral frontoparietal	High	Iso	High	No	DWI > conventional	DWI > conventional
2	Left hemisphere	High	Low	High	No	Conventional = DWI	DWI > conventional
3	Right frontoparietal, left frontal	High	Iso	High	No	DWI > conventional	DWI > conventional
4	Both hemispheres	High	Low	High	No	Conventional = DWI	DWI > conventional
5	Bilateral parietooccipital	High	Iso	High	No	DWI > conventional	DWI > conventional

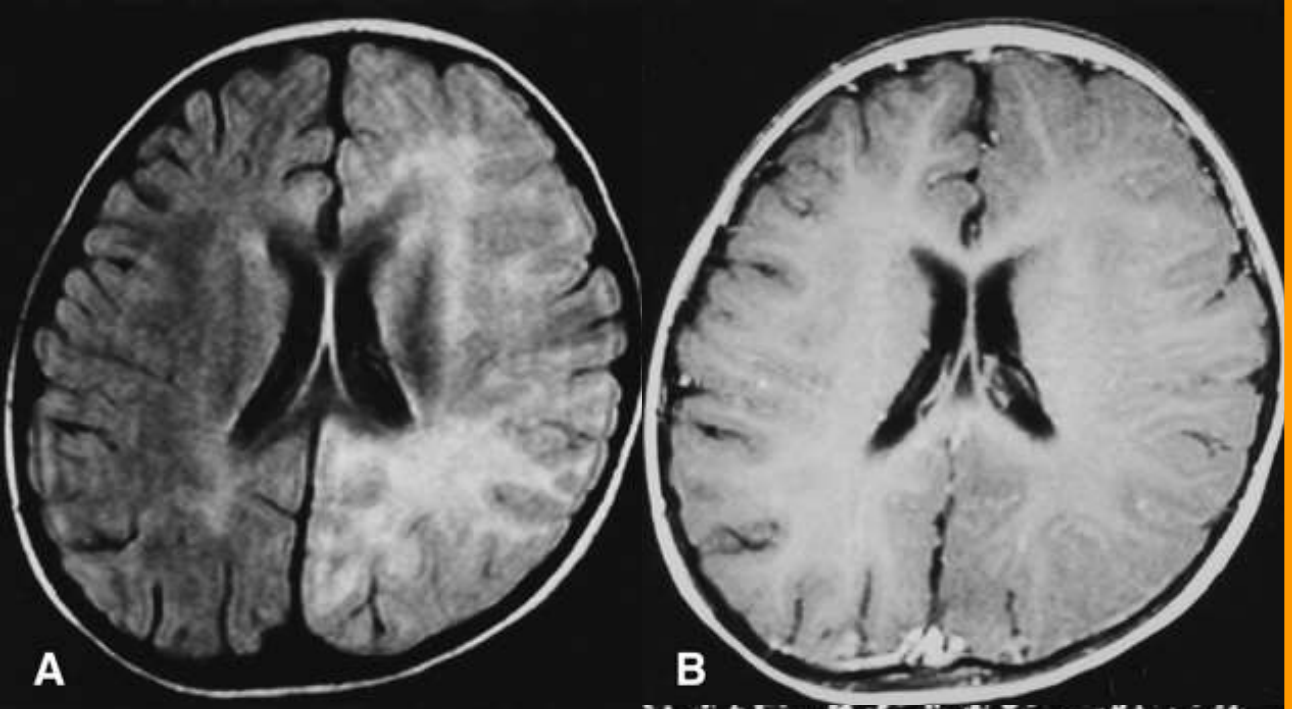
DWI, diffusion-weighted imaging; T2WI and T1WI, T2- and T1-weighted imaging; FLAIR, fluid-attenuated inversion recovery.

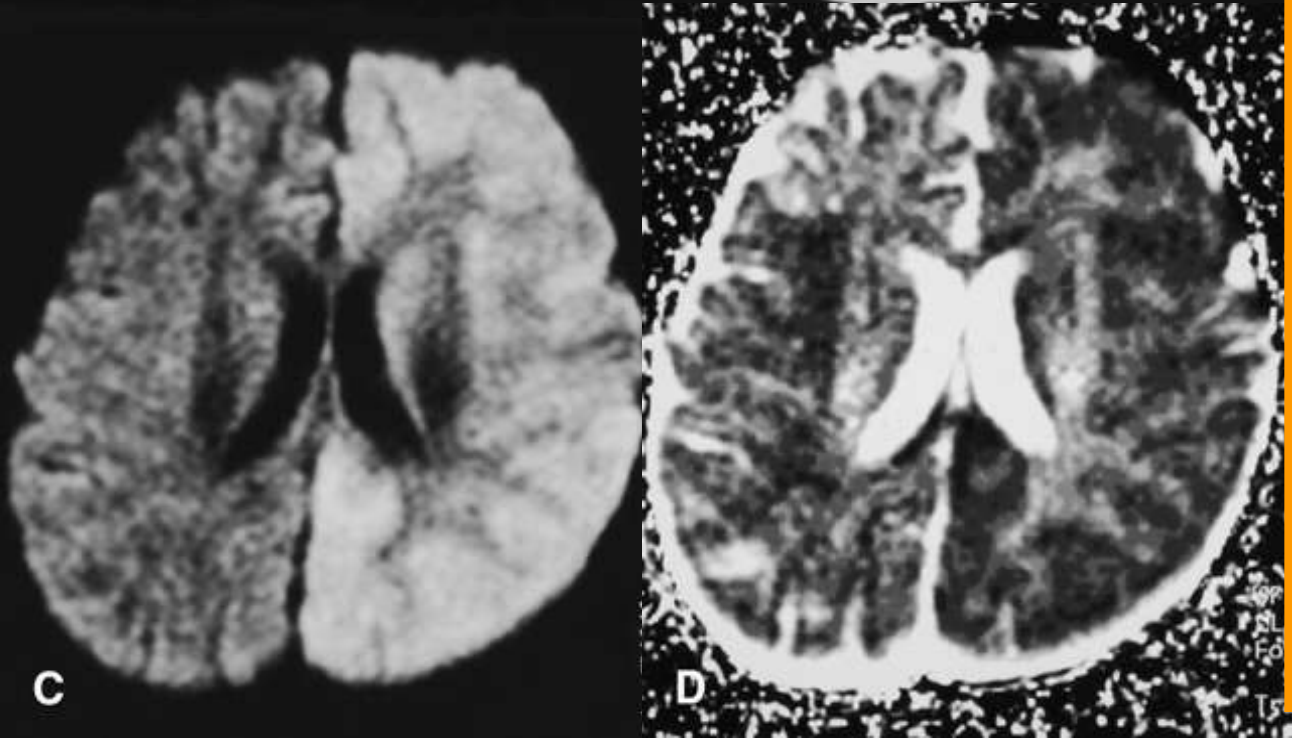
MRI of Influenza Encephalopathy in Children: Value of Diffusion-Weighted Imaging

Tsuchiya, Kazuhiro; Katase, Shichiro; Yoshino, Ayako; Hachiya, Junichi Volume 24(2), March/April 2000, pp 303-307



E and F: Single shot echo planar diffusion-weighted image shows clear hyperintensity in the frontoparietal cortex and adjacent subcortical white matter bilaterally (arrows). The apparent diffusion coefficient map shows hypointensity of the lesions representing restricted diffusion (arrows).





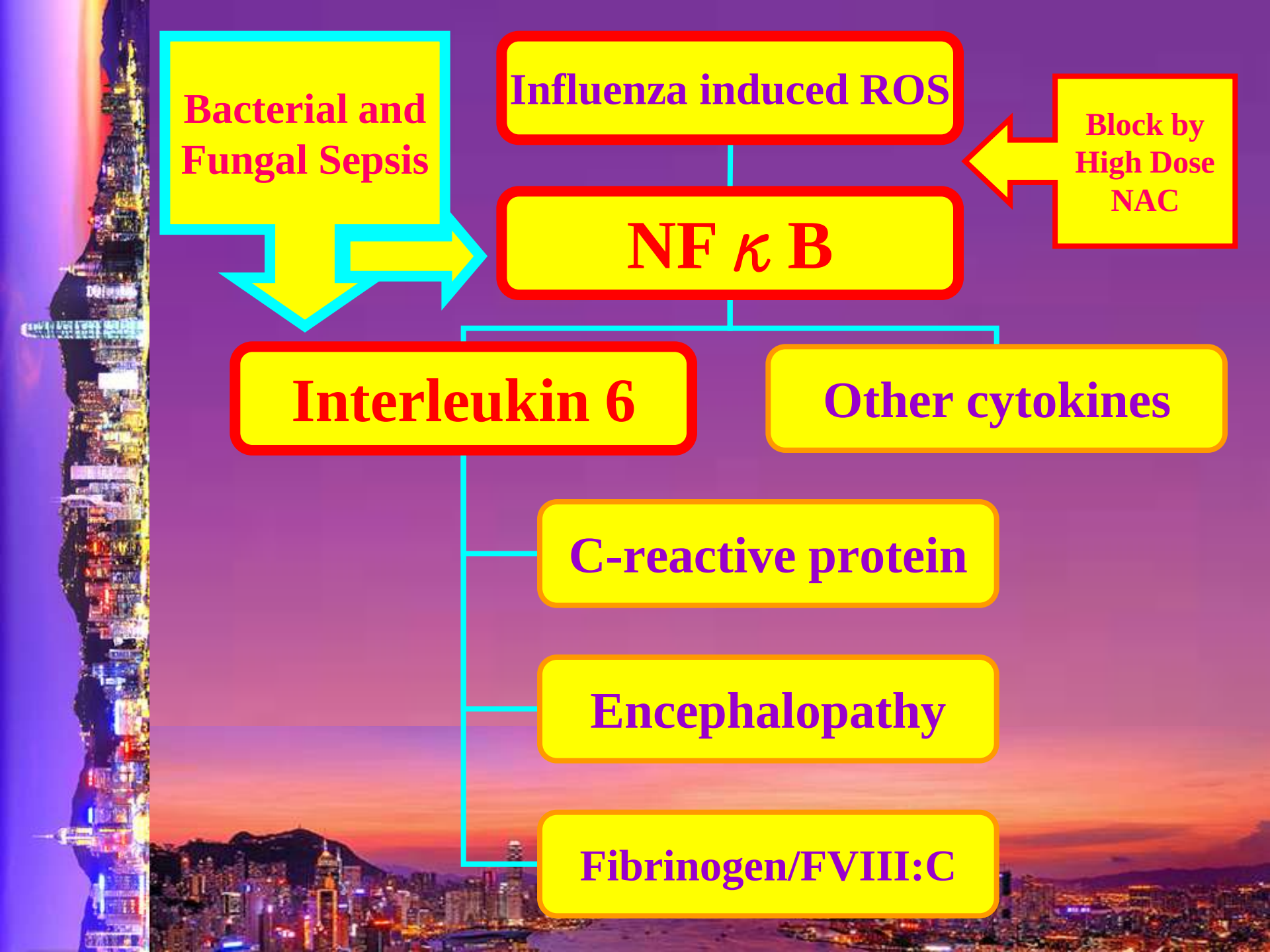
A 1.6-year-old girl examined 12 days after the onset of symptoms.
A: FLAIR image shows mild hyperintensity in the left cerebral hemisphere.
B: Postcontrast T1-weighted image shows no lesion enhancement but enhancement within sulci probably due to venous congestion.
C: Single shot echo planar diffusion-weighted image shows hyperintensity of the lesion in similar extent to the FLAIR image. However, the lesions are more conspicuously demonstrated on this image.
D: The apparent diffusion coefficient map shows hypointensity of the lesion due to restricted diffusion.

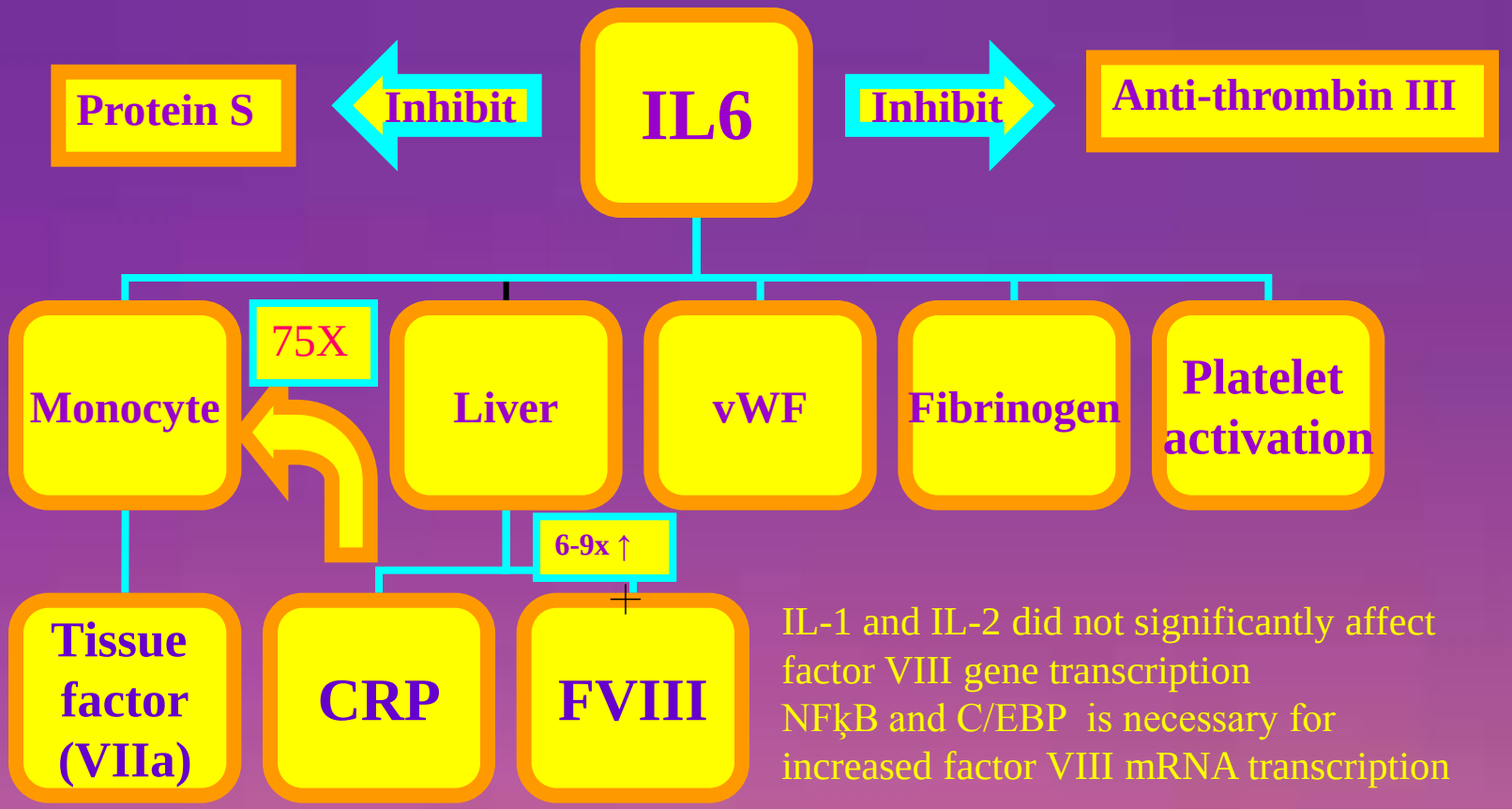
CRP Response to High Dose N-acetylcysteine (100mg/Kg infusion Daily) (An experience in 9 patients)

Patient		D1	D2	D3	D4	D5
1 (F/48)	Chronicsmoker and drinker	183		38.8		11.7
2 (M/58)	NPC 4th relapse bulbar palsy	158	143	61.2	36.2	21.0
3 (M/48)	HT DM Obesity	150	58	39.5		
4 (F/31)	HELLP Eclampsia Cx by ADEM		48.4	23.8	13.1	10.0
5 (M/43)	Asthma Panhypopituitaris Addisonian crisis	109		127	37.7	19.2
6 (M/55)	Ht, DM, IHD CRI OldTB with bronchiectsis	48.3	43.3	21.8	13.1	10.0
7 (F/51)	Status asthmaticus HCV carrier	12.3	6.1	<3.0		
8 (M/55)	Obesity	141	123	135		
9 (M/45)	NPC relapse Post hemotherapy and RT with neutorpnic sepsis	115	50.4			88.8 (onset of neutropenic sepsis

Death

Responders have a rapid drop in CRP

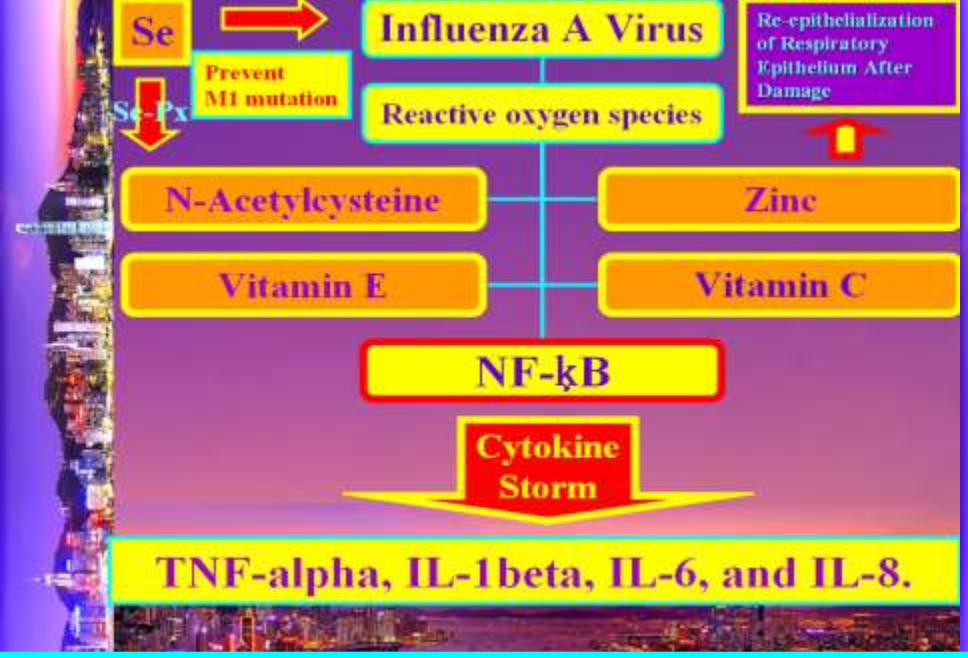

Bacterial and Fungal Sepsis
Influenza induced ROS
Block by High Dose NAC
NF κ B
Interleukin 6
Other cytokines
C-reactive protein
Encephalopathy
Fibrinogen/FVIII:C

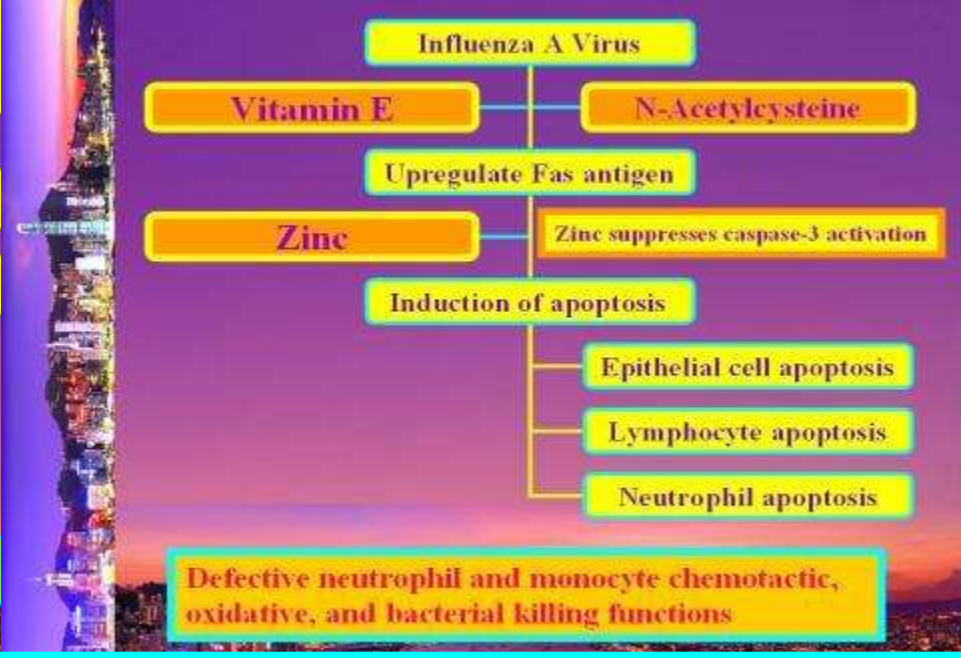


IL-1 and IL-2 did not significantly affect factor VIII gene transcription
NFķB and C/EBP is necessary for increased factor VIII mRNA transcription

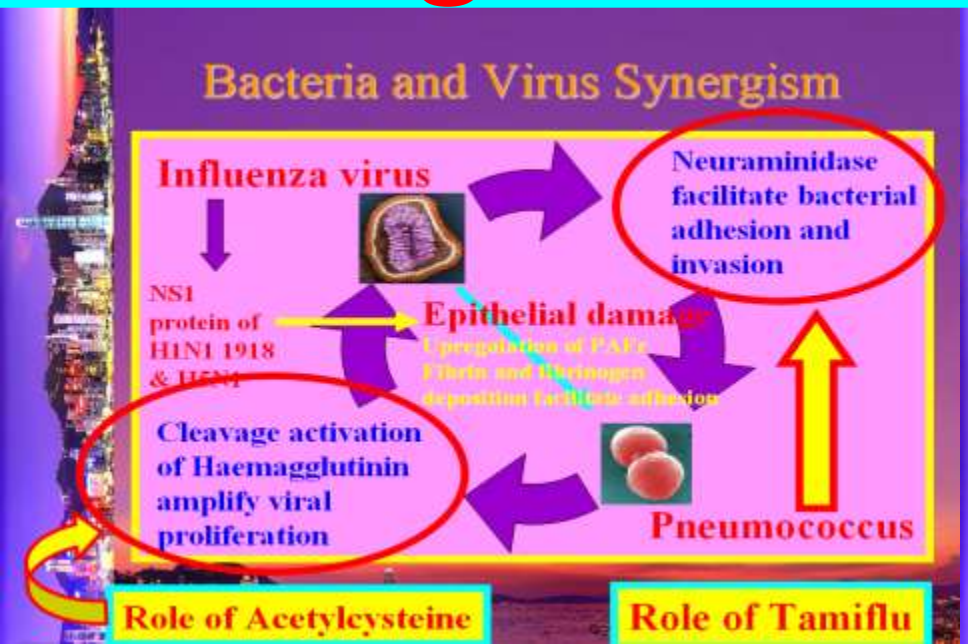
Pathways by which IL-6 contributes towards haemostasis – an overview

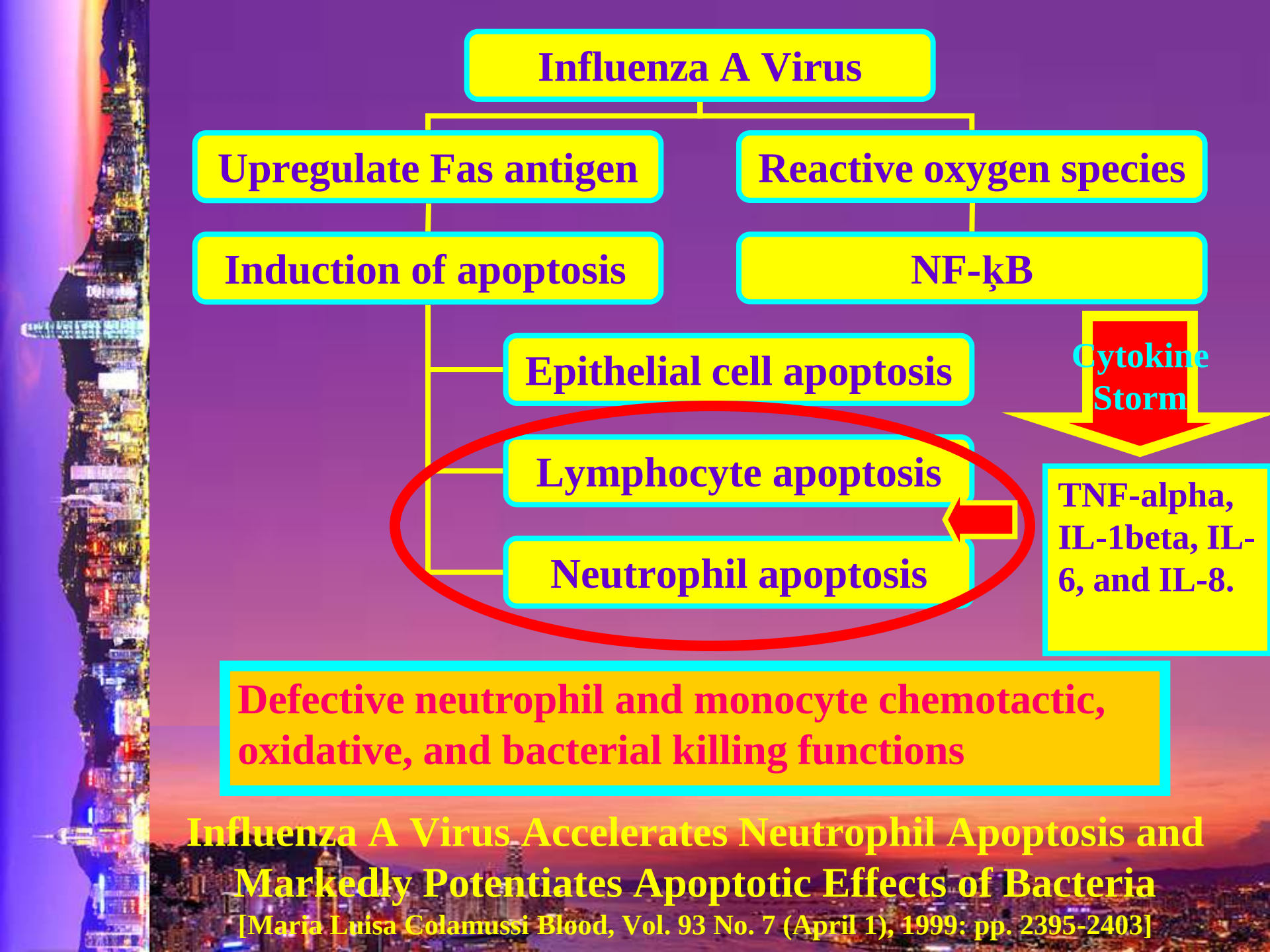
Kerr: Br J Haematol, Volume 115(1).October 2001.3-12





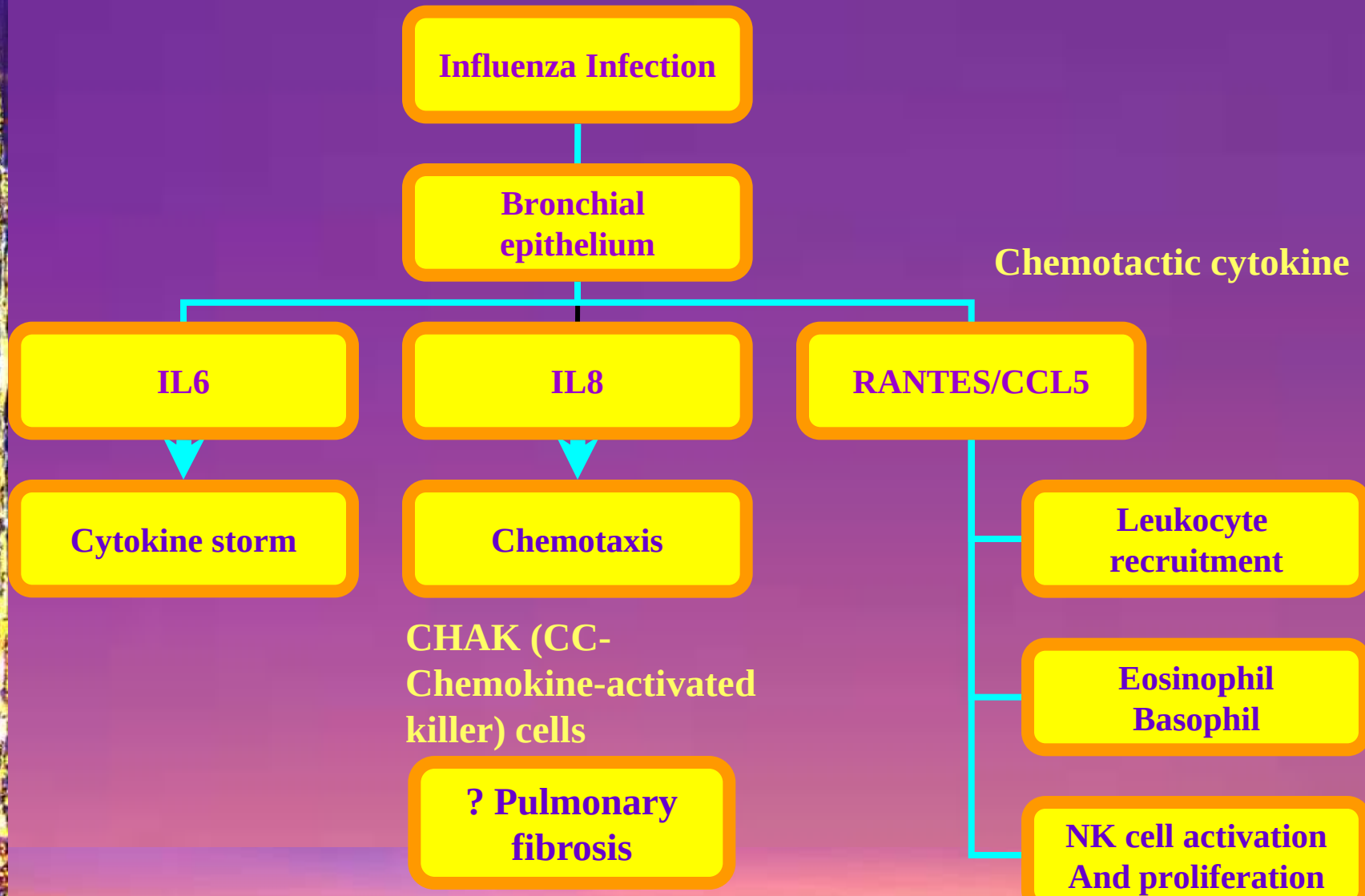
Pathogenesis of Influenza Virus





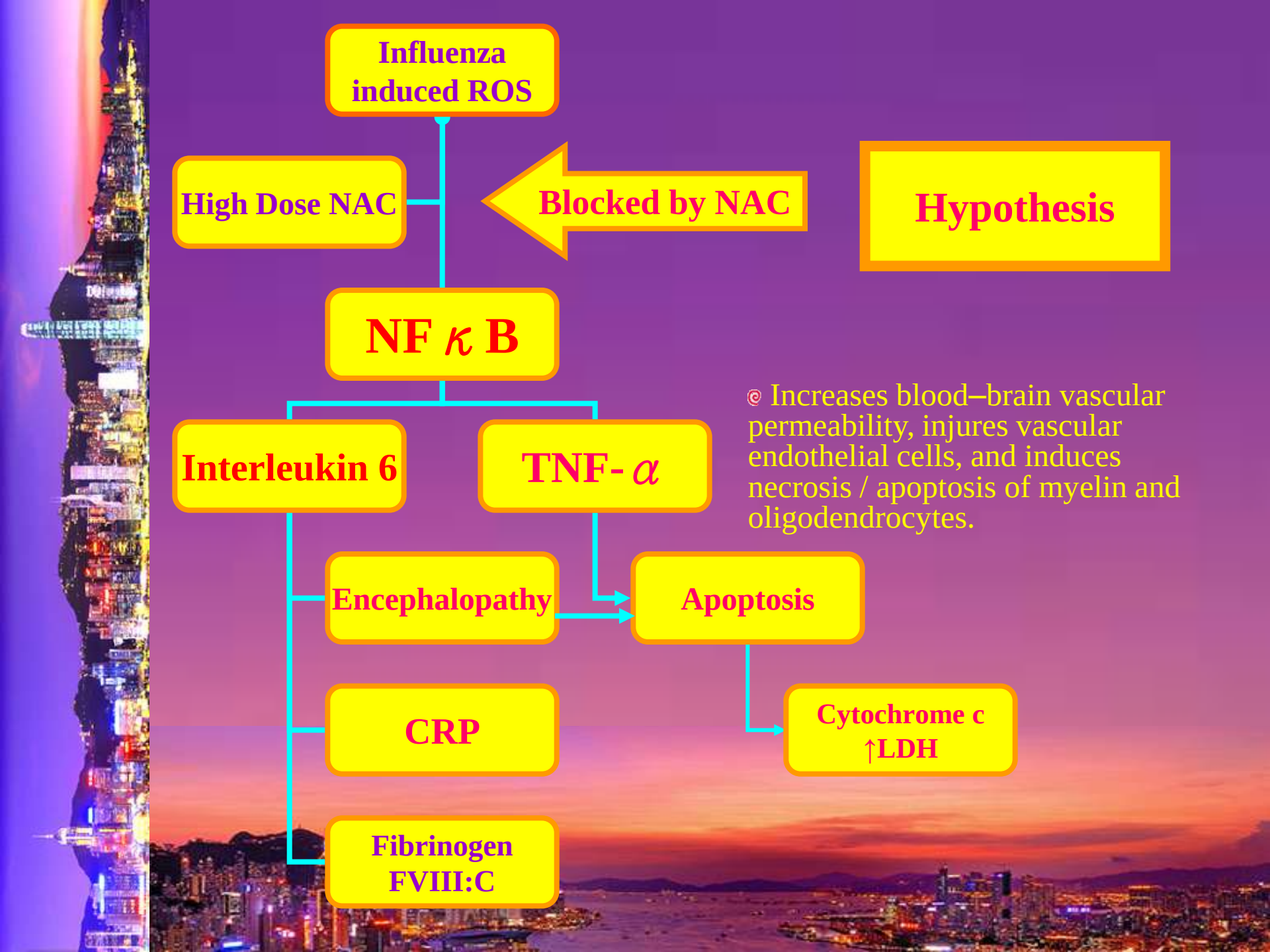
Influenza A Virus Accelerates Neutrophil Apoptosis and Markedly Potentiates Apoptotic Effects of Bacteria

[Maria Luisa Colamussi Blood, Vol. 93 No. 7 (April 1), 1999: pp. 2395-2403]



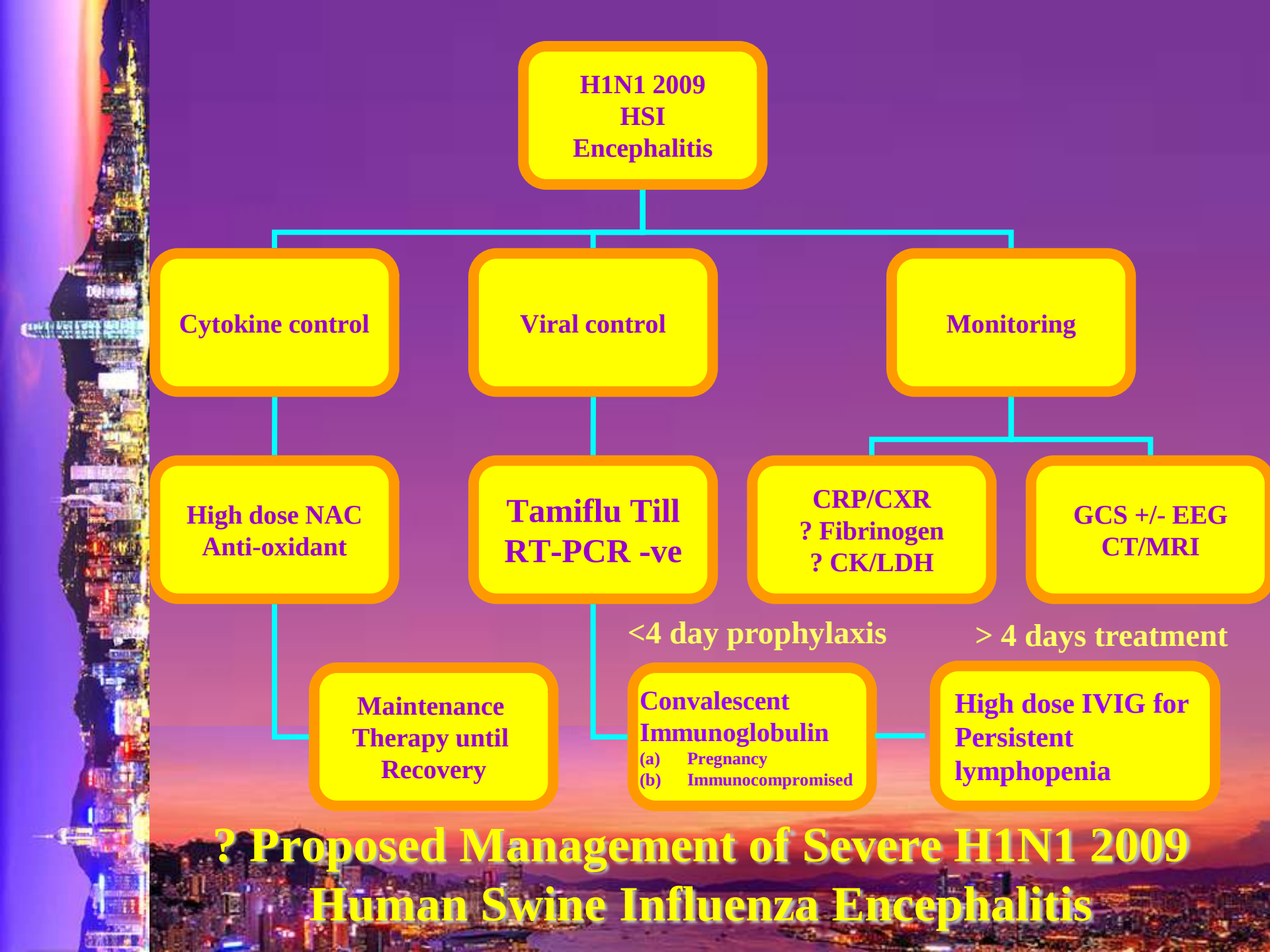
Expression of IL-6, IL-8, and RANTES on human bronchial epithelial cells, NCI-H292, induced by influenza virus A.

Matsukura S, Kokubu F, Noda H, Tokunaga H, Adachi M J Allergy Clin Immunol. 1996 Dec;98(6 Pt 1):1080-7


Influenza induced ROS
High Dose NAC
Blocked by NAC
Hypothesis
NF κ B
Interleukin 6
TNF- α
Encephalopathy
Apoptosis
CRP
Cytochrome c
↑LDH
Fibrinogen
FVIII:C
Increases blood–brain vascular permeability, injures vascular endothelial cells, and induces necrosis / apoptosis of myelin and oligodendrocytes.

Hypothesis

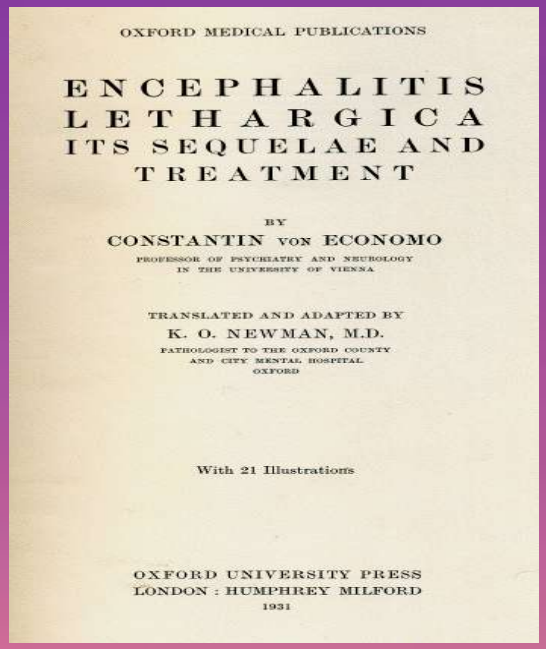
- In our patients, high dose N-acetylcysteine can cause a rapid and drastic decrease in CRP, an acute phase protein.
- IL- 6 is a major regulator of CRP production.
- There is close correlation in the severity of influenza encephalopathy and the interleukin level.
- Currently there is no medication that can suppress IL-6 production without major immunosuppression.
- High dose N-acetylcysteine has a potential role in rapid control of CRP or perhaps IL6 level during novel H1N1 2009 encephalopathy.
- Prospective randomized trial should be conducted to confirm this hypothesis.



? Proposed Management of Severe H1N1 2009 Human Swine Influenza Encephalitis

Any Questions ?

Would Epidemic Encephalitis Lethargica Re-emerge After Novel 2009 H1N1 Human Swine Influenza Pandemic ?



OXFORD MEDICAL PUBLICATIONS

ENCEPHALITIS LETHARGICA
ITS SEQUELAE AND TREATMENT

BY

CONSTANTIN von ECONOMO

PROFESSOR OF PSYCHIATRY AND NEUROLOGY IN THE UNIVERSITY OF VIENNA

TRANSLATED AND ADAPTED BY

K. O. NEWMAN, M.D.

PATHOLOGIST TO THE OXFORD COUNTY AND CITY MENTAL HOSPITAL OXFORD

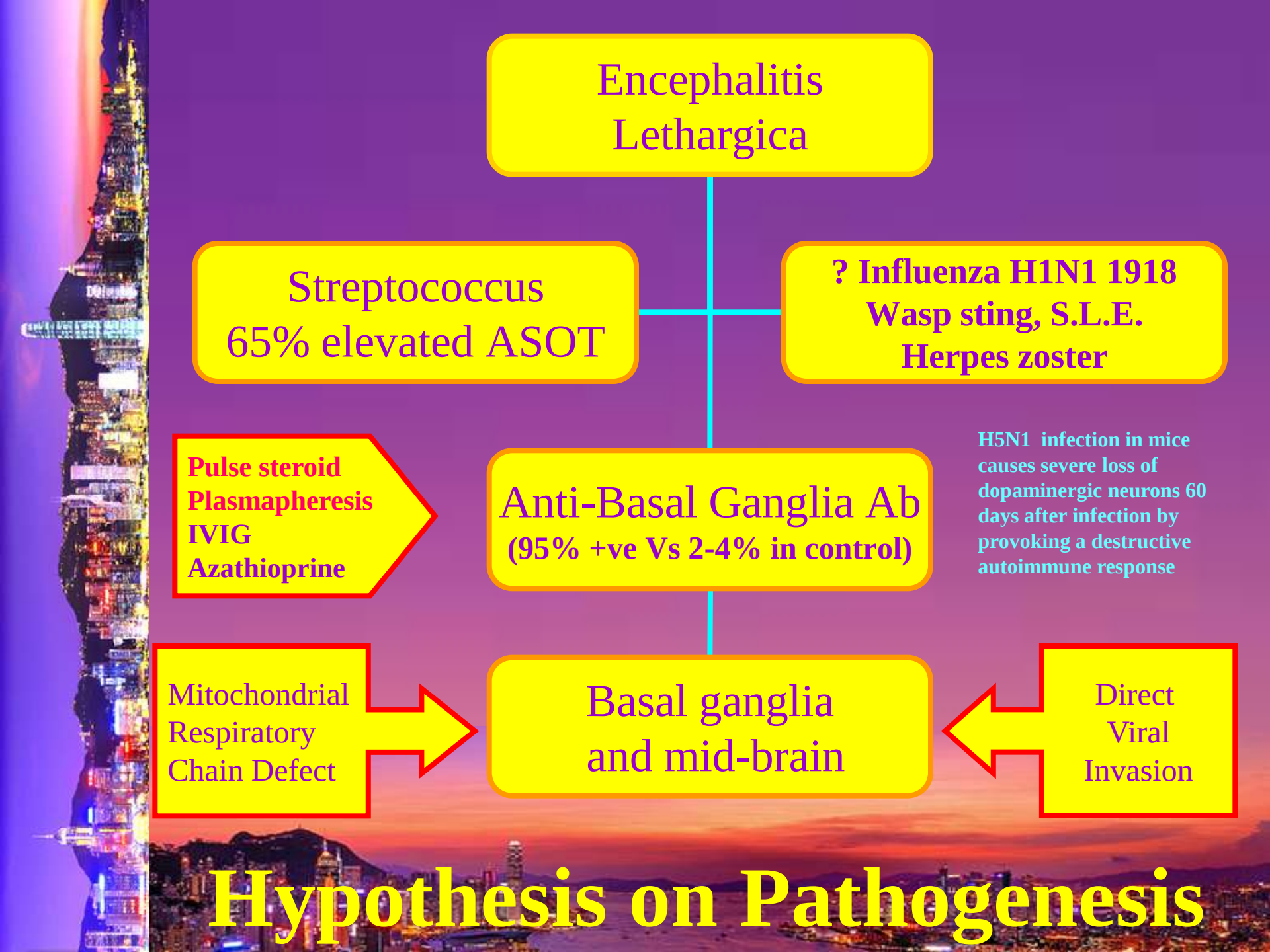
With 21 Illustrations

OXFORD UNIVERSITY PRESS
LONDON : HUMPHREY MILFORD
1931

Dr. Lai Kang Yiu

Intensive Care Unit

Queen Elizabeth Hospital


Encephalitis Lethargica
Streptococcus 65% elevated ASOT
? Influenza H1N1 1918 Wasp sting, S.L.E. Herpes zoster
Pulse steroid Plasmapheresis IVIG Azathioprine
Anti-Basal Ganglia Ab (95% +ve Vs 2-4% in control)
H5N1 infection in mice causes severe loss of dopaminergic neurons 60 days after infection by provoking a destructive autoimmune response
Mitochondrial Respiratory Chain Defect
Basal ganglia and mid-brain
Direct Viral Invasion
Hypothesis on Pathogenesis

Clinical Features and Laboratory Findings

Encephalitis Lethargica
(55% has preceding pharyngitis)

Sleep disorders
Iomnolence, Sleep inversion, Insomnia

Lethargy

Extrapyramidal symptoms
(Parkinsonism, dyskinesias)

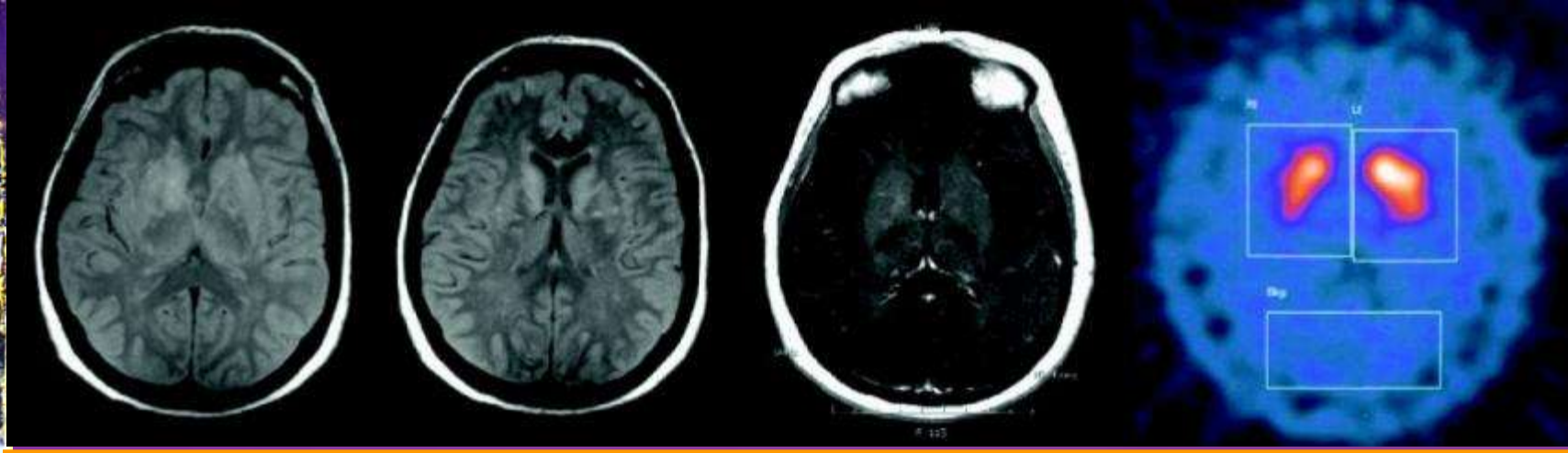
Oculogyric crisis
Ocular palsy and ptosis

Neuropsychiatric Diorders
Catatonia, obsessive±compulsive disorder and mutism
apathy and conduct disorders

Central cardiorespiratory Features (e.g. hiccup)

LP: Lymphocyrosis, elevated proteins,
Intrathecal oligoclonal band
Human anti-basal ganglia neuronal Ab

MRI: 60% normal and 40%
deep grey matter inflammation

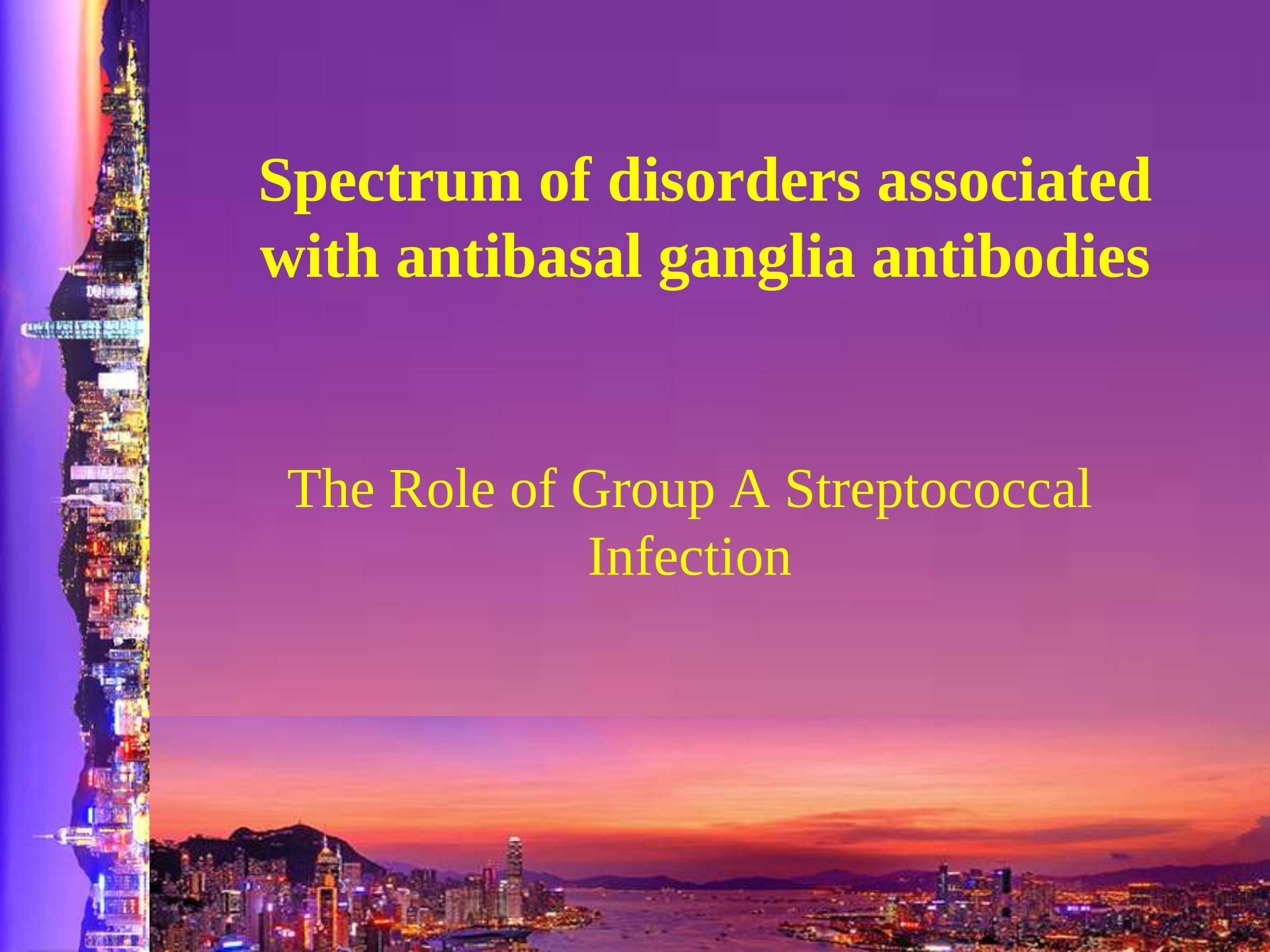


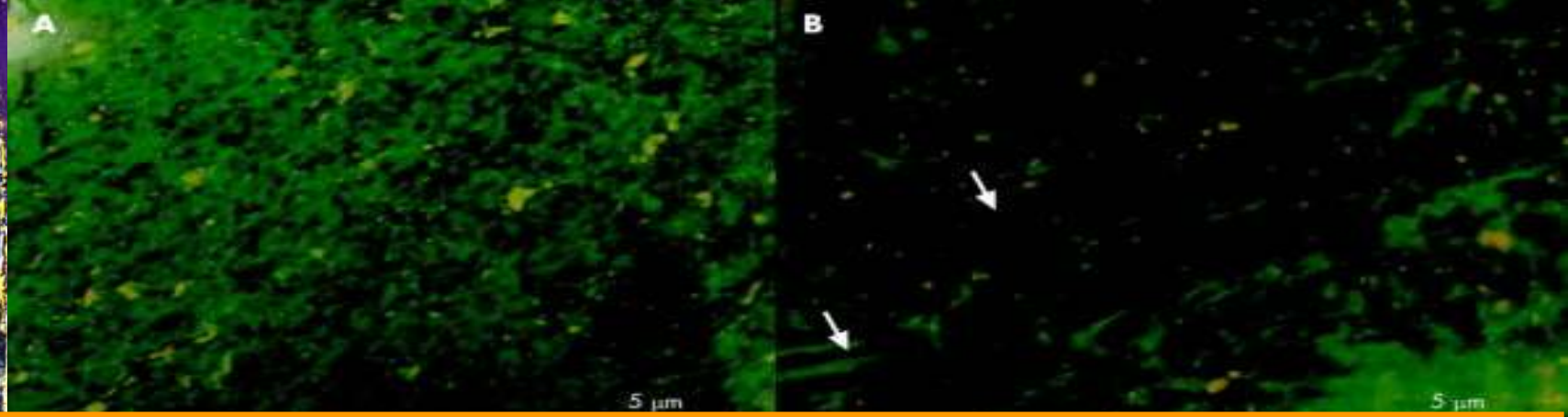
MRI and DAT scan. A middle-aged woman with encephalitis lethargica presented with double vision, headache and a behavioural disorder, followed by increasing confusion and reduced level of consciousness due to hypersomnolence. She later developed oculogyric crises and hiccoughing. On recovery she was parkinsonian, with rigidity and bradykinesia, with superimposed tics and dystonic posturing of the right arm. Unfortunately, she was left with chronic obsessive-compulsive behaviour, anxiety, panic attacks and dysthymia. The MRI study during the acute encephalitic crisis showed bilateral swelling of the striatum, with associated signal change on the T2- (left) and proton density-weighted images (centre). These areas were shown to enhance diffusely after the administration of gadolinium (right). The abnormal signal change also extended into the posterior hypothalamus and mid-brain (images not shown). On the far right is an abnormal striatal dopamine transporter (DAT) study, with [123I]beta-CIT ([123I]2beta-carbomethoxy-3beta-(4-iodophenyl)tropane) single photon emission computed tomography (SPECT) showing bilaterally reduced and asymmetrical dopamine transporter density in the striatum. This patient's serum was positive for ABGAs.

Are antibasal ganglia antibodies important, and clinically useful?.Martino D. Church A. Giovannoni G. Practical Neurology. 7(1):32-41, 2007 Feb.

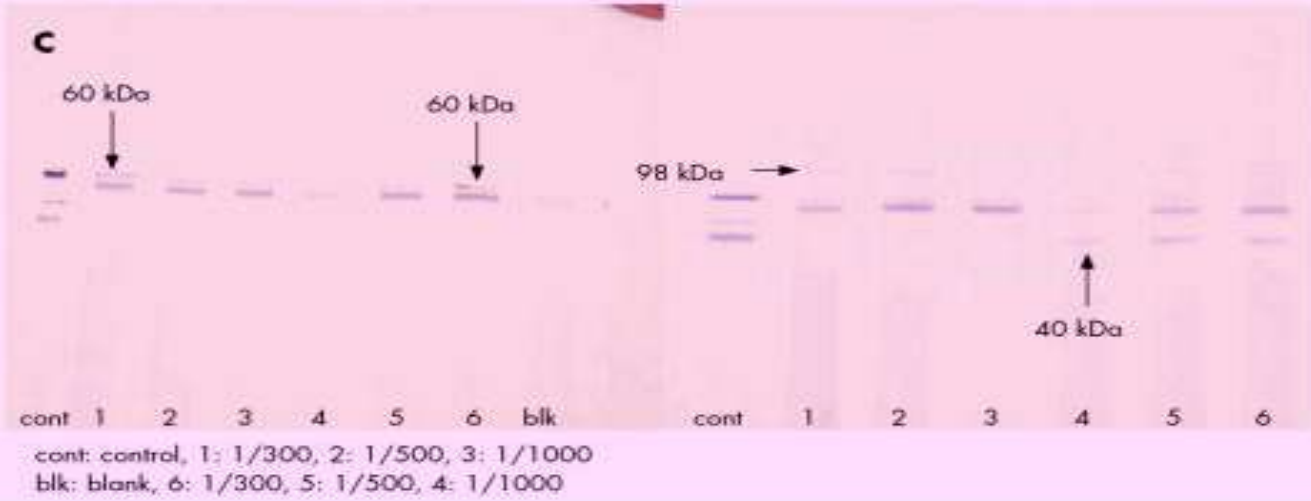
Spectrum of disorders associated with antibasal ganglia antibodies

The Role of Group A Streptococcal Infection





Are antibasal ganglia antibodies important, and clinically useful?.Martino D. Church A. Giovannoni G. Practical Neurology. 7(1):32-41, 2007 Feb.



Immuofluorescence microscopy and Western blot of ABGAs. (A) Normal control diluted 1/50 tested against human basal ganglia with no specific staining (magnification ×200). (B) Sample from a patient with Sydenham's chorea diluted 1/50 and tested against human basal ganglia tissue; IgG staining of axons (arrows) (magnification ×200). (C) Western blots showing serial dilution of strongly positive ABGAs in patients with post-streptococcal movement disorder.

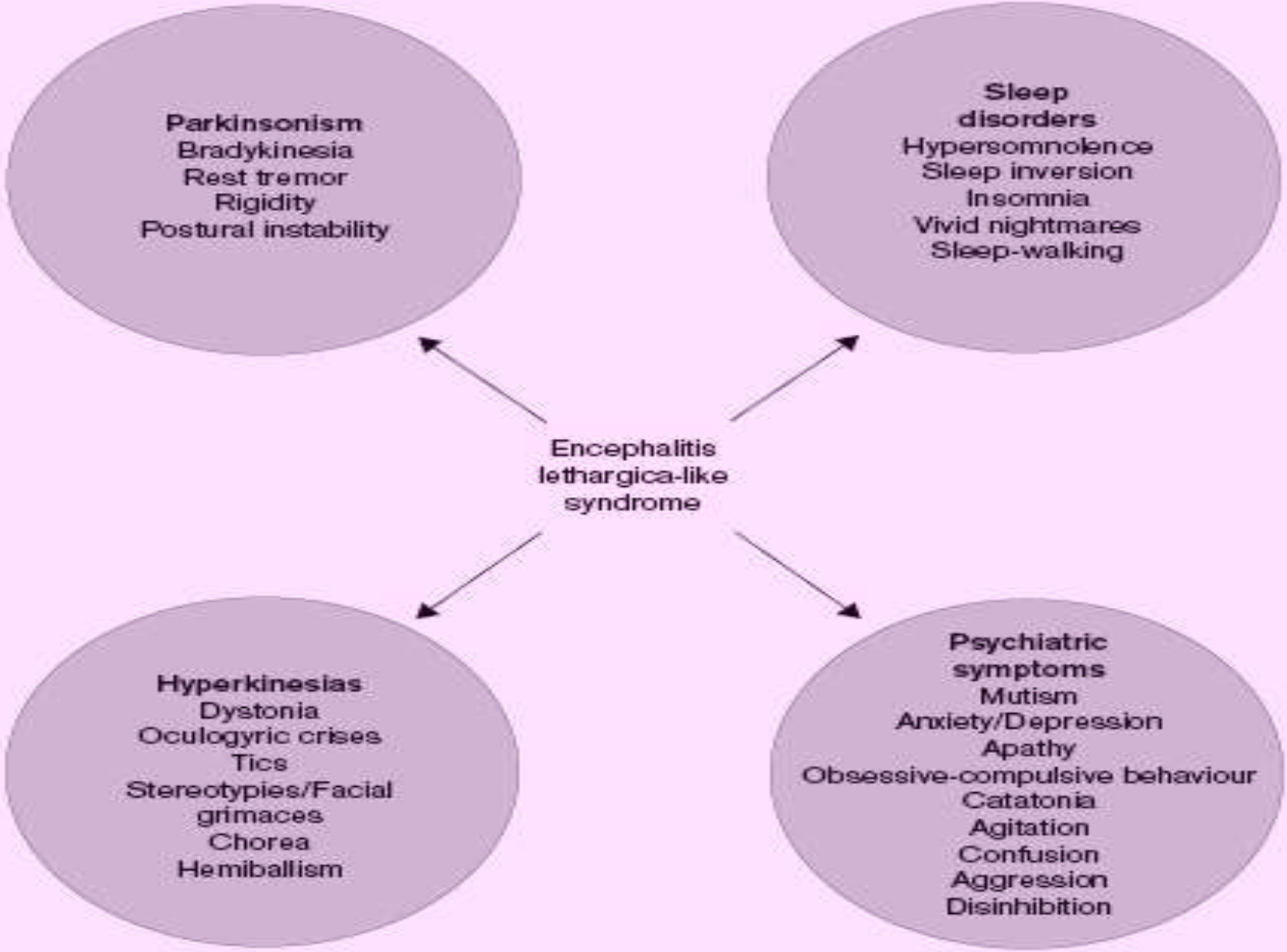
- Sydenham's chorea (prototype)
- Post-streptococcal acute disseminated encephalomyelitis
- Encephalitis lethargica
- Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)
- Gilles de la Tourette syndrome
- Obsessive-compulsive disorder
- Infantile bilateral striatal necrosis
- Paroxysmal dystonic choreoathetosis
- Fixed dystonia syndrome
- Anxiety disorders
- Depressive disorders
- Enuresis
- Conduct disorder
- Attention deficit hyperactivity disorder, usually as a comorbidity with Tourette's or obsessive-compulsive disorder

Spectrum of disorders associated with antibasal ganglia antibodies

The extended spectrum of post-streptococcal neuropsychiatric disorders

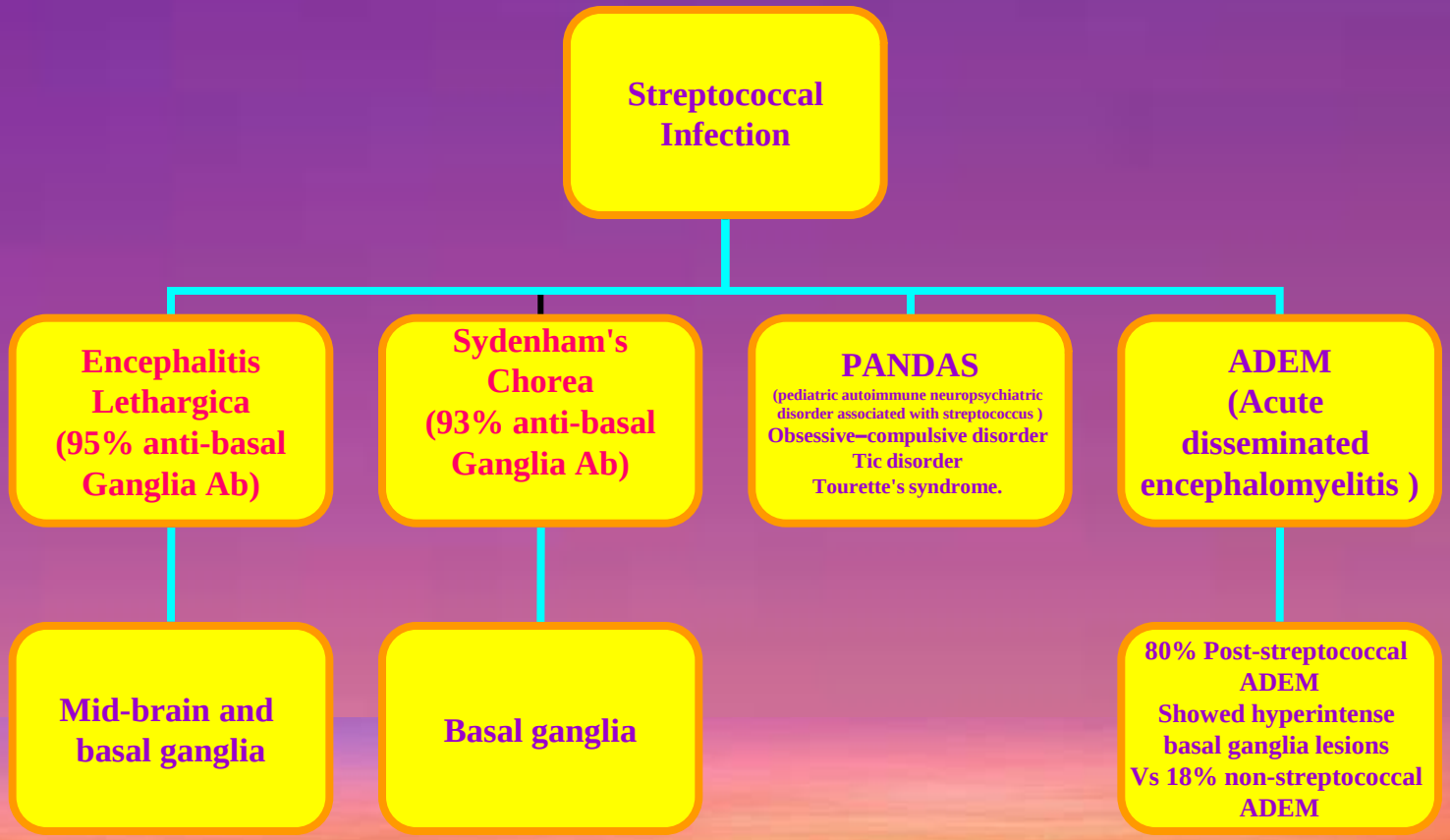
Movement disorders		Psychiatric symptoms	
Chorea	20 (50%)	Aggressive, oppositional or disruptive behaviour	14 (35%)
Vocal tics	17 (42.5%)	Emotional lability	13 (32.5%)
Motor tics	16 (40%)	Anxiety	11 (27.5%)
Dystonia	5 (12.5%)	Obsessive–compulsive behaviour	9 (22.5%)
Tremor	3 (7.5%)	Sleep disorders	9 (22.5%)
Stereotypies	2 (5%)	Depression	7 (17.5%)
Opsoclonus	2 (5%)	Attention deficit	7 (17.5%)
Myoclonus	1 (2.5%)	Echolalia	4 (10%)
Paroxysmal dystonic choreoathetosis	1 (2.5%)	Visual hallucinations	2 (5%)
		Social disinterest	2 (5%)

Modified from Dale *et al.*



Antibasal ganglia antibodies and their relevance to movement disorders.
Martino D. Giovannoni G. Current Opinion in Neurology. 17(4):425-32, 2004 Aug.

Anti-Basal Ganglia Antibody Post-Streptococcal Infection



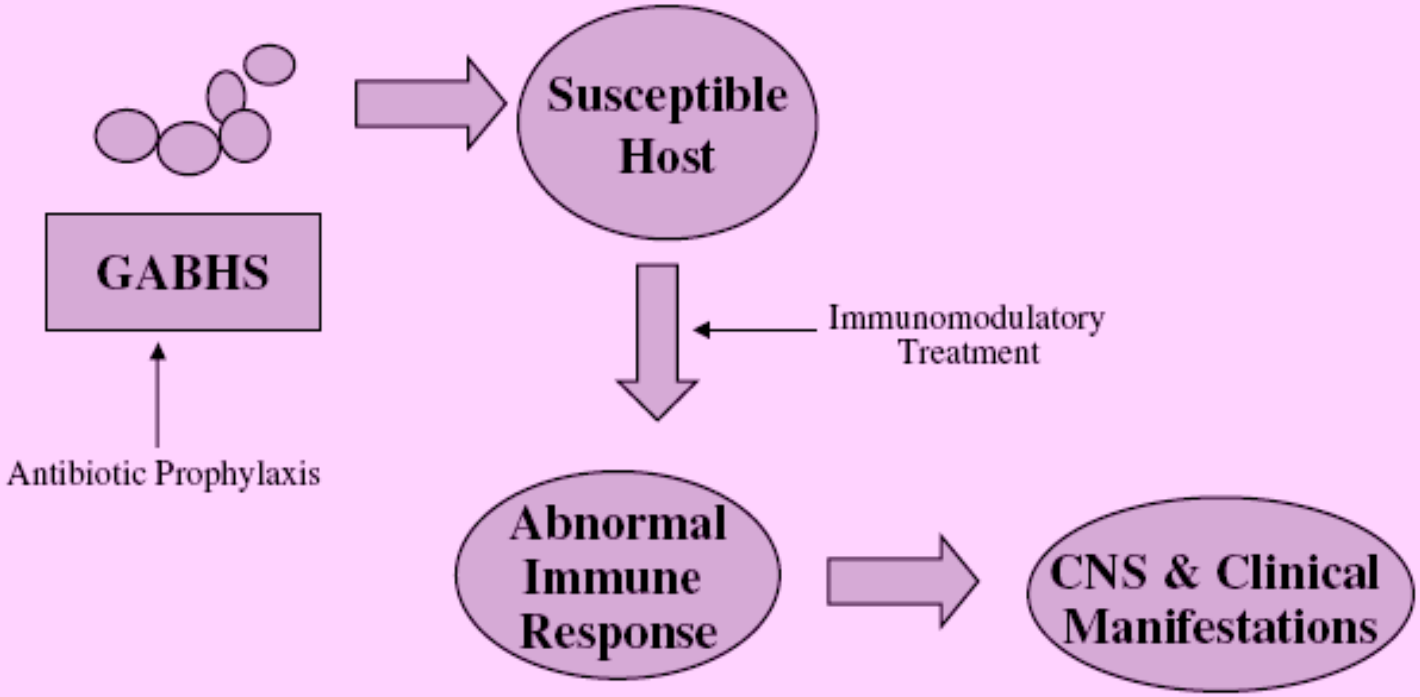
Anti-Basal Ganglia Antibody Post-Streptococcal Infection

Streptococcal
Infection

Ab to GAS epitope N-acetylglucosamine
cross react with Lysoganglioside on neuronal cells

Induction of calcium calmodulin-dependent protein kinase I
Increased tyrosine hydrolase and dopamine release

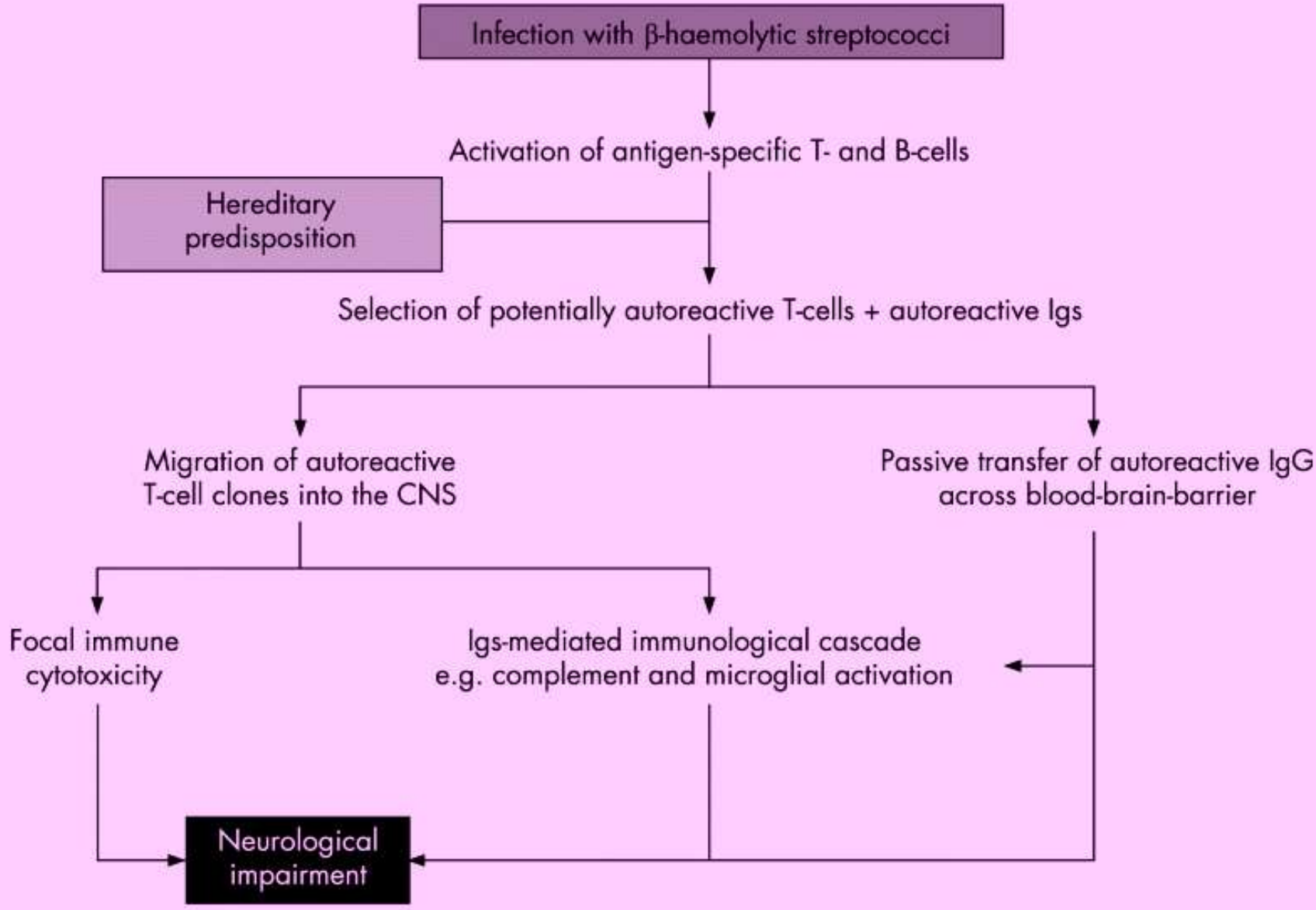
Model of Pathogenesis for PANDAS



Model of etiopathogenesis for SC and the PANDAS subgroup.

PANDAS: current status and directions for research

Snider LA. Swedo SE. Molecular Psychiatry. 9(10):900-7, 2004 Oct.



Pathogenesis of Post-streptococcal Neurological Disorder

Antibasal ganglia antibodies and their relevance to movement disorders. Martino D, Giovannoni G. Current Opinion in Neurology. 17(4):425-32, 2004 Aug

PANDAS Diagnostic Criteria (Swedo et al. in 1998)

- OCD and/or chronic tic disorder (Tourette's, chronic motor, or vocal tic disorder) that meets the DSM-IV diagnostic criteria;
- age at onset between 3 years and the onset of puberty;
- Clinical course with an abrupt onset of symptoms and/or a pattern of dramatic recurrent exacerbations and remissions;
- Temporal relation between GAS infection and onset and/or exacerbations of clinical symptoms;
- Neurologic abnormalities such as motoric hyperactivity, tics, or choreiform activity during an exacerbation

Are antibasal ganglia antibodies important, and clinically useful?

Martino D. Church A. Giovannoni G. Practical Neurology. 7(1):32-41, 2007 Feb.

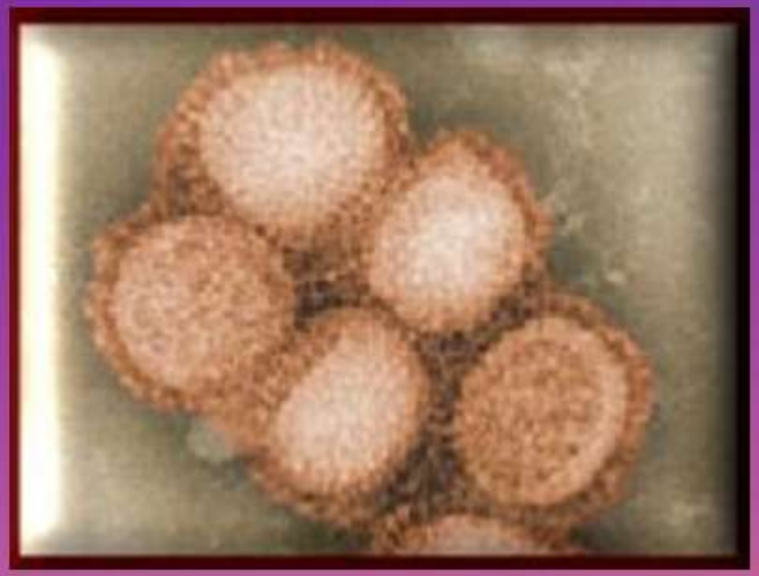
- There is a group of putative autoimmune diseases of the central nervous system characterised by ABGAs associated with recent streptococcal infection.
- ABGAs are a potentially useful diagnostic marker of immune-mediated basal ganglia disorders triggered by a streptococcal infection.
- Patients typically present with a neuropsychiatric syndrome with both hyper- and hypokinetic movement disorders; Sydenham's chorea is the prototypical disorder associated with ABGAs.
- Apart from Sydenham's chorea, the association of ABGAs with other clinical phenotypes is not widely accepted.

Are antibasal ganglia antibodies important, and clinically useful?

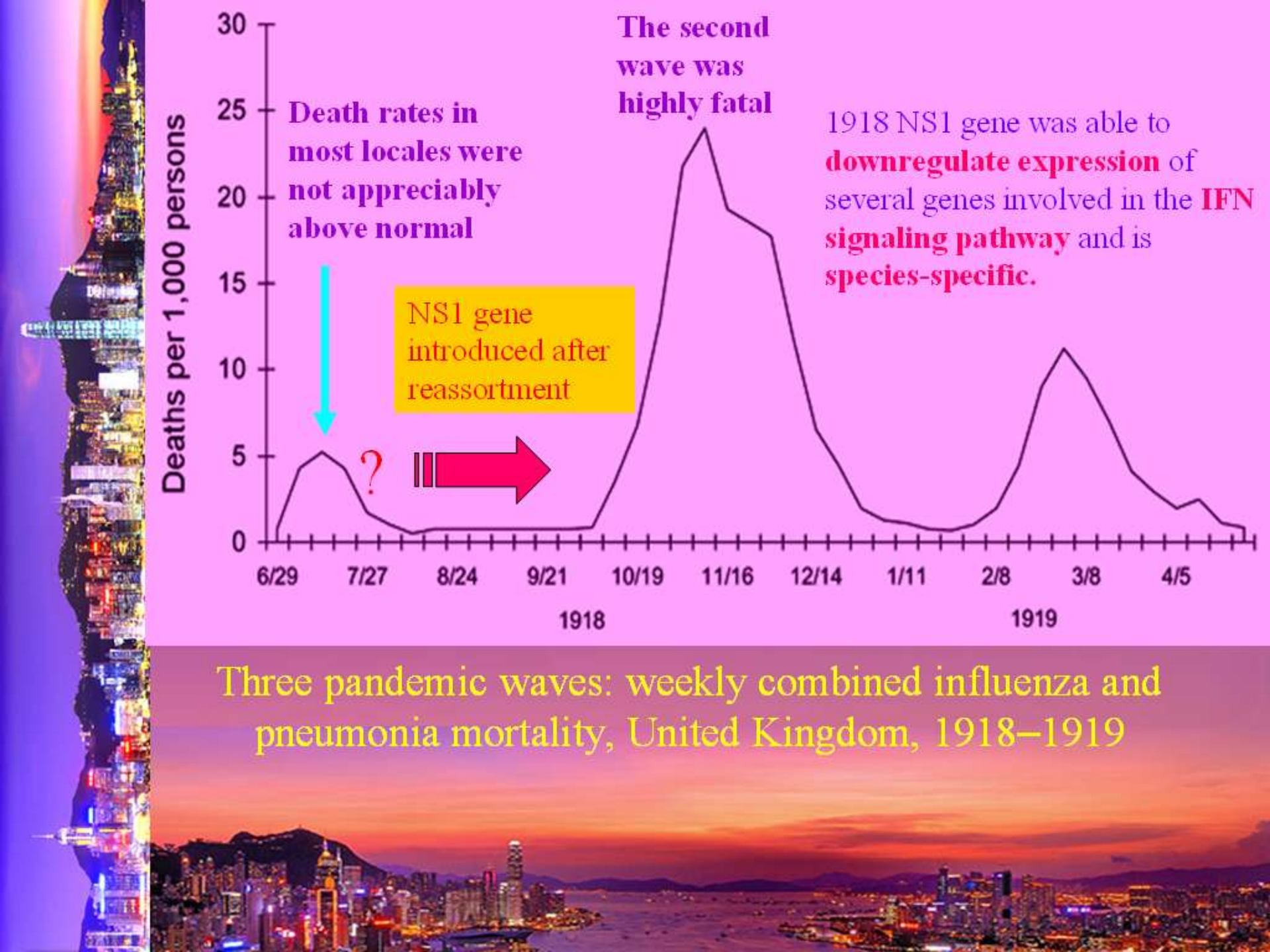
Martino D. Church A. Giovannoni G. Practical Neurology. 7(1):32-41, 2007 Feb.

- Long-term antibiotic prophylaxis is indicated in patients with Sydenham's chorea but there is no evidence supporting this policy in other ABGAassociated disorders.
- Immunotherapy should not be given routinely to patients with ABGAassociated disorders until further controlled trials establish its efficacy.
- There is a scientific rationale for a therapeutic trial of immunomodulatory therapy in patients who are significantly disabled from their disorder.
- Our anecdotal experience is that the sooner the patients are treated after the onset of their symptoms, the more likely they are to respond to immunotherapy.

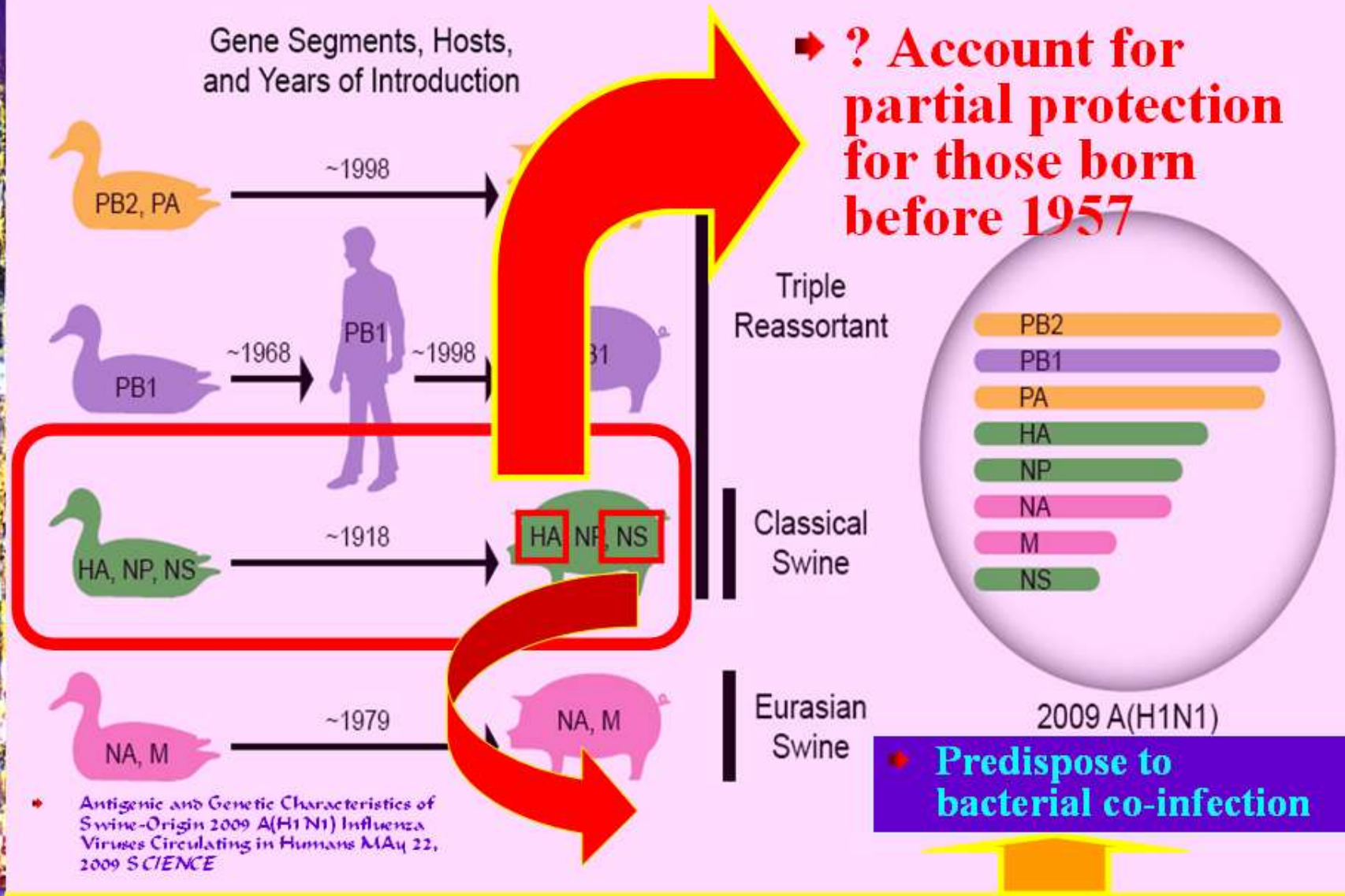
Human Swine Influenza



Dr. Lai Kang Yiu
Intensive Care Unit
Queen Elizabeth Hospital



Three pandemic waves: weekly combined influenza and pneumonia mortality, United Kingdom, 1918–1919



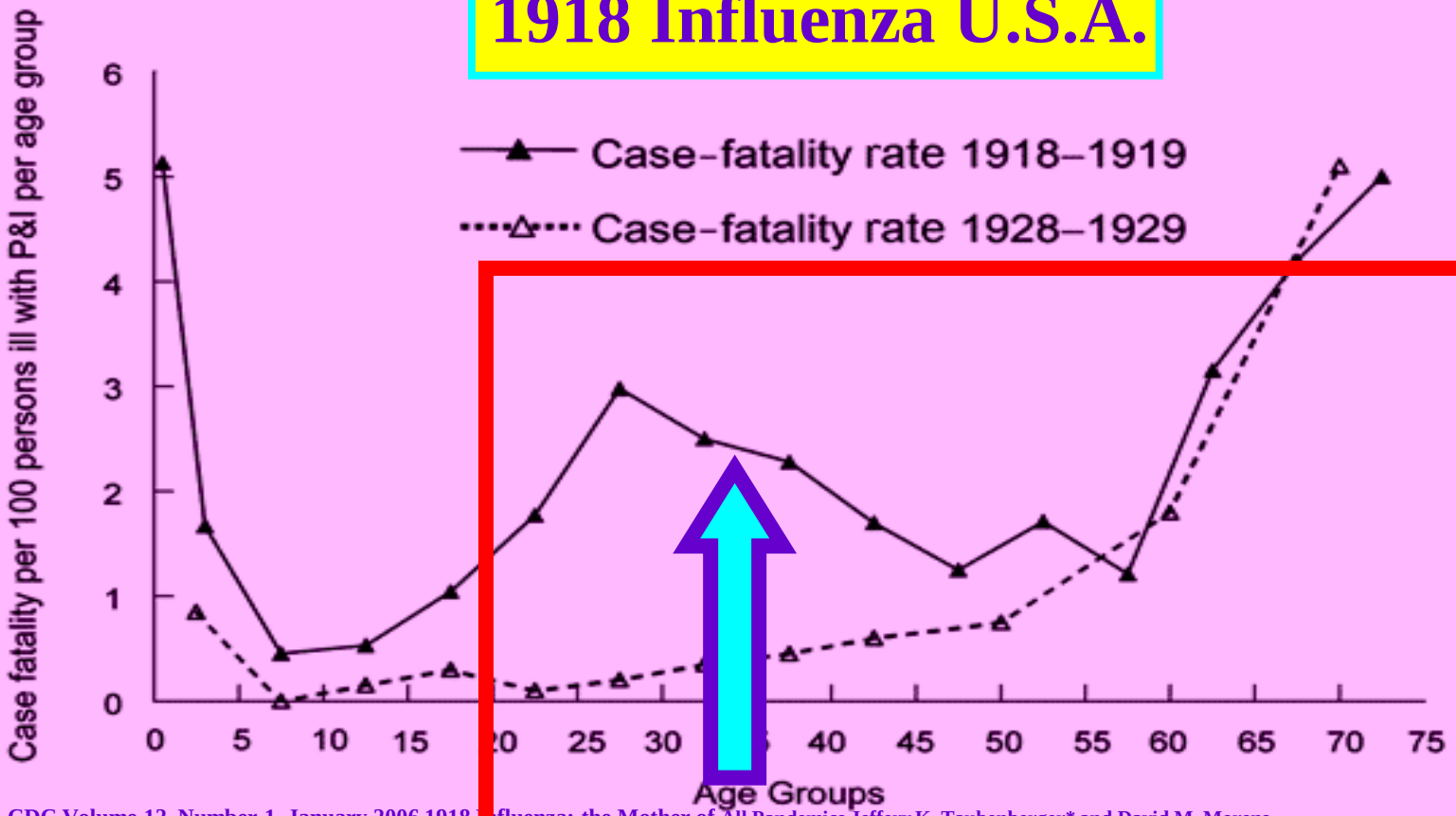
- **Suppression of innate immune response leading to initial rapid proliferation of influenza virus and severe mucosal damage**

Mexican Flu, Swine Flu, H1N1 Pandemic Pandemonium Origin

- It is believed that a five year old boy in La Gloria, Mexico was the very first person that tested positive for the Mexican Flu.
- The outbreak may started as early as 15/2/2009

W.H.O. has raised pandemic alert from phase 5 to phase 6 on 11/6/2009

1918 Influenza U.S.A.

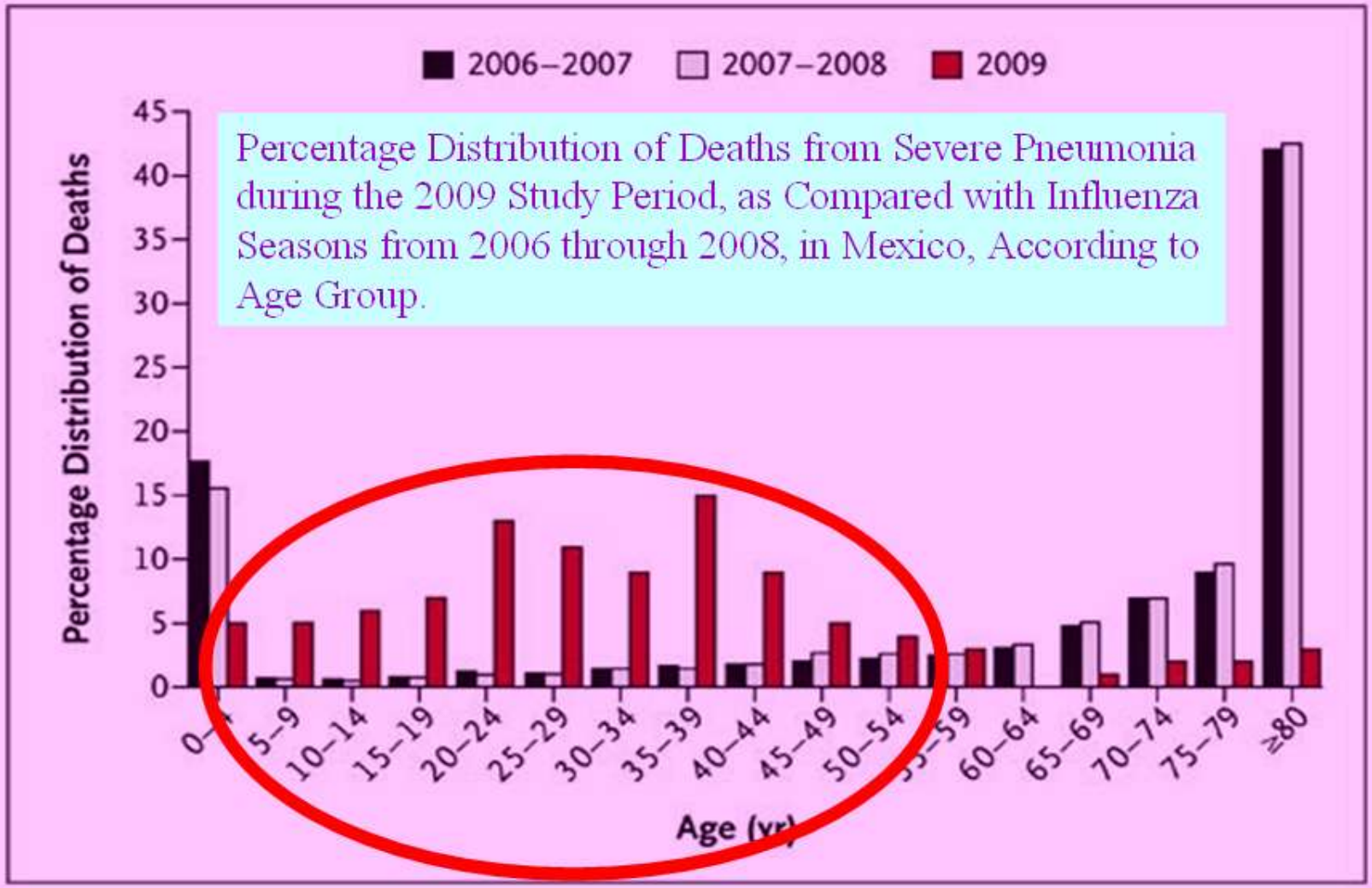


CDC Volume 12, Number 1, January 2006 1918 Influenza: the Mother of All Pandemics Jeffery K. Taubenberger* and David M. Morens

Mexico	0.6%	0.38%	2.74%	4.06%	3.8%	5.0%	5.1%
Age	0-9	10-19	20-29	30-39	40-49	50-59	60+

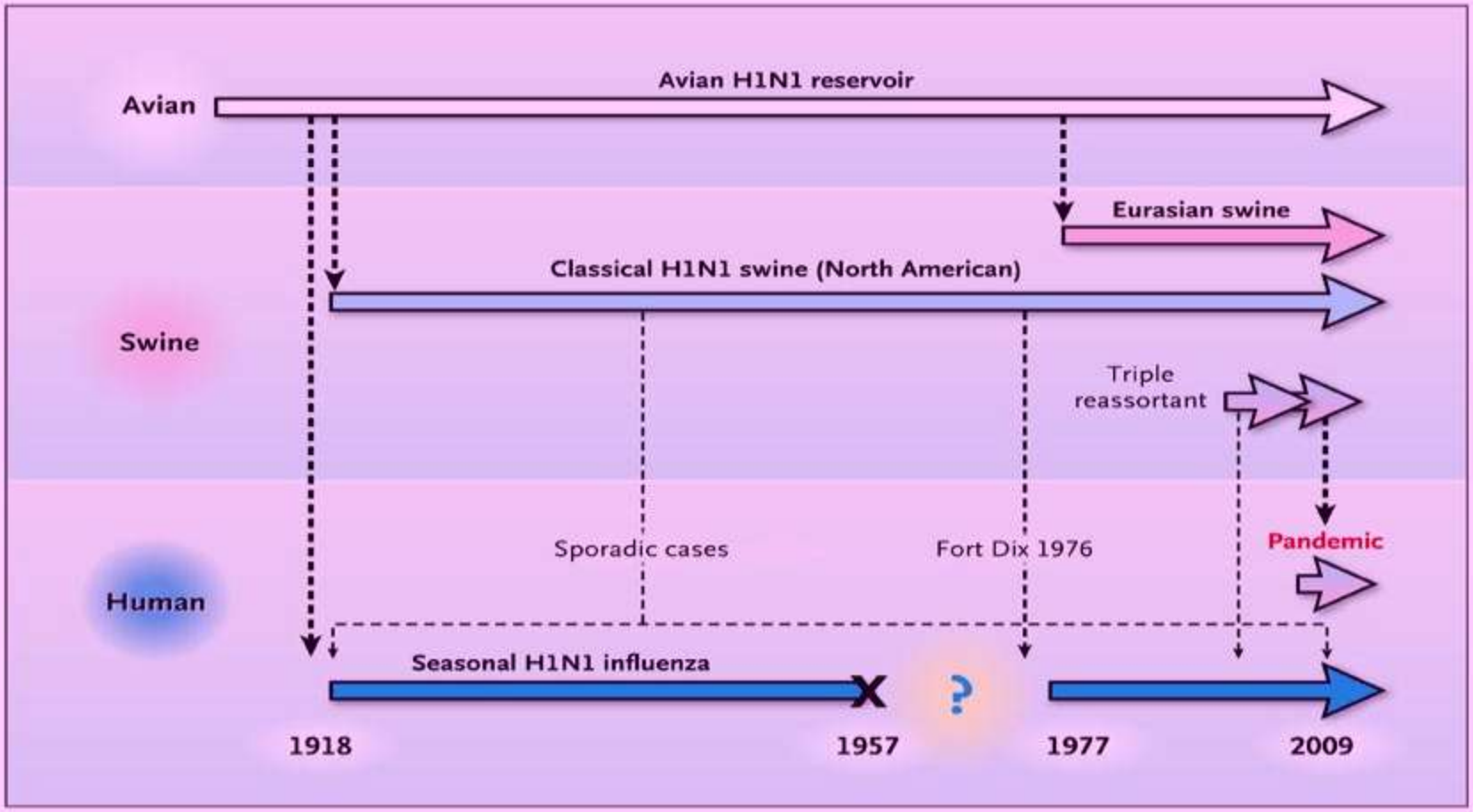
Very similar Mortality Rate

? Protected by Immunization Program with major reduction in mortality



March 24 to April 29, 2009, a total of 2155 cases of severe pneumonia, involving 821 hospitalizations and 100 deaths

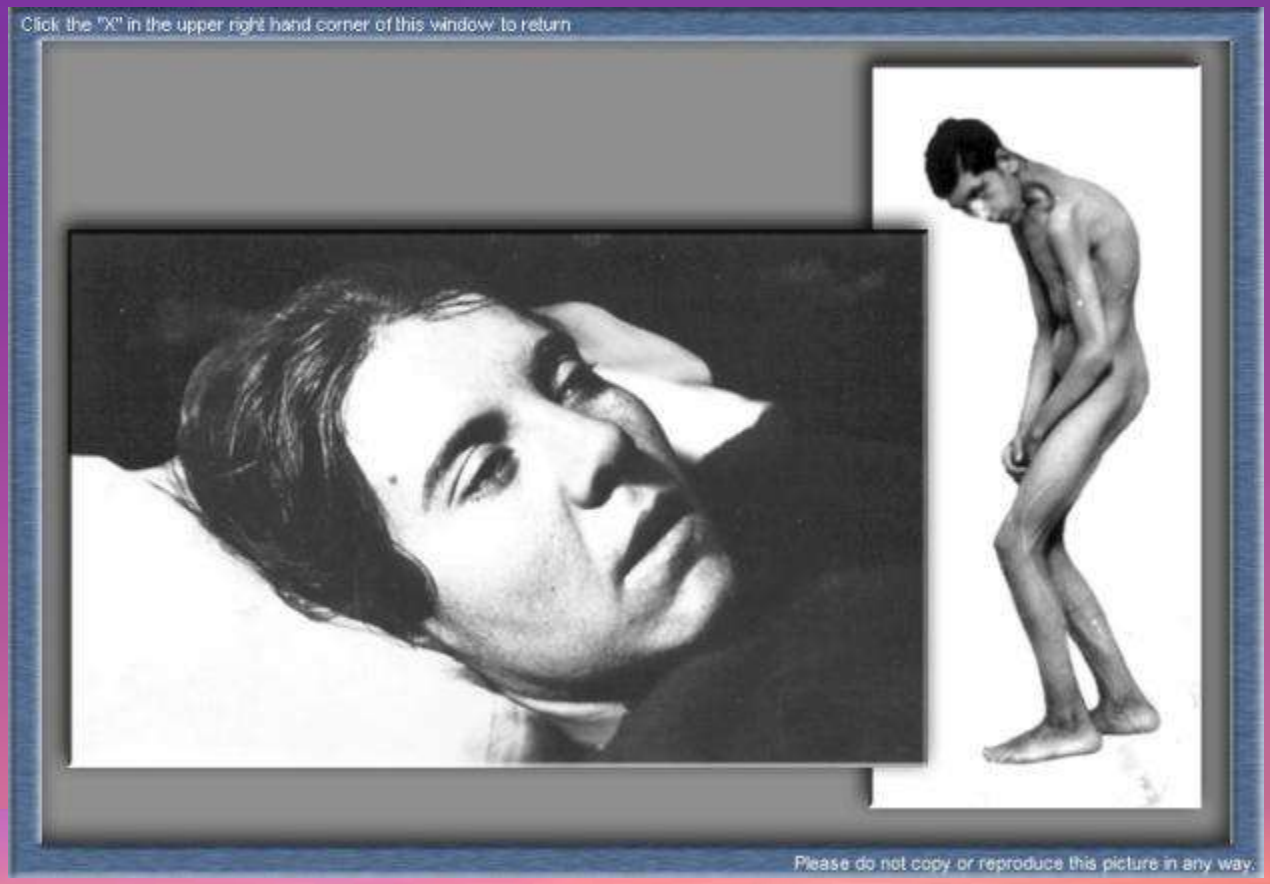
Severe Respiratory Disease Concurrent with the Circulation of H1N1 Influenza Gerardo Chowell, Ph.D., Stefano M. Bertozzi, NEJM June 29 2009



Sporadic cases of Post-encephalitis Parkinsonism and Post encephalitis lethargica have been reported recently after H1N1 was reintroduced in 1977 although no viral etiology has been documented. (Rail et al., 1981; Clough et al., 1983; Howard and Lees, 1987; Geddes et al., 1993; Barletta et al., 1995).

Historical Perspective — Emergence of Influenza A (H1N1) Viruses
Shanta M. Zimmer, M.D., and Donald S. Burke, M.D. **Volume 361:279-285 July 16, 2009 Number 3**

Encephalitis Lethargica



Sleeping sickness

“ Nona”

Post-encephalitic Parkinsonism

Encephalitis Lethargica
First Report 1917 in central Europe.

Epidemic in the winter of 1918/1919
Spread to Russia and North America

In epidemic form in winter seasons
Spread to rest of world (1918- 1927)

- **65000 reported case with mortality**
  30% in the acute stage and during relapse
- **50% survivors had persistent or recurrent neuro-psychiatric illness/Parkinsonism**
- **Recurrent or chronic illness with downhill course**
  Prone to sudden death
  60/300 young patient healthy after 2 years

Was encephalitis lethargica a post-influenzal or some other phenomenon? Time to re-examine the problem.

Mortimer PP. Epidemiology & Infection. 137(4):449-55, 2009 Apr.

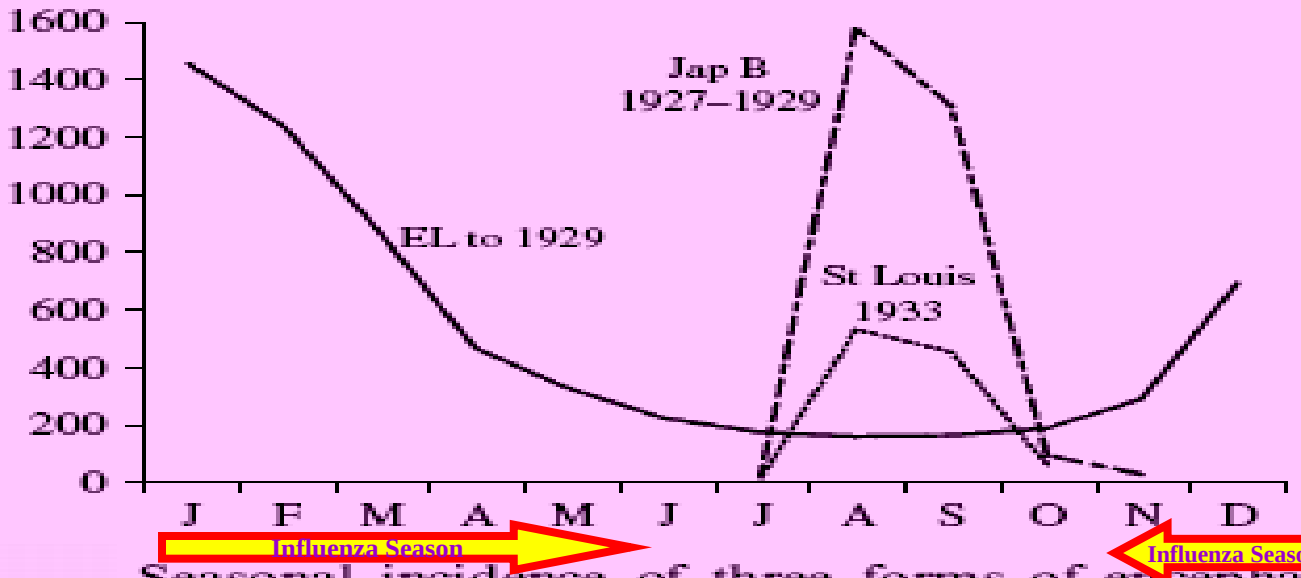
Temporal Relationship of 1918 Influenza Encephalitis lethargica, Parkinsonism

Successful quarantining of American Samoa from influenza in 1919 spared those islands from Encephalitis lethargica in subsequent years.

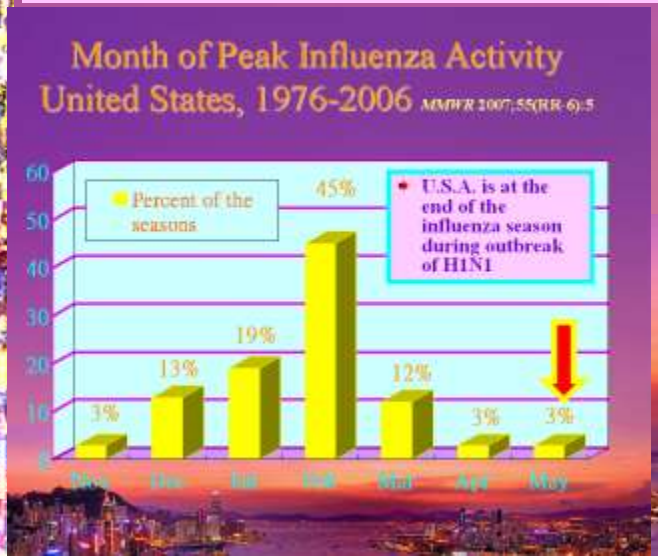
Epidemic influenza years in Seattle after 1919 were followed by peaks of cases of encephalitis lethargica

1918 Influenza, encephalitis lethargica, Parkinsonism

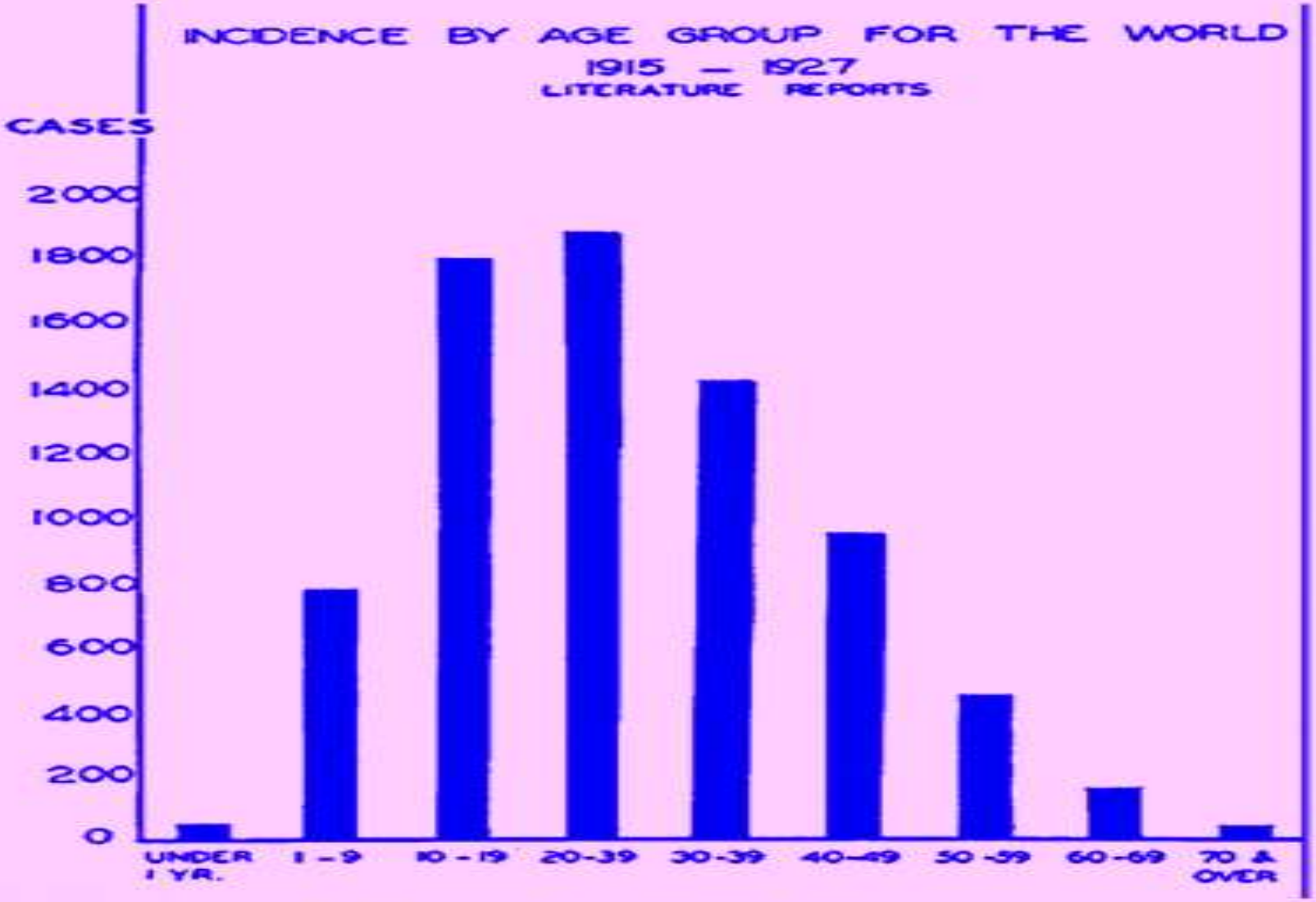
Ravenholt RT, Foege WH. Lancet 1982; ii : 860–864.



Seasonal incidence of three forms of encephalitis: 7876 cases of encephalitis lethargica (EL) (up to 1929); 3118 cases of Japanese B encephalitis (Jap B) (1927–1929); and 1097 cases of St Louis encephalitis (1933). Acute EL was predominantly a winter illness (source: Matheson Commission, *3rd Report* [3]).



Encephalitis Lethargica Coincide with Influenza Season (e.g. in U.S.A. Influenza season begins at November and ends at May)

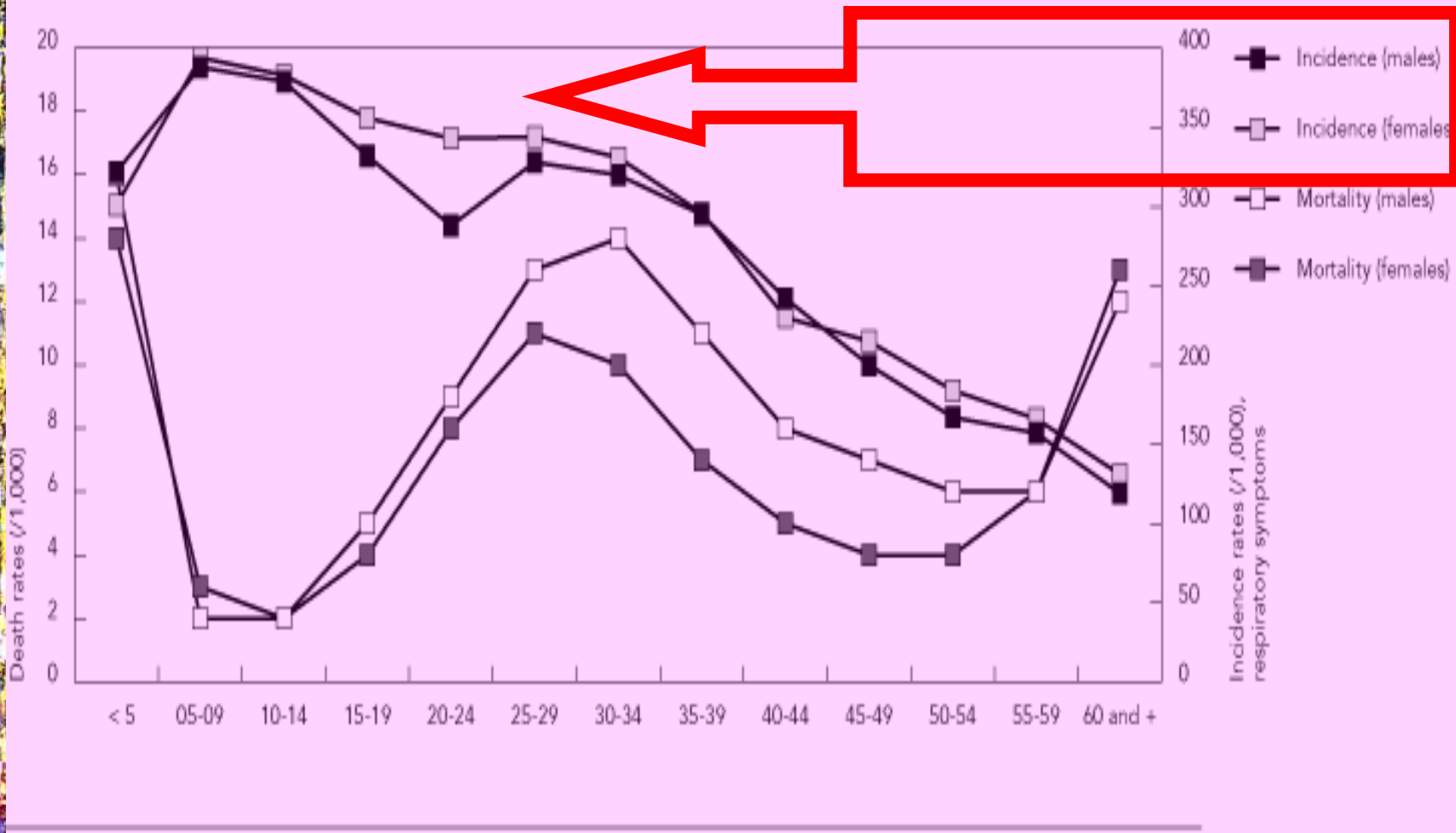


Age distribution of encephalitis lethargica

Children and encephalitis lethargica: a historical review.

Vilensky JA. Foley P. Gilman S. Pediatric Neurology. 37(2):79-84, 2007 Aug.

1918-1919 Influenza and pneumonia morbidity and mortality (/1,000) by sex and age. US Registration States.



Source: Collins (1930); Crosby (1989); US Bureau of the Census (1955).

Age Distribution Curve of 1918 H1N1 Influenza
Similar Age Distribution To Encephalitis Lethargica

Clinical Features and Laboratory Findings

Encephalitis Lethargica
(55% has preceding pharyngitis)

Sleep disorders
Iomnolence, Sleep inversion, Insomnia

Lethargy

Extrapyramidal symptoms
(Parkinsonism, dyskinesias)

Oculogyric crisis
Ocular palsy and ptosis

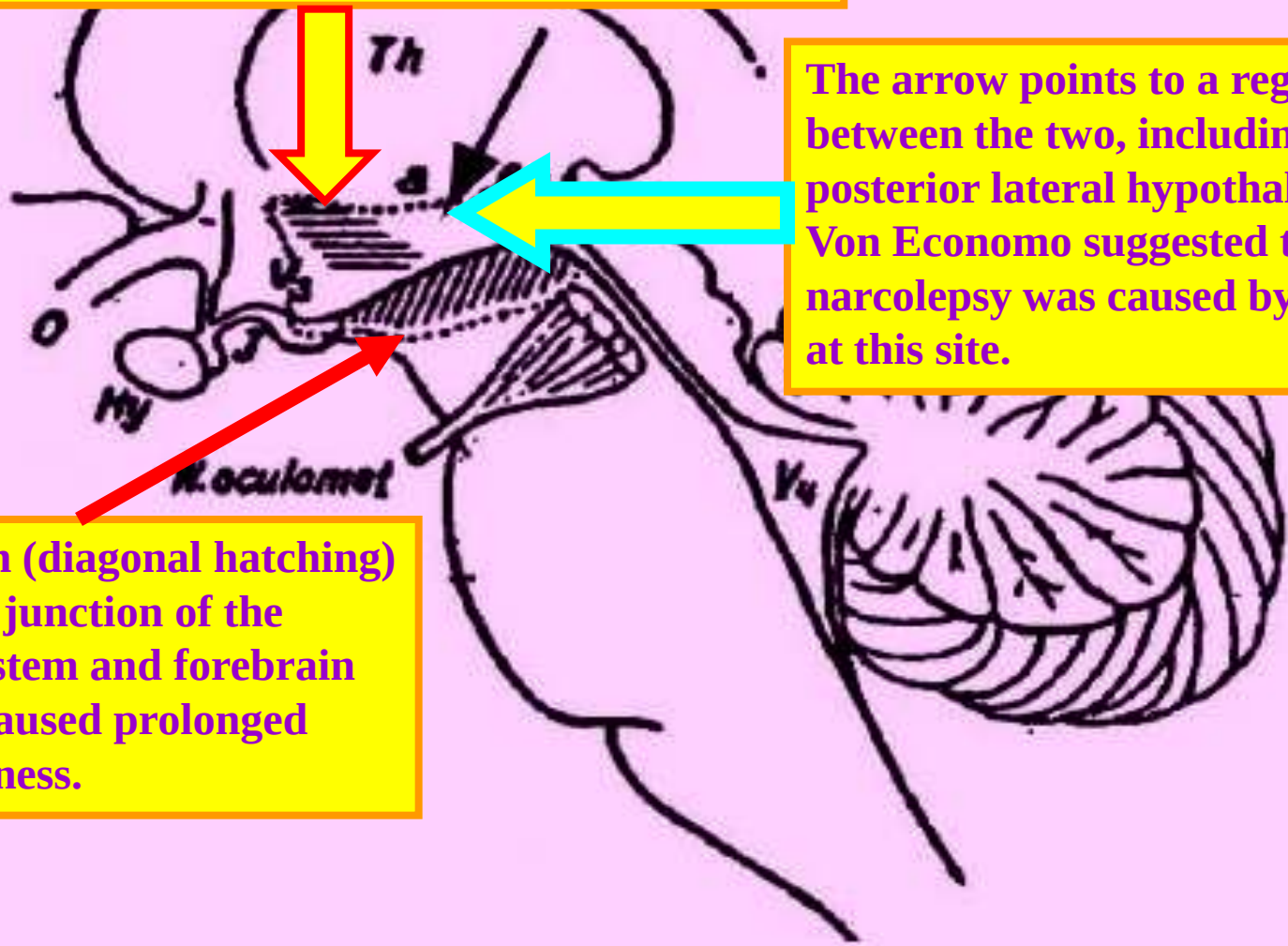
Neuropsychiatric Diorders
Catatonia, obsessive±compulsive disorder and mutism
apathy and conduct disorders

Central cardiorespiratory Features (e.g. hiccup)

LP: Lymphocyrosis, elevated proteins,
Intrathecal oligoclonal band
Human anti-basal ganglia neuronal Ab

MRI: 60% normal and 40%
deep grey matter inflammation

Lesion (horizontal hatching) in the anterior hypothalamus that caused prolonged insomnia

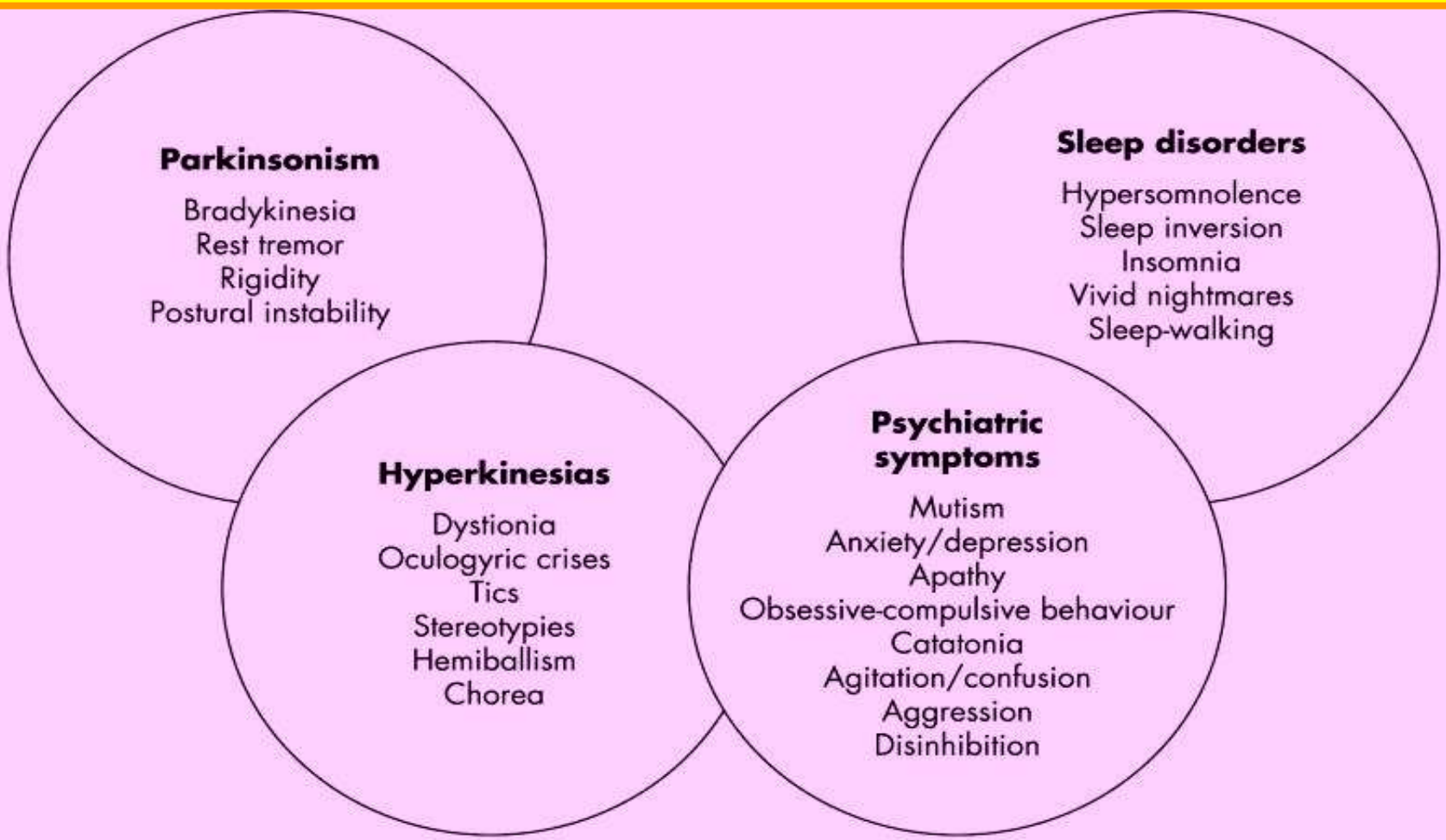


The arrow points to a region between the two, including the posterior lateral hypothalamus. Von Economo suggested that narcolepsy was caused by lesions at this site.

Lesion (diagonal hatching) at the junction of the brainstem and forebrain that caused prolonged sleepiness.

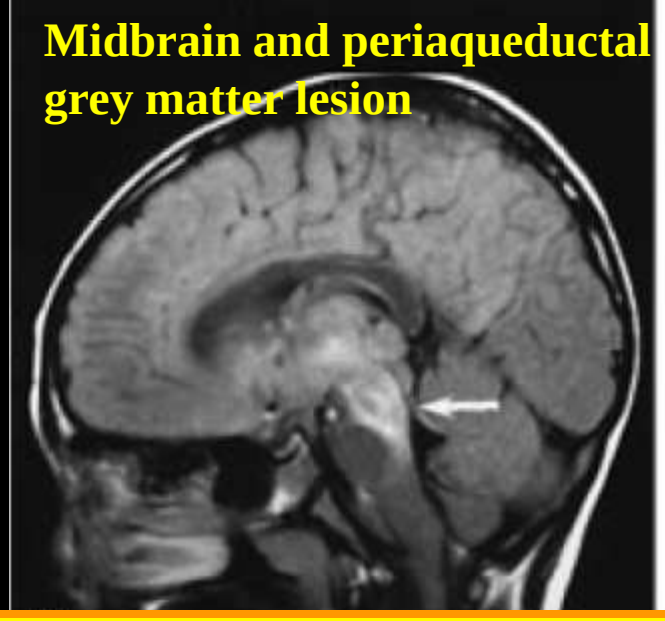
A drawing of the human brainstem, taken from von Economo's original work.

Cortico–striato–thalamo–cortical circuitry of the brain which controls motor, emotional and cognitive domains.

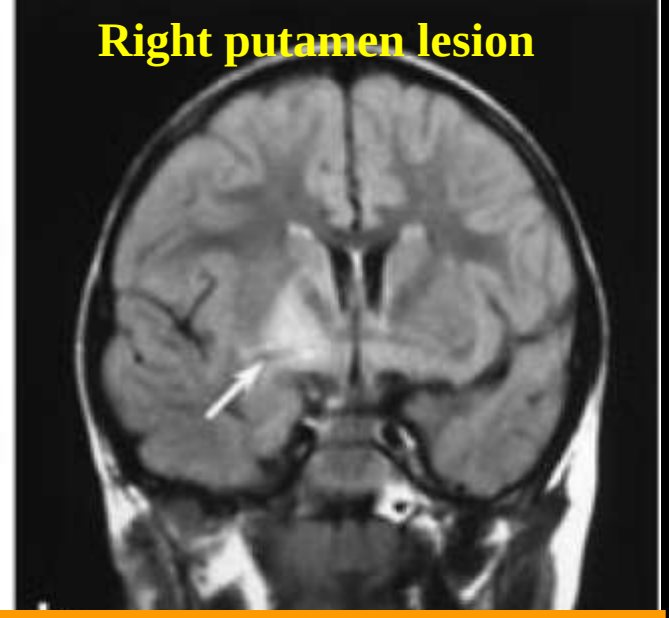


The encephalitis lethargica syndrome is a neuropsychiatric syndrome with a movement disorder—either hypokinetic or hyperkinetic—prominent psychiatric features and a sleep disorder. This constellation of symptoms and signs results from pathological involvement of the diencephalon and mid-brain structures.

Midbrain and periaqueductal grey matter lesion



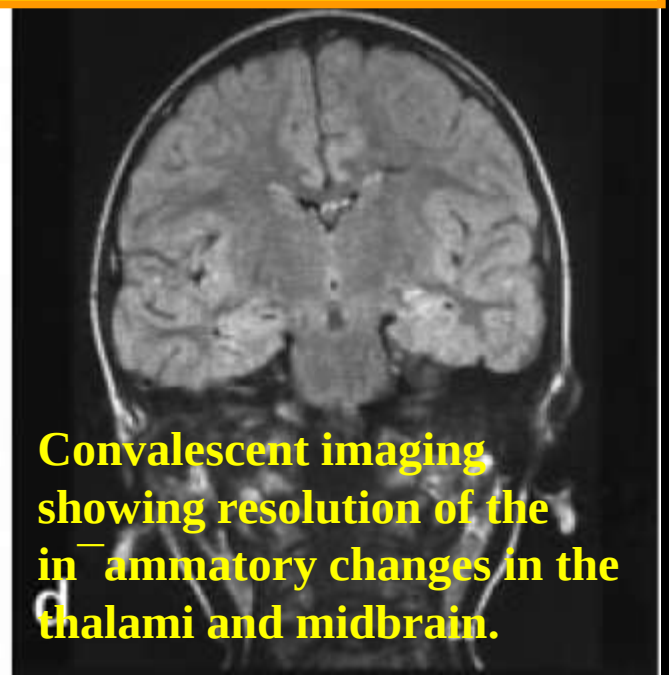
Right putamen lesion



MRI of the brain in a somnolent patient with bradykinesia and rigidity

Encephalitis lethargica syndrome: 20 new cases and evidence of basal ganglia autoimmunity
Russell C. Dale et al October 21, 2003 Brain (2004), 127, 21-33

Bilateral thalami and midbrain lesion

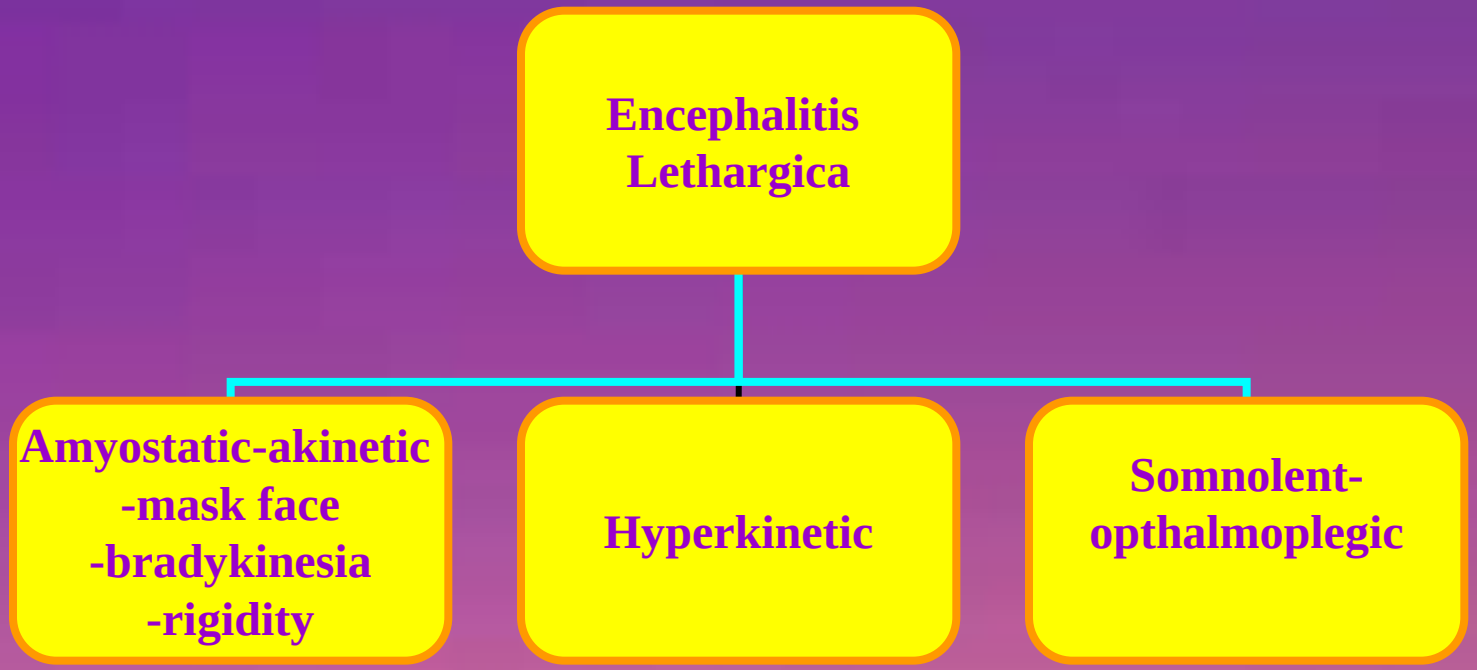


Convalescent imaging showing resolution of the in¯ammatory changes in the thalami and midbrain.

- Howard and Lees Proposed Clinical Diagnostic Criteria
- Three of the following major criteria:
  - (1) signs of basal ganglia involvement,
  - (2) oculogyric crises,
  - (3) ophthalmoplegia,
  - (4) obsessive-compulsive behavior,
  - (5) akinetic mutism,
  - (6) central respiratory irregularities
  - (7) somnolence and/or sleep inversion

Encephalitic lethargica: a report of four recent cases. Howard R, Lees A. Brain. 1987;110:19-28.

Encephalitis Lethargica



DDx idiopathic parkinsonism

➔ Occur at younger age group with onset before age 40 years

28 types of manifestation of encephalitis lethargica has been described but 3 forms are most common: paralysis agitans-like, abortive, cerebellar, hyperkinetic, hemiplegic, cortical, spinal, polyneuritic, cataleptic, meningeal, progressive, aberrant, monosymptomatic, insomniac, paralytic, myoclonic, thalamic, and juvenile pseudo-psychopathic manifestation types.

Name	Signs/symptoms	Speculated anatomical site
1. Somnolent- ophthalmoplegic (sometimes together, sometimes as separate types)[5 10 11 24 – 28 30 32 33]	Profound somnolence (but sometimes insomnia); diplopia, strabismus, ptosis; facial paralysis, speech/swallowing disturbances	Cranial nerve III, sometimes other cranial nervess especially IV, V, VI; midbrain
2. Paralysis agitans (amyostatic, pallidal)[5 12 19 21 24 – 28 32 33]	Parkinsonism with bradykinesia, rigidity, tremor, festination, masked face, spasticity	Striatum, globus pallidus
3. Psychiatric[5 19 24 25 27 28 30 32 33]	Hallucinations, illusions, delirium, depression, incontinence	Multiple foci in telencephalon
4. Abortive (mild, transient)[5 10 – 12 26 32 33]	Tightness, tenseness in muscles; mild fixity of expression; slight tremors; patient typically recovers completely after brief period	
5. Cerebellar[11 12 24 – 26 29 32]	Ataxia of gait and speech; patients generally recover	Cerebellum
6. Hyperkinetic (sometimes differentiated by type of movement disorder; neostriatal)[5 12 21 24 25 30 32]	Chorea, athetosis, seizures, restlessness	
7. Hemiplegic (hemiparetic)[12 28 – 30 33]	Hemiplegic signs/symptoms; early stabilisation allows differentiation from typical adult hemiplegia	
8. Cortical (cerebral cortical)[5 11 12 26 29]	Convulsions, amnesia, disorientation, dysarthria, lethargy	Cerebral cortex
9. Spinal (radicular-spinal)[5 10 – 12 24]	Paresis, loss of knee jerks, myoclonic movements and fasciculations	Spinal cord
10. Polyneuritic[10 – 12 24 33]	Peripheral nerve lesions	Peripheral nerves
11. Cataleptic[12 27 19 21]	Catalepsy, vertigo, nystagmus, ataxia	
12. Meningeal[24 27 30 33]	Dull pounding headache; stiff neck	Meninges
13. Anterior poliomyelitic[5,7,11]	Lower motor neuron weakness similar to infantile paralysis; affects lower limbs	Lower motor neurons
14. Hyperalgesic (posterior poliomyelitic)[19,29,33]	Segmental pain similar to post-herpetic neuralgia	Dorsal root ganglion or posterior horns of spinal cord
15. General symptoms without localising signs[10,11,26]	Headache, confusion, sleep disorders	Brain stem
16. Infantile[19,33]	Infants with identical encephalitis lethargica symptoms as adults	
17. Progressive[12,26]	Progressive symptoms	Renewal of inflammatory process
18. Aberrant/autonomic[25,32]	Intestinal, cutaneous, vagal symptoms	
19. Monosymptomatic[5,25]	Single symptom, usually hiccups	
20. Tabetic[32]	Arygll-Robertson pupils, loss of deep tendon reflexes, lancinating pain	Posterior columns, dorsal roots
21. Insomnia[28]	Insomnia	
22. Paralytic[32]	Akinesia, hypokinesia	Nuclei of corresponding motor
23. Myelitic[27]	Urinary incontinence, Babinski sign, disturbed reflexes, clonus	
24. Pallido-pyramidal[12]	Combination of spastic paralysis and parkinsonism (more complete paralysis); clonus, Babinski sign	Pyramidal and pallidal system involvement
25. Mixed striatal[12]	Bizarre combinations uniting elements of chorea and paralysis agitans	
26. Myoclonic[12]	Rare; rhythmical movements of distal parts of extremities	Striatum
27. Thalamic[12]	Spontaneous pain of intolerable intensity; ataxia	
28. Juvenile pseudo- psychopathia[25]	Only in juveniles; lack of inhibitions (morals) but no intellectual defect	

Somnolent-Ophthalmoplegic

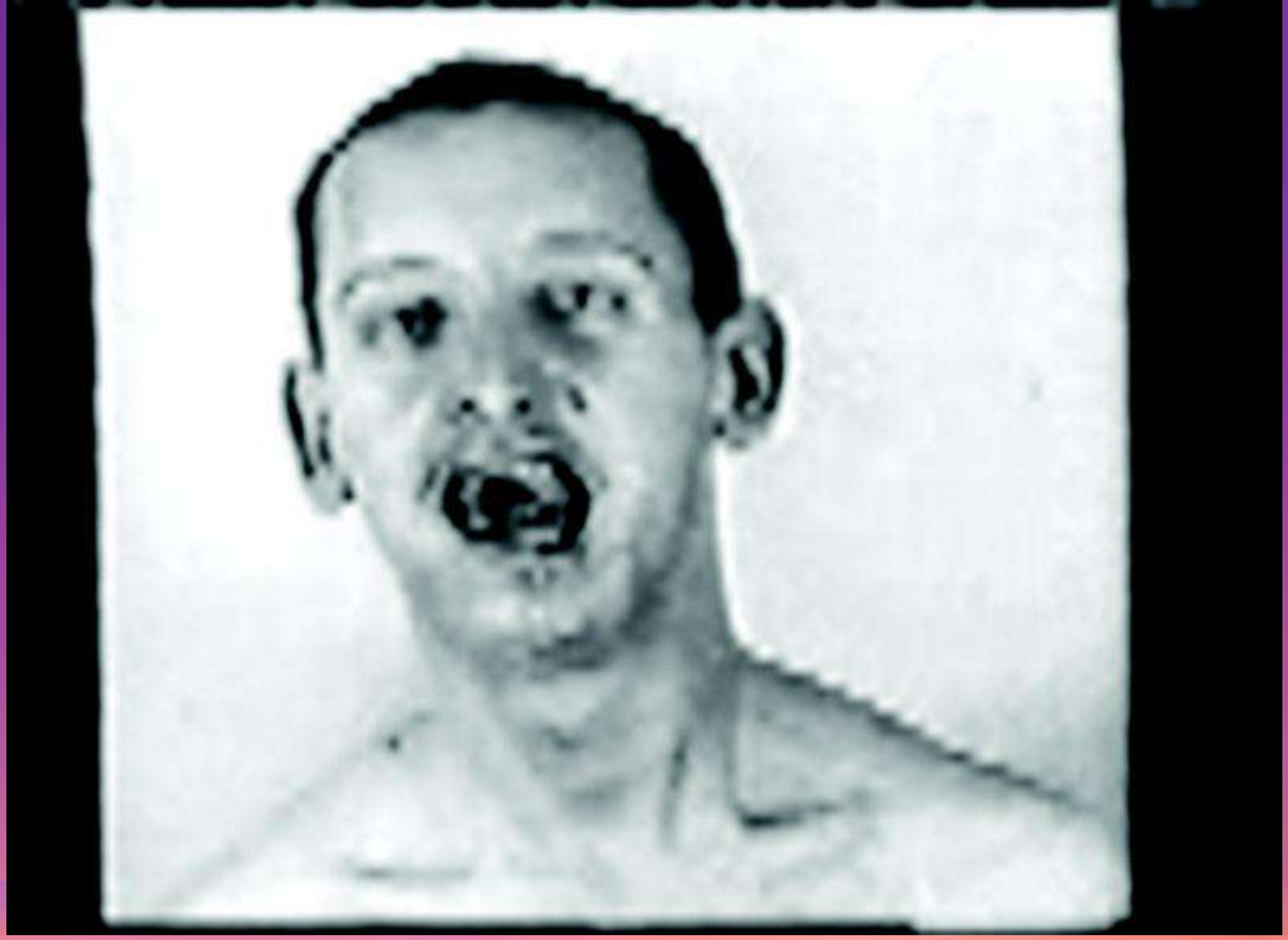
- The prodromal phenomena consists of general discomfort, shivering, headache, and slight pharyngitis. The temperature is generally only a little raised to slightly above 98°F.... **Von Economo emphasized that the sudden high fever, myalgias, and upper respiratory symptoms characteristic of influenza were absent**
- Within the next few days, **somnolence** begins to predominate. The patients left to themselves fall asleep in the act of sitting and standing, and even while walking, or during meals with food in the mouth.... If aroused, they wake up quickly and completely, are oriented and fully conscious... but soon drop back to sleep. Sleep in this form may last for weeks or even months but frequently deepens to a state of most intense stupor or even a comatose condition which may terminate fatally after some days or weeks.
- Generally, during the first days of the illness **(cranial nerve) palsies** appear. **Ptosis** is one of the first and most frequent symptoms. The **frequent bilateral occurrence of ocular palsies, incomplete, usually asymmetrical**, suggest that it is, in most cases, a **nuclear palsy**. Rarely observed are supranuclear paralyses, paresis of convergence, nystagmus, optic neuritis, papilledema, pupillary disturbances, and even Argyll Robertson's sign
- Mortality 50%, but chronic debility and neurologic sequelae were uncommon

Hyperkinetic

- In the winter of 1920, there was observed a very large group of hyperkinetic cases, first in Italy then Austria. Chorea and hemichorea as well as myoclonic twitches which were observed may degenerate into wild jactations.
- On the other hand, it may find its mental expression in a general, curious restlessness of an anxious or hypomanic type. In most of these cases, there is a very distinct sleep disturbance and generally the condition is one of troublesome sleeplessness.
- Mortality 40%, although complete recovery was less common than in the somnolent form.

Amyostatic-Akinetic

- Third place in order of frequency, the amyostatic-akinetic form, is characterized by a rigidity, without a real palsy and without symptoms arising from the pyramidal tract. This form of encephalitis lethargica is particularly common in the chronic cases, dominating the clinical picture as Parkinsonism. I reserve the name 'Parkinsonism,' though symptomatically identical with the amyostatic-akinetic form, rather for the chronic cases. To look at these patients one would suppose them to be in a state of profound secondary dementia. Emotions are scarcely noticeable in the face, but they are mentally intact.
- Mortality in the acute stage of this form of EL was somewhat less than in the other forms, although progression to a chronic form was much more likely.



Young adult man with encephalitis lethargica with a chronically open mouth and masked face with constant drooling.

OCULOGYRIC CRISES

- Oculogyric crisis was the one of the outstanding features of postencephalitic parkinsonism.
- Of particular interest are the visual fits, described by French authors as ‘crises ocuogyres' (van Bogaert, Bing, and Schwartz, Marinesco and Radovici), in English as "tonic eye-fits" or, more commonly, as oculogyric crises. **They consist of tonic visual convulsions, occurring in fits and generally lasting only a few minutes, during which the patients as a rule look upwards and sideways**.... Frequently, the convulsive twisting of the eyes is also accompanied by other convulsive movements, such as contortion of the head in the direction of vision, tonic stretching of the neck, even of the trunk and extremities.... 4

Young adult woman with encephalitis lethargica during an oculogyric crisis. Note the typical combination of torticollis with forced lateral and upward eye movements and flexed posture of the right arm.

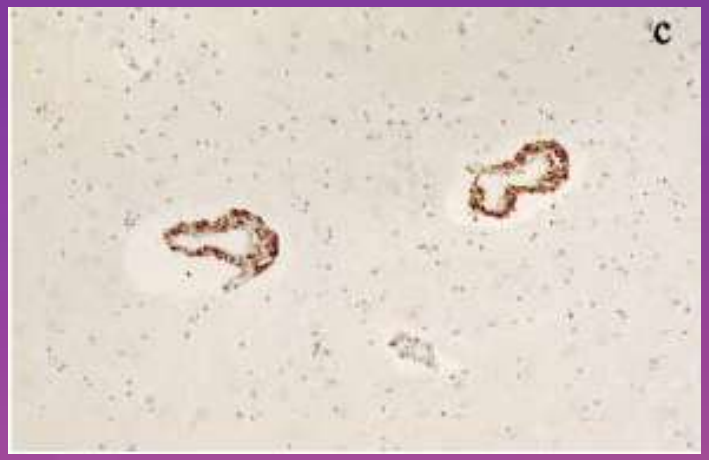
Encephalitis Lethargica

- The CSF was abnormal in about 50% of epidemic EL cases, mild elevation of protein and mild lymphocytosis being characteristic (von Economo, 1931; McCall et al., 2001).
  - Recent studies showed all CSF PCR studies were negative, making a neurotropic viral encephalitis unlikely.
  - The presence of intrathecal synthesis of OCB has been proposed to be a useful marker of disease (Williams et al., 1979; Howard and Lees, 1987).
- 40% showed increased signal in the basal ganglia, substantia nigra and tegmentum. The enhancement resolved after the acute stage in the few patients who had convalescent imaging.

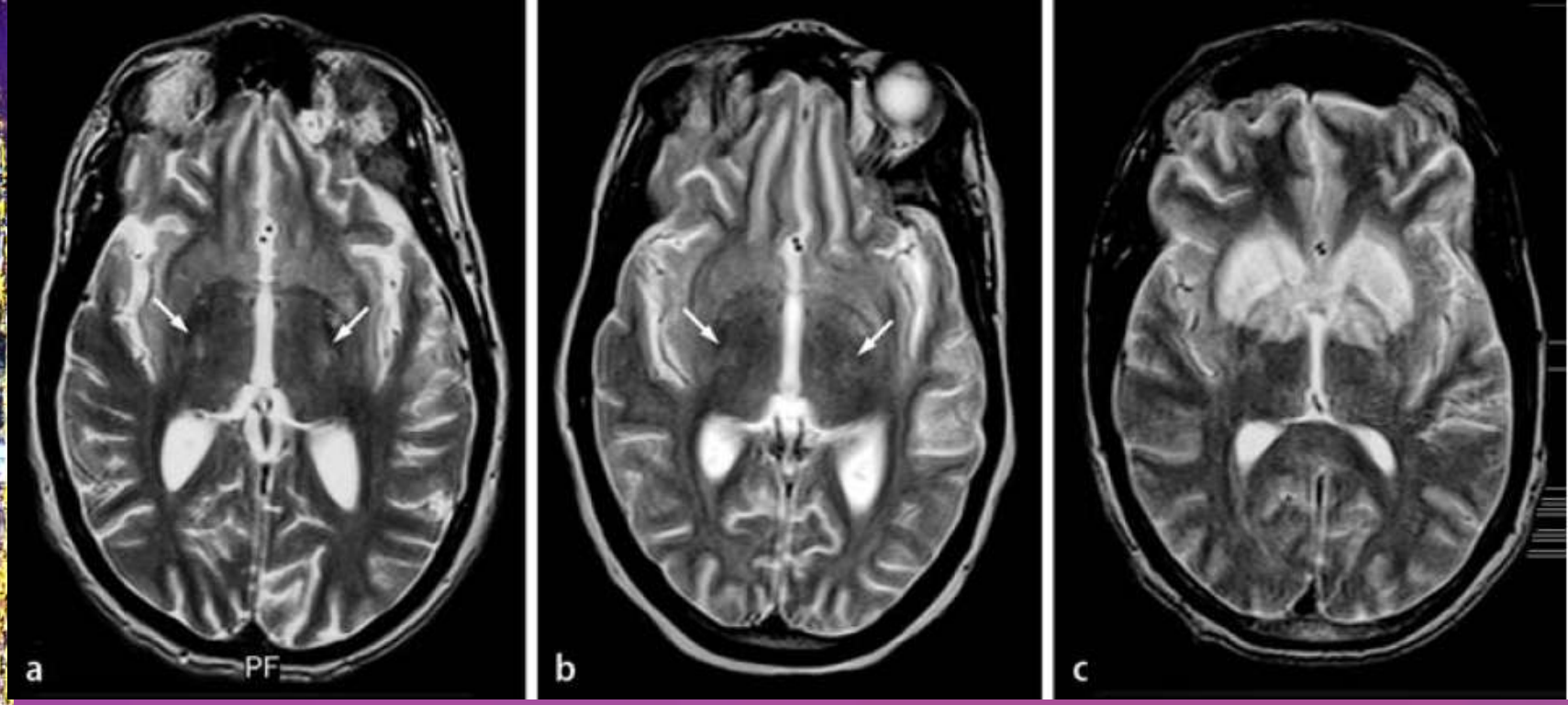
Encephalitis Lethargica

- Brain pathology:
  - Perivascular lymphocytic (plasma cell) cuffing, which predominantly involves the midbrain and basal ganglia.(von Economo, 1931; Rail et al., 1981; Kiley and Esiri, 2001).
  - The lymphocytes were both T and mature B lymphocytes. Other than secondary reactive astrocytes and macrophage activation, there were no other striking pathological features.
  - Brain specimens for 1918 influenza virus RNA was negative. Viral inclusion were negative.
  - Chronic changes included neuronal loss and neurofibrillary degeneration in the midbrain and basal ganglia.

Encephalitis Lethargica



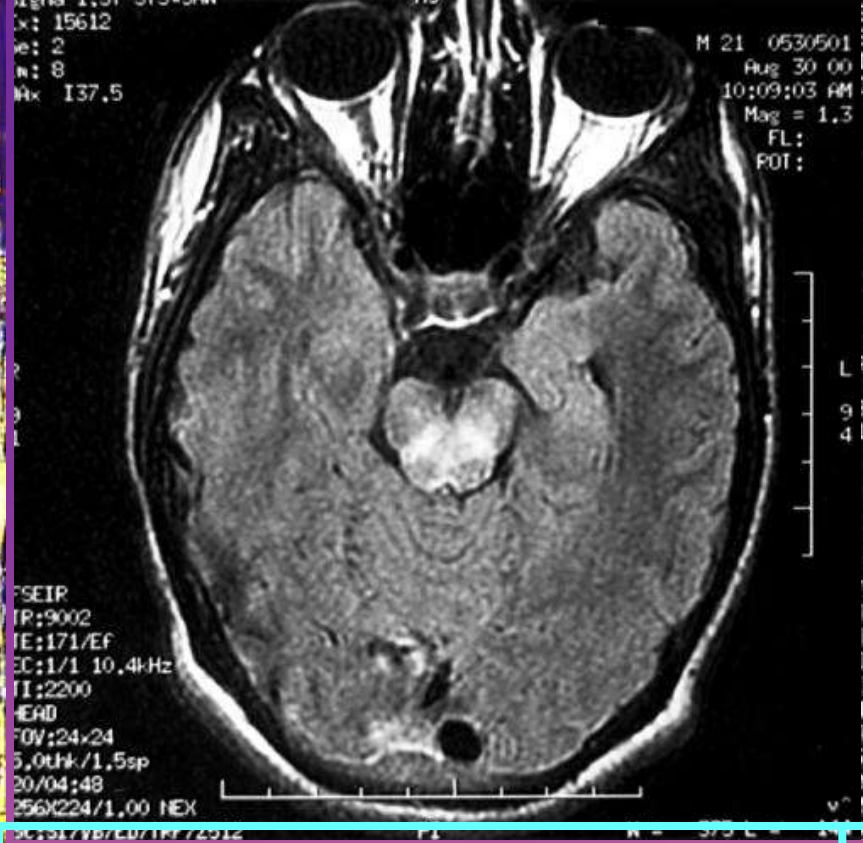
Histopathology of striatum demonstrates perivenous lymphocytic infiltration. Additional staining with (b) CD3 and (c) CD20 identifies infiltrating cells as T and mature B lymphocytes respectively.



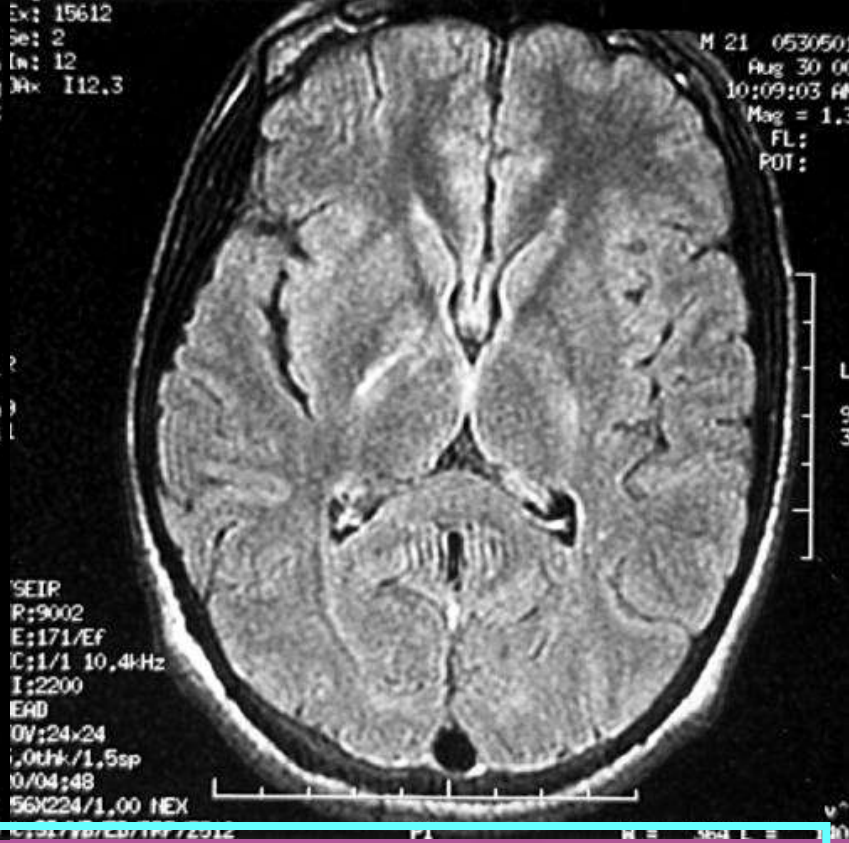
MRI (FLAIR sequences) findings: case 1 (a), and case 5 (b) had hyperintense thalamic signal abnormalities. C Case 8 had profound hyperintense basal ganglia signal abnormalities. Abnormal signals are demonstrated with white arrows

Contemporary Encephalitis Lethargica: phenotype, laboratory findings and treatment outcomes.

Lopez-Alberola R. Georgiou M. Stakianakis GN. Singer C. Papapetropoulos S. Journal of Neurology. 256(3):396-404, 2009 Mar.



Bilateral hyperintense lesions of the substantia nigra on MRI flair image on day four.

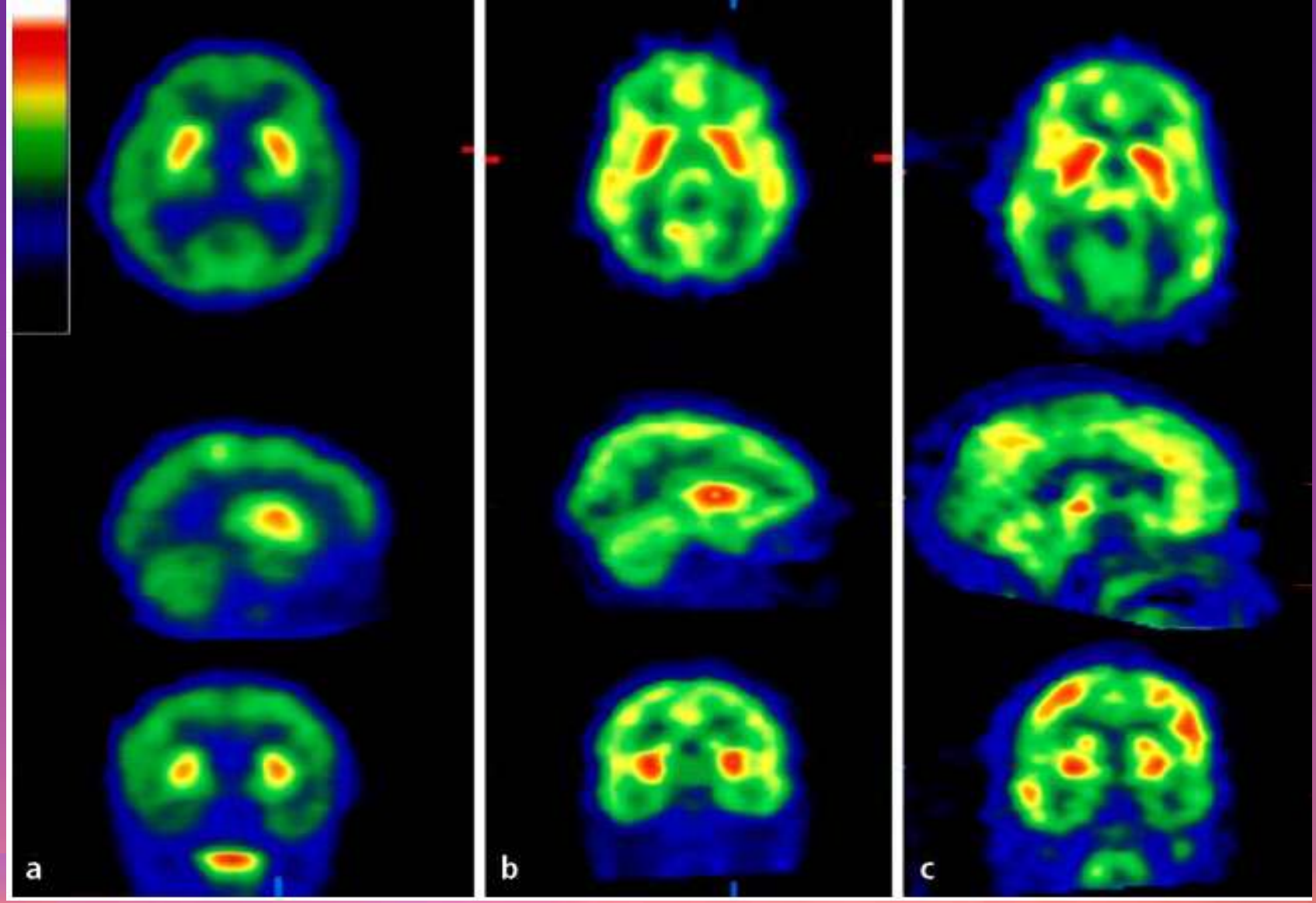


Hyperintense lesion of the right striatum on MRI flair image on day four.

A seroconversion was noted for Coxsackie virus type B3 (titre 0 on day 4, 1/320 on day 25)
➔ indicating similar clinical features can be due to other viral infection.

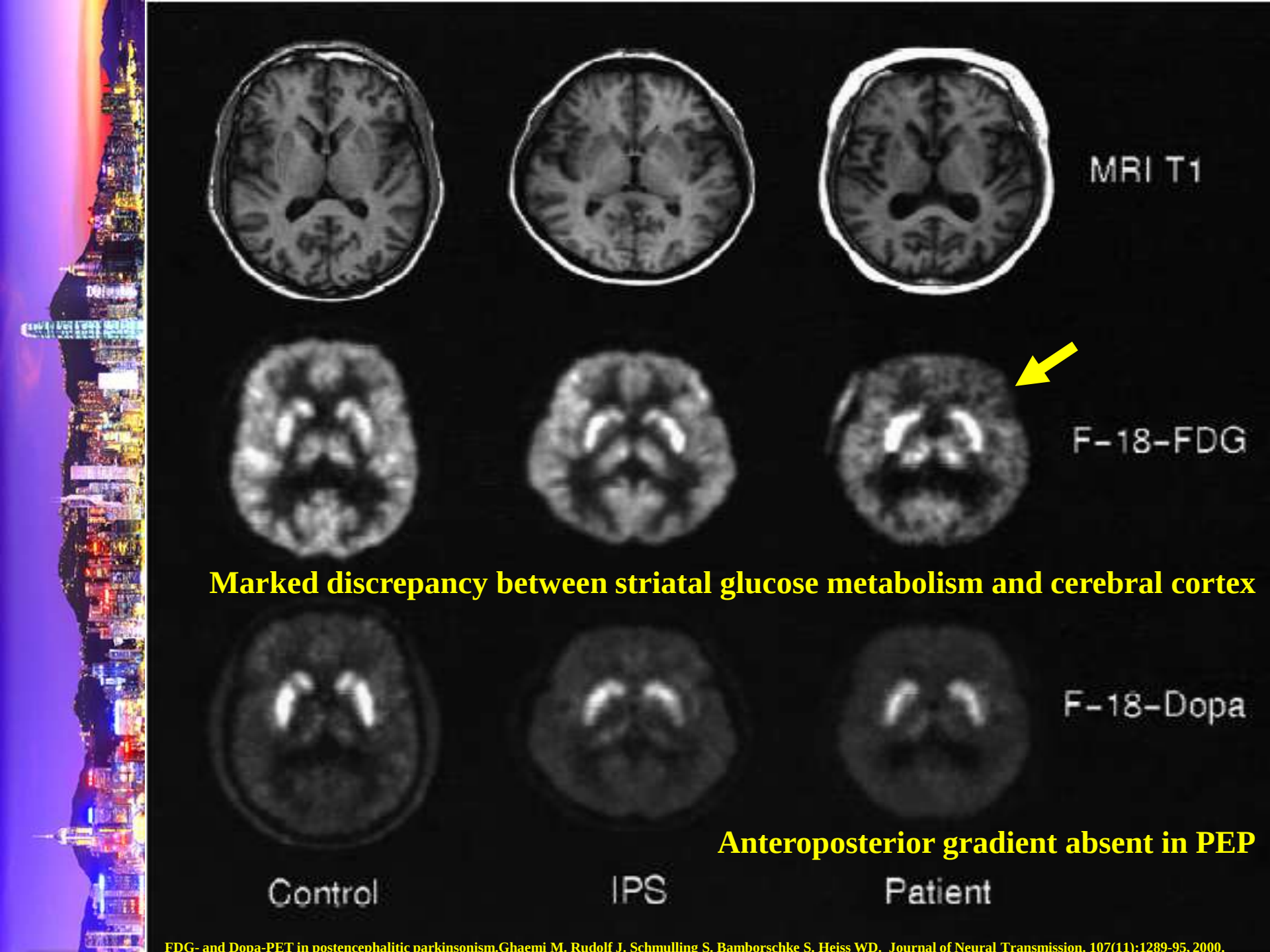
Bilateral substantia nigra lesions on magnetic resonance imaging in a patient with encephalitis lethargica

VERSCHUEREN, H; CROLS, R Journal of Neurology, Neurosurgery, & Psychiatry Issue: Volume 71(2), 1 August 2001, p 275



Characteristic 18F-FDG PET imaging findings:

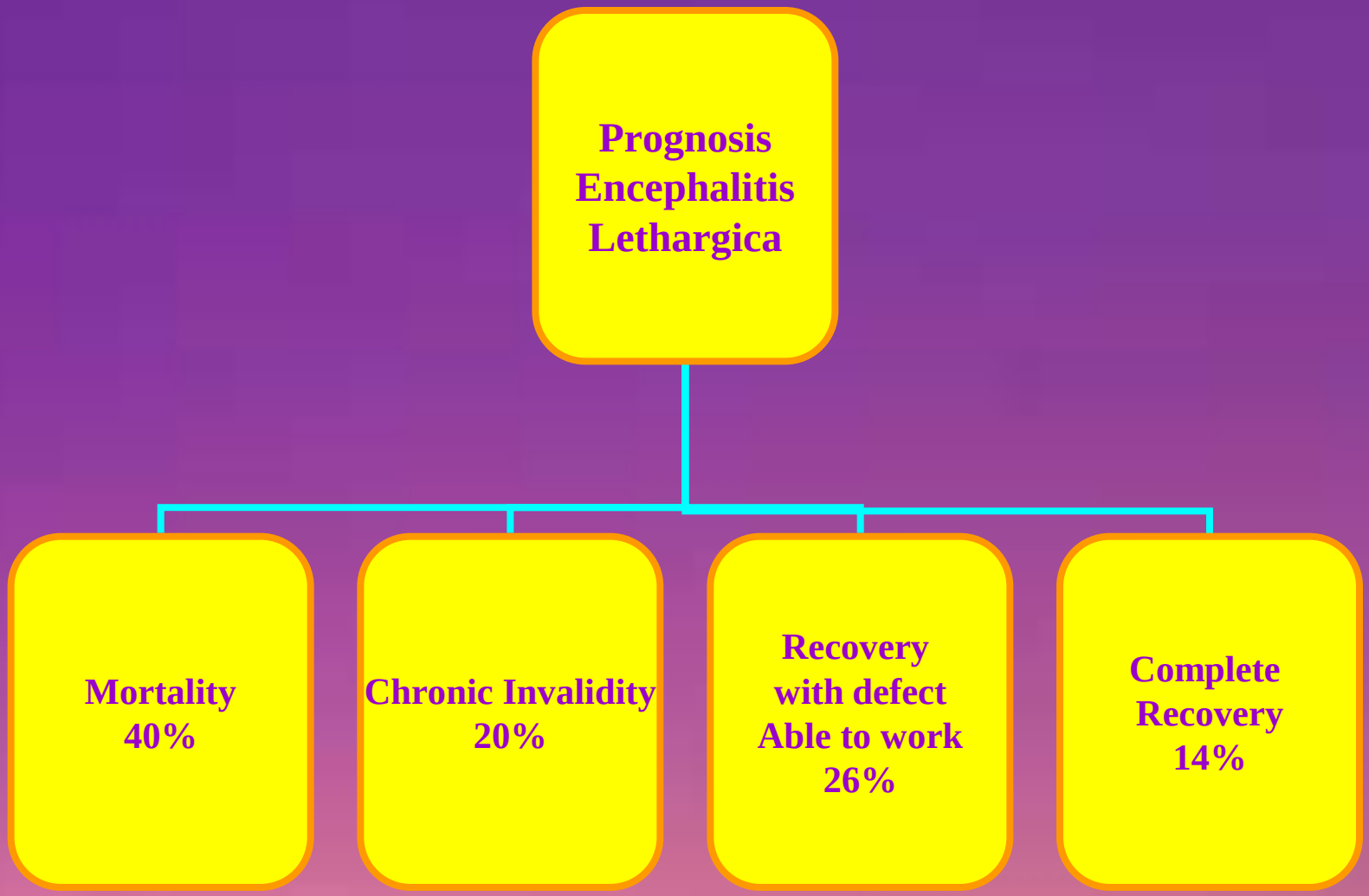
Variable degrees of suppression of metabolic cortical activity with bilateral basal ganglia hyperactivity



Marked discrepancy between striatal glucose metabolism and cerebral cortex

Anteroposterior gradient absent in PEP

FDG- and Dopa-PET in postencephalitic parkinsonism.Ghaemi M, Rudolf J, Schmulling S, Bamborschke S, Heiss WD. Journal of Neural Transmission. 107(11):1289-95, 2000.



Encephalitis Lethargica: Its Sequelae and Treatment.

Von Economo C. Translated by K.O. Newman, Oxford University Press: London, England; 1931.

Encephalitis Lethargica

- Mortality 20-40%
- Morbidity:
  - Parkinsonism, dyskinesias or psychiatric disease.
  - The course of disease was monophasic or fluctuating, unlike the progressive course characteristic of the metabolic, biochemical or inherited causes of parkinsonism.

It is unlikely that the 1918 influenza virus was neurotropic and directly responsible for the outbreak of EL because several studies has failed to detected the presence of influenza viral genes from patients suffering from Encephalitis lethargica

Influenza RNA not detected in archival brain tissues from acute encephalitis lethargica cases or in postencephalitic Parkinson cases
Jellinger KA. Journal of Neuropathology & Experimental Neurology. 60(11):1121-2, 2001 Nov.

Influenza RNA not detected in archival brain tissues from acute encephalitis lethargica cases or in postencephalitic Parkinson cases
McCall S. Henry JM. Reid AH. Taubenberger JK. Journal of Neuropathology & Experimental Neurology. 60(7):696-704, 2001 Jul.

Lack of detection of influenza genes in archived formalin-fixed, paraffin wax-embedded brain samples of encephalitis lethargica patients from 1916 to 1920.
Lo KC. Geddes JF. Daniels RS. Oxford JS. Virchows Archiv. 442(6):591-6, 2003 Jun.

? Autoimmunity

- Anti-basal ganglia neuronal antibodies in sera
- Oligoclonal banding in cerebrospinal fluid of EL patients
- Steroid response
- Negative virological tests

Both patients respond dramaticially to pulse steroid therapy

(a) Methylprednisolone 0.5g IVI daily for 5 days or
(b) Methylprednisolone 1g IVI daily for 3 days

Steroid treatment should be considered in the acute phase of patients with features suggestive of encephalitis lethargica.

Clinical features and management of two cases of encephalitis lethargica.
Blunt SB, Lane RJ, Turjanski N, Perkin GD Mov Disord. 1997 May;12(3):354-9.

Clinical Aspect of Encephalitis Lethargica in Children

Dr. Lai Kang Yiu
Intensive Care Unit
Queen Elizabeth Hospital

Clinical Features and Laboratory Findings

Encephalitis Lethargica
(55% has preceding pharyngitis)

Sleep disorders
Iomnolence, Sleep inversion, Insomnia

Lethargy

Extrapyramidal symptoms
(Parkinsonism, dyskinesias)

Oculogyric crisis
Ocular palsy and ptosis

Neuropsychiatric Diorders
Catatonia, obsessive±compulsive disorder and mutism
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Central cardiorespiratory Features (e.g. hiccup)

LP: Lymphocyrosis, elevated proteins,
Intrathecal oligoclonal band
Human anti-basal ganglia neuronal Ab

MRI: 60% normal and 40%
deep grey matter inflammation

Contemporary Encephalitis Lethargica: phenotype, laboratory findings and treatment outcomes.

Lopez-Alberola R. Georgiou M. Sfakianakis GN. Singer C. Papapetropoulos S. Journal of Neurology. 256(3):396-404, 2009 Mar.

- Sporadic cases of encephalitis lethargica still occur
- Contemporary EL is more frequent in paediatric (including adolescent) than in adult patients.
- (M/F: 5/3) ranged from 2–28 years (mean 9.3 ± 9.5).
- Encephalopathy, sleep disturbances and extrapyramidal symptoms were present in all cases.
- Laboratory investigations revealed CSF leukocytosis in 5/8 patients and anti-BG Ab in 4/7 patients.
- MRIs revealed structural abnormalities in 7/8 cases. 18F-FDG PET showed basal ganglionic hypermetabolism in 4/7 patients.
- Treatment approaches included immunomodulating and symptomatic therapies.

Children and encephalitis lethargica: a historical review.

Vilensky JA. Foley P. Gilman S. Pediatric Neurology. 37(2):79-84, 2007 Aug.

- Encephalitis lethargica was at least as devastating for children as for adults, typically causing severe psychiatric as well as motor disorders;
- The psychiatric effects in children were virtually pathognomonic for encephalitis lethargica, so that a recurrence of encephalitis lethargica might initially be most readily identifiable in children;

Encephalitis lethargica (嗜睡性腦炎) is an acute encephalopathic illness characterised by sleep disturbance, neuropsychiatric and extrapyramidal symptoms.

The diagnosis in children is made by exclusion of infective, biochemical, degenerative, autoimmune, toxic or metabolic causes of acute encephalopathy.

Encephalitis Lethargica in a Twelve-year-old Girl: The Response to Levodopa Therapy

B Chan, KY Chan, KC Yau HK J Paediatr (New Series) 2009;14:122-125

Gradual onset, marked lethargy and asthenia, headache, low irregular temperature, cranial nerve and other palsies, and often a masked face

Encephalitis Lethargica In children

Other possible features included catatonia, marked tremors, choreiform movements, profuse sweating, insomnia, delirium, and myoclonus. Vomiting was common.

Lethargic Amyostatic-akinetic

Drowsy state
Mask-like face
Rigidity
Facial myoclonus

Irritable

Marked restlessness
Excitability and virtually
continuous crying.

Lethargic with paralysis

Drowsiness
Paralysis (Motor & cranial n. palsy)
Frequent convulsions.

Of 58 childhood cases of encephalitis lethargica described by Neal, 44 were male, 34 recovered, 14 died, and 10 were “cured.”

Boy with encephalitis lethargica depicting an abnormal posture of flexed body, retracted arms, head leaning forward, and open mouth.

Psychiatric Manifestation in Children

- Whereas 70% of pediatric encephalitis lethargica survivors showed some psychological changes, approximately one third exhibited behavioral disorders.
- **Marked personality changes, always negative**. The term "Apache" was used to characterize the most aggressive of these children, a pejorative reference to Apache Indians
  - **Excitation crises (usually evening): agitation, screams, or insomnias;**
  - **Impulsiveness;**
  - **Infantile or precocious sexuality;**
  - **Self-mutilation tics;**
  - **Vandalism;**
  - **Malicious cruelty coupled with feigned friendliness; and**
  - **Theft**
- Memory loss, true psychosis, and depression, on the other hand, were regarded as uncommon.

Approximately one third of affected children underwent a rapid transformation from normal behavior to delinquency, often leading to institutionalization !

Encephalitis lethargica triggered behavioral changes in children that are not duplicated by any other neurologic condition, with the possible exception of traumatic brain injury. These unique behavioral abnormalities may provide the earliest clear indication of new encephalitis lethargica cases, whether alone or in concert with an influenza epidemic.

Children and encephalitis lethargica: a historical review.

Vilensky JA. Foley P. Gilman S. Pediatric Neurology. 37(2):79-84, 2007 Aug.

Whereas the neurologic lesions are the same for adults and children with encephalitis lethargica, adults do not exhibit the "deterioration of character" unique to encephalitis lethargica in children. [JUVENILE PSEUDOPSYCHOPATHIA]

Many of these children with antisocial behavior are being send to a state institution or mental institutions or arrested as a result of their uncontrolled, delinquent behavior. Some has undergone frontal leucotomy.

Remarks on the psychopathology of oculogyric crises in epidemic encephalitis.

Wexberg E. J Nerv Ment Dis 1937;85:56-69

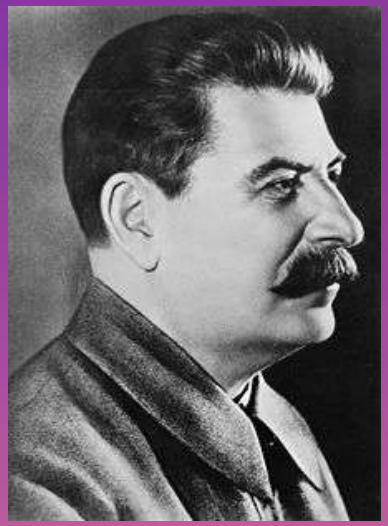
Institute for Juvenile Research in Chicago

- Six behaviors that best distinguished children with encephalitis lethargica from those without encephalitis lethargica (although these control subjects were not “normal” children):
  - **Change of personality;**
  - Emotional instability, changeable moods, and crying spells;
  - Irritability and temper tantrums, and quarrelsomeness;
  - Nervousness, restlessness, and restlessness in sleep, and irregular sleep habits;
  - Disobedience and defiant attitude; and
  - Listlessness.

They do not evade detection.
They are indifferent to punishment

Encephalitis Lethargica
Neuropsychiatric manifestations
?Emotional Lability

Joseph Stalin



Adolf Hitler

Violent and aggressive behaviour and gesticulation of Hitler may have been due, at least partly to Encephalitis Lethargica !

Lancet Editorial. Anon. 1981; ii : 1396–1397.

Any Questions ?