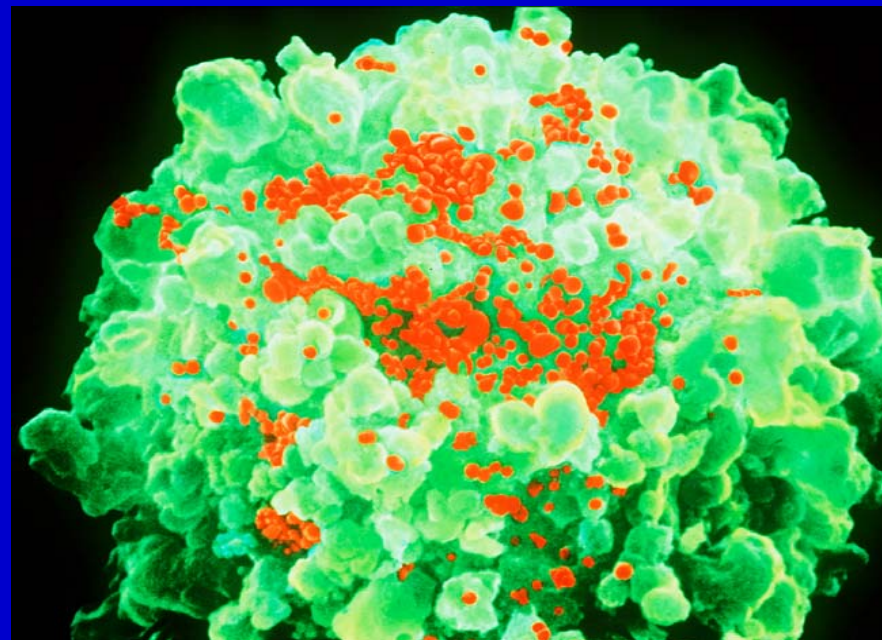


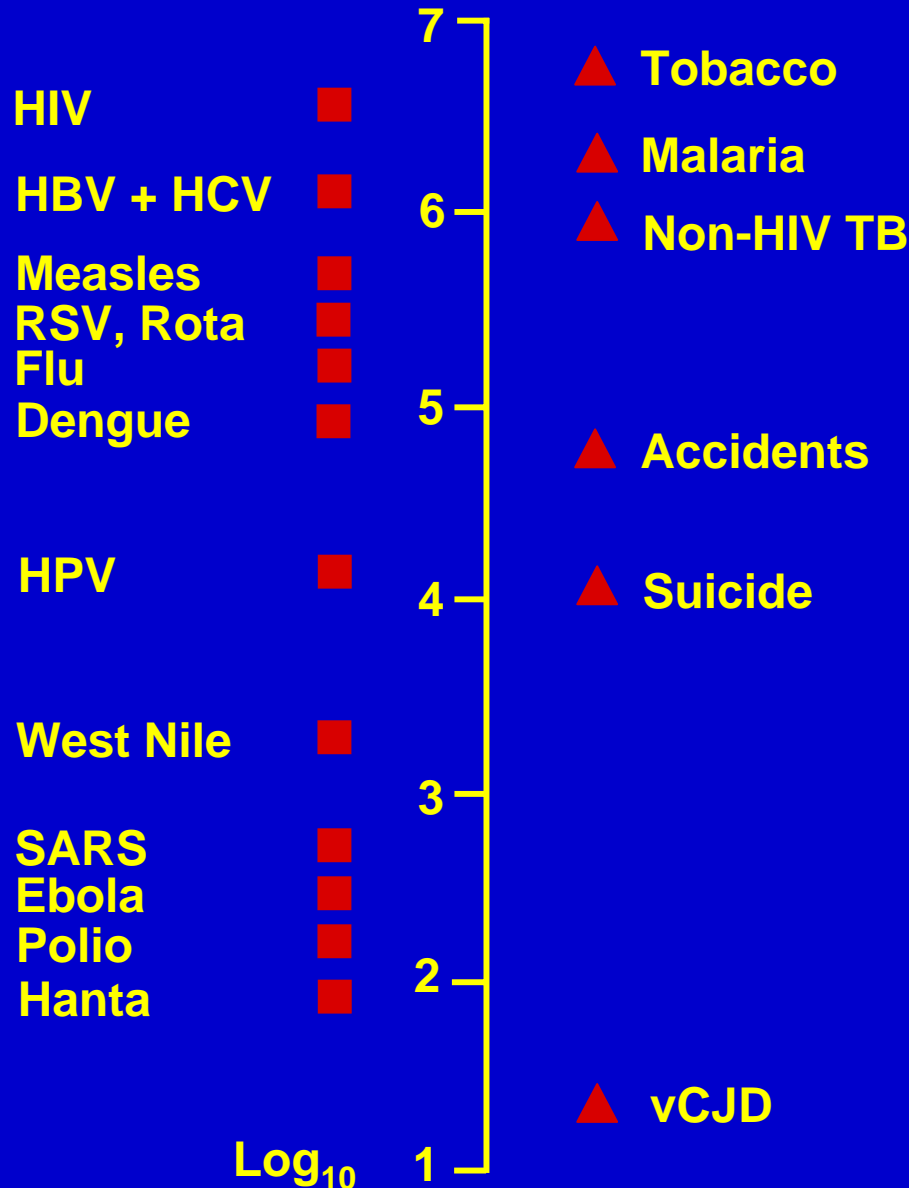
# Do Viruses Play a Role in Childhood Leukaemia?

Robin A. Weiss



# Natural Bioweapons of Mass Destruction

## A Richter Scale of Viruses and Global Mortality



Vaccines -  
weapons of mass  
protection - led to  
the eradication or  
reduction of:

Smallpox  
Yellow Fever  
Polio  
MMR

# Human Global Cancer Burden

- ~  $5 \times 10^6$  new cases each year
- ~  $1 \times 10^6$  due to infection
- Potentially preventable by vaccination
- Viruses (DNA, RNA)
- Bacteria (*H. pylori*)
- Helminths

# Human viruses associated with malignancy

<b>Virus</b>	<b>Malignancy</b>	<b>Incubation Period (years)</b>
<b>Human Papilloma Viruses</b>		
HPV types 16, 18:	Cervical cancer	5 - 50
HPV types 5, 8:	Skin cancer	5 - 50
Hepatitis B virus (HBV)	Liver cancer	10 - 50
Hepatitis C virus (HCV)	Liver cancer	10 - 50
Epstein-Barr virus (EBV)	Lymphoma	5 - 50
	Carcinoma	20 - 60
KSHV (HHV-8)	Kaposi's sarcoma	20 - 70
	Lymphoma	?
Human T-cell leukaemia virus (HTLV-1)	Leukaemia	30 - 50
HIV	Kaposi's, Lymphoma	5 - 15

# **Leukaemia and Lymphoma caused by Animal Viruses**

## **Retroviruses**

**CLL, ALL, AML,  
Lymphoma**

**Primates, cattle, cats,  
mice, chickens, fish**

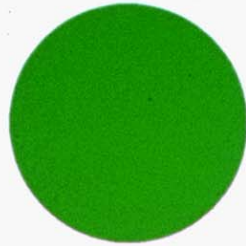
## **Herpesviruses**

**Lymphoma**

**Primates, chickens,  
frogs**

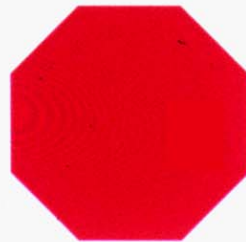
# Genes involved in cancer

GO



ONCOGENES

STOP



TUMOUR  
SUPPRESSOR  
GENES

DIE



PROGRAMMED  
CELL DEATH

CHECK



DNA DAMAGE  
& REPAIR

# How do viruses affect oncogenesis?

## Direct

- **EBV:** Virus encodes oncogenes
- **HTLV-I:** Virus activates oncogene
- **HPV:** Virus knocks out tumour suppressor genes

## Indirect

- **HCV:** Tissue destruction  
→ regeneration + mutation
- **HIV:** Immune deficiency  
→ opportunistic infections  
opportunistic tumours

# Multifactorial Causes of Cancer

## 1. Liver cancer

- HBV alone: medium frequency
- Aflatoxin alone: rare
- HBV + aflatoxin: synergistic  
70-fold relative risk

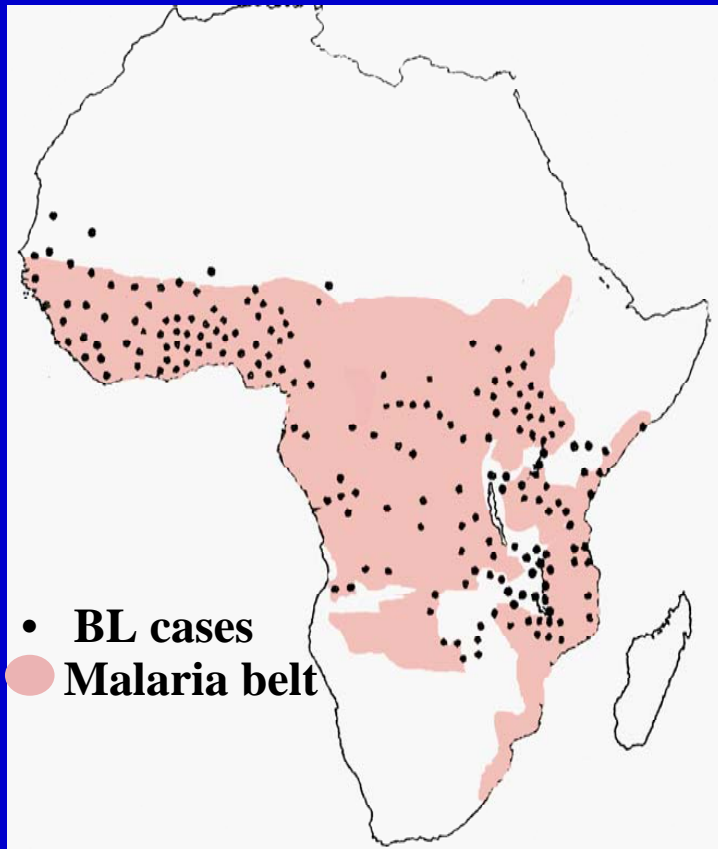
## 2. Squamous skin cancer

- Ultraviolet light
- Papilloma viruses
- Epidermodysplasia verruciformis gene



# Multifactorial Causes of Cancer

## 3. Burkitt's Lymphoma



**Epstein-Barr Virus (EBV)**

**Holoendemic malaria**

**Chromosome translocation  
involving *c-myc***

**Inflammation in the jaw?**

# One virus → two or more diseases

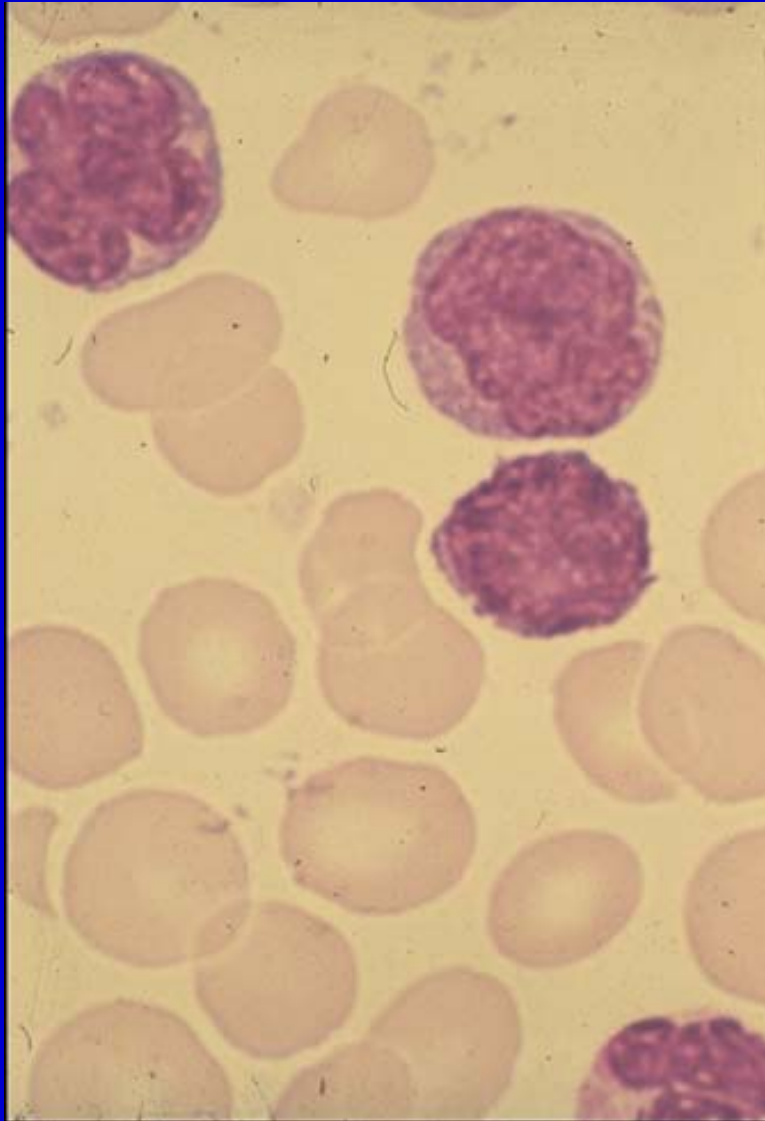
**EBV:**            **Infectious mononucleosis**  
**Burkitt's lymphoma**  
**Immunoblastic lymphoma**  
**Hodgkin's disease**  
**Nasopharyngeal carcinoma**  
**Leiomyosarcoma**

**KSHV:**           **Kaposi's sarcoma**  
**Primary effusion lymphoma**  
**Multicentric Castleman's disease**

**HTLV:**           **Adult T-cell leukaemia**  
**Spastic paraparesis**

**However, most infected people develop none of these diseases.**

# Adult T-cell leukaemia (ATL)



**A malignancy of CD4<sup>+</sup> T-helper lymphocytes**

**Mean survival after diagnosis 5 months**

**The commonest leukaemia in Japan; also frequent in the West Indies and West Africa**

**Caused by human T-cell leukaemia virus type 1**

**Transmitted in infancy by milk, but only presents in adults**

# **Paradox: oncogenic human viruses that don't cause cancer**

**Adenoviruses: AdV 2, 5 & 12**

**Highly oncogenic in new born rats due to E1A,  
E1B, E4 & E5**

**Papovaviruses: BK, JC**

**Highly oncogenic in baby hamsters due to  
Large T and small t transformation**

**SV40: The 'BK' virus of macaques**

**Oncogenic in rodents**

**Not oncogenic in monkeys**

**Reported in human mesothelioma,**

**osteosarcoma and paediatric neural tumors?**

# **Epidemiological evidence for viruses in childhood leukaemia?**

- **Kinlen: population mixing**
- **Rare outcome of common infection**
- **No specific virus identified**
- **Rural versus urban: zoonosis?  
Lymphocytic chorio-meningitis virus?**
- **Leukaemia in children with AIDS?**

# The 'hygiene' hypothesis

**Is early infection protective?**

- **asthma**

**Is delayed infection more pathogenic?**

- **Polio virus: infantile paralysis**
- **EBV: infectious mononucleosis**

**If this hypothesis applied to childhood leukaemia:**

- **↑ incidence with social class**
- **↑ incidence with age**

# Conclusions

- **No direct evidence for a virus**
- **Could be more than one kind of virus**
- **Could be an infection other than a virus**
- **Infection may be necessary but not sufficient**
- **Infection might not be relevant to childhood leukaemia**

Welcome to Church House  
and the  
International Scientific Conference  
for  
Childhood Leukaemia  
incidence  
causal mechanisms  
prevention