Emerging Infections

Scott M. Hammer, M.D.

Emerging/Re-Emerging Infections

- New, previously unknown infectious agent and disease
- Previously described infectious agent presenting
  - In a new geographic location
  - As a new syndrome
  - In a new type of host
  - With an increased drug resistance pattern or other new genetic characteristic (that changes host range or pathogenicity)
- New or previously described infectious agents used as bioweapons

Selected Emerging/Re-Emerging Infections in Past 30 Years

- AIDS
- HTLV-I and II
- HHV 6 and 8
- Hantavirus pulmonary syndrome
- West Nile virus
- Ebola virus
- Nipah/Hendra viruses
- GB virus C
- Transfusion-transmitted virus (TTV)
- SARS
- Monkeypox
- Avian influenza virus
- Legionnaire's disease
- Lyme disease
- Toxic-shock syndrome
- Ehrlichiosis
- Bovine spongiform encephalopathy (vCJD)
- Escherichia coli 0157:H7
- Helicobacter pylori
- Tuberculosis, esp. multidrug resistant TB
- Vancomycin resistant enterococci
- Vancomycin intermediate/resistant Staph. aureus
- Use of anthrax as a bioweapon

Emerging/Re-Emerging Infections: Why?

- Ecologic changes
  - Agriculture
  - Flood/drought/climate change
  - Famine
- Human demographics, behavior
  - Population growth and migration
  - War or civil conflict
  - Urban decay
  - Sexual behavior/injection drug use
- International travel and commerce
  - Worldwide movement of goods and people

Adapted from Morse SS: Emerg Infect Dis 1995;1:7-15

Emerging/Re-Emerging Infections: Why?

- Technology and industry
  - Globalization of food supplies
  - Organ/tissue transplantation
  - Immunosuppressive drugs
  - Widespread antibiotic use
- Microbial adaptation and change
  - Microbial evolution
  - Response to selection in environment
- Breakdown in public health measures
  - Curtailment or reduction in prevention programs
  - Inadequate sanitation and vector control measures
- Advances in basic science research
  - Improved cultivation/detection/characterization of micro-organisms

Adapted from Morse SS: Emerg Infect Dis 1995;1:7-15

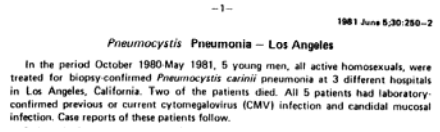
Emerging Infectious Diseases: Examples

- HIV/AIDS
- Hantavirus pulmonary syndrome
- Severe acute respiratory syndrome
- Avian influenza
- Variant Creutzfeldt-Jakob disease (vCJD) (Bovine spongiform encephalopathy)

Example #1: HIV/AIDS

New Agent and Disease

First Clinical Description of AIDS:



–1–

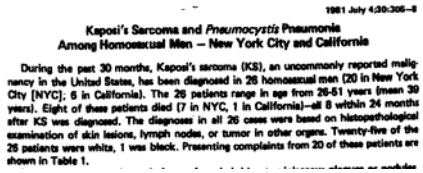
1981 June 5;30:250–2

Pneumocystis Pneumonia – Los Angeles

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

MMWR 1981:30:250-252

Follow-Up: First 26 Cases of Kaposi's Sarcoma



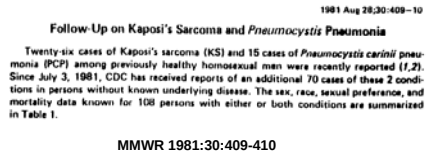
1981 July 4;30:305–8

Kaposi's Sarcoma and *Pneumocystis* Pneumonia
Among Homosexual Men – New York City and California

During the past 30 months, Kaposi's sarcoma (KS), an uncommonly reported malignancy in the United States, has been diagnosed in 26 homosexual men (20 in New York City [NYC]; 6 in California). The 26 patients range in age from 26-51 years (mean 39 years). Eight of these patients died (7 in NYC, 1 in California)–all 8 within 24 months after KS was diagnosed. The diagnoses in all 26 cases were based on histopathological examination of skin lesions, lymph nodes, or tumor in other organs. Twenty-five of the 26 patients were white, 1 was black. Presenting complaints from 20 of these patients are shown in Table 1.

MMWR 1981:30:306-308

Follow-Up: First 108 Cases



1981 Aug 28;30:409–10

Follow-Up on Kaposi's Sarcoma and *Pneumocystis* Pneumonia

Twenty-six cases of Kaposi's sarcoma (KS) and 15 cases of *Pneumocystis carinii* pneumonia (PCP) among previously healthy homosexual men were recently reported (*1*,*2*). Since July 3, 1981, CDC has received reports of an additional 70 cases of these 2 conditions in persons without known underlying disease. The sex, race, sexual preference, and mortality data known for 108 persons with either or both conditions are summarized in Table 1.

MMWR 1981:30:409-410

Early Events in the AIDS Epidemic

- **1981 – Clusters of cases of *Pneumocystis carinii* (now *jiroveci*) pneumonia and Kaposi's sarcoma in gay men reported**
- **1981-83 – Opportunistic infections reported in hemophiliacs, injection drug users and transfusion recipients**
- **1983 – Virus isolated in tissue culture**
  - **HTLV-III, LAI – later renamed as HIV-1**
- **1985 – Blood screening test became commercially available**

Early Questions in AIDS Epidemic

- **Was this one disease or multiple diseases?**
- **Was this due to a known or unknown pathogen or toxin?**
- **If infectious, what type of agents was it and how was it transmitted?**
- **What steps could be taken to protect individual and public health prior to identification of the etiologic agent?**

Postulated Causes of AIDS

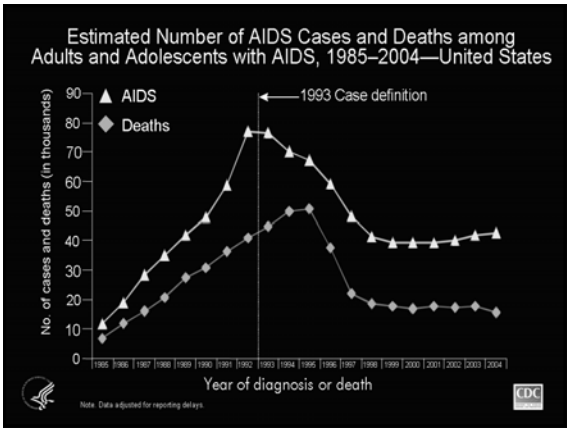
- **Known viruses**
  - **e.g., cytomegalovirus or Epstein-Barr virus**
- **Toxic recreational drug exposure**
  - **Amyl nitrite**
- **New pathogen**

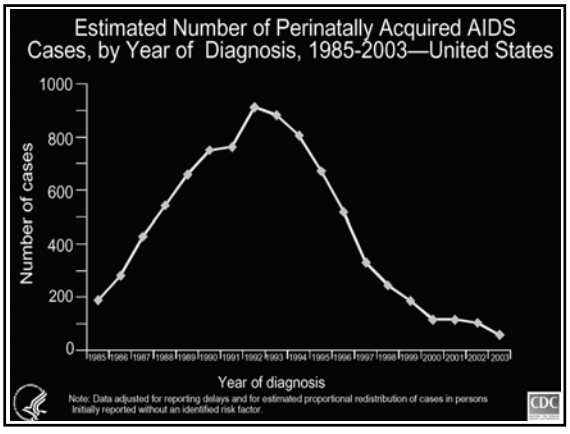
Scientific Progress Which Facilitated the Discovery of HIV-1

- **Identification of T-cell growth factor (IL-2) permitting in vitro culture of PBMC's**
- **Identification of T cell subsets and surface markers characterizing helper (CD4) and suppressor (CD8) cells**
- **Identification of human retroviruses**
  - **HTLV-1 and HTLV-2**

Search for Causality in AIDS

- **Clinical observations**
- **Available data**
  - **Ecologic studies suggested 4 high risk groups**
    - **MSM, IDUs, hemophiliacs, Haitians**
      - **Latter illustrates potential to be misled and damage it can cause**
- **Case-control and cohort studies**
  - **Individual risks began to be identified but key was isolation of HIV in culture**
- **Randomized trials**
  - **Specific anti-HIV treatment and prophylaxis trials provided additional evidence of causality**





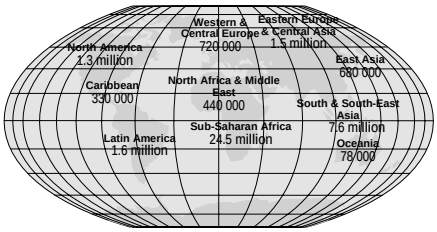
Evidence for a Causal Relationship for Infectious Diseases Henle and Koch's Postulates

- **The organism is always found with the disease**
- **The organism is not found with any other disease**
- **The organism, isolated from one who has the disease, and cultured through several generations, produces the disease (in experimental animals)**
- **Even when an infectious disease cannot be transmitted to animals, the 'regular' and 'exclusive' presence of the organism [postulates 1 and 2] proves a causal relationship**

Does HIV Fulfill Koch's Postulates?

- **Virus isolated from all patients with AIDS**
- **Cell culture models and knowledge of virus life cycle support hypothesis**
- **No adequate animal model but SIV and SHIV in rhesus macaques produce AIDS-like illnesses**
- **Transfusion cases, needle stick acquisitions come closest to human model of infection and disease**

Adults and Children Estimated to be Living with HIV, 2005



Total: 38.6 (33.4 – 46.0) million

Example #2: Hantavirus Pulmonary Syndrome

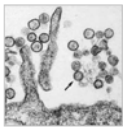
New Agent and Disease

Hantavirus Pulmonary Syndrome: First Description

- **Rapidly fatal illnesses with respiratory failure reported initially in a couple, ages 21 and 19, living in rural New Mexico reported on May 14, 1993**
- **Cluster of cases reported from Four Corners area**
  - **New Mexico, Arizona, Colorado, Utah**
- **New agent – Sin Nombre Virus identified**
  - **A hantavirus**
- **Rodent host identified**
  - **Deer mouse**
- **Cases outside of Four Corners area reported**

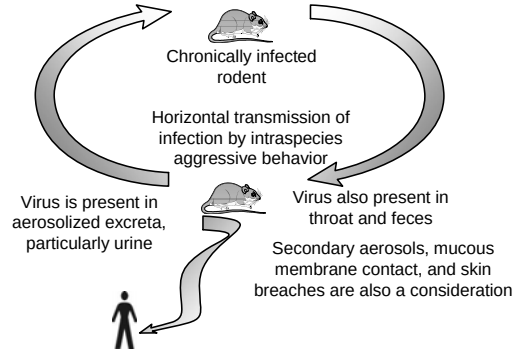
Duchin JS et al: NEJM 1994;330:949-955

Hantaviruses

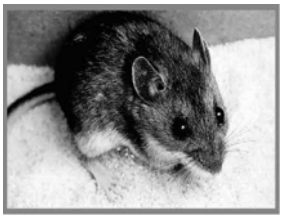


- **Members of the family Bunyaviridae**
- **Segmented RNA, enveloped viruses**
- **Two basic syndromes**
  - **Hemorrhagic fever with renal syndrome (HFRS)**
  - **Hantavirus pulmonary syndrome (HPS)**
- **Reservoirs in nature**
  - **Chronically infected rodents of the family Muridae**
  - **Subfamilies**
    - **Murinae (Old World rodents) are reservoirs for Hantaan, Dobrava and Seoul viruses (HFRS causing)**
    - **Arvicolinae (voles) are reservoirs for Puumala virus and Prospect Hill virus (HFRS causing)**
    - **Sigmodontinae (New World rats and mice) are the reservoirs for Sin Nombre virus (HPS causing)**

Transmission of Hantaviruses



Rodent Reservoir of Sin Nombre Virus



Peromyscus maniculatus
Deer mouse

Hantavirus Pulmonary Syndrome: Pathogenesis

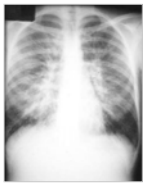
- Inhalation of particle contaminated with infectious virus
  - Deposition in terminal respiratory bronchiole or alveolus
- Local replication with viremia
- Widespread infection of pulmonary endothelium
  - Cell invasion may be mediated by B3 integrins
- Infiltration by CD4 and CD8 cells
- Loss of vascular integrity in lungs
- Capillary leak syndrome
- Myocardial depression also seen

Hantavirus Pulmonary Syndrome: Clinical Findings

- Onset 14-17 days after exposure
- Myalgia, malaise and fever
- Anorexia, nausea, vomiting and abdominal pain may ensue
- Cough, tachypnea and tachycardia
- Rapid progression to respiratory failure
- Laboratory
  - Hemoconcentration (elevated Hct)
  - Leukocytosis with left shift; atypical lymphocytes also seen
  - Thrombocytopenia
  - Elevated liver enzymes, proteinuria, elevated creatinine may be seen
  - Interstitial edema on chest film → air space disease and pleural effusions

Hantavirus Pulmonary Syndrome Radiographic Findings

- Bilateral interstitial infiltrates
  - moderate to rapid progression
- Bilateral alveolar infiltrates
- Pleural effusion



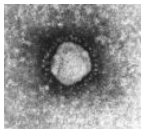
Example #3: SARS - Severe Acute Respiratory Syndrome

Evolving Pathogen and New Disease

SARS

- Etiology:
  - Newly described coronavirus
    - Fully sequenced by two groups within a few weeks after isolation
- Origin
  - Perhaps cross-species infection and viral recombination
- Power of information and laboratory technologies highlighted by this outbreak
- Globalization of infectious disease outbreaks and economic impact also highlighted

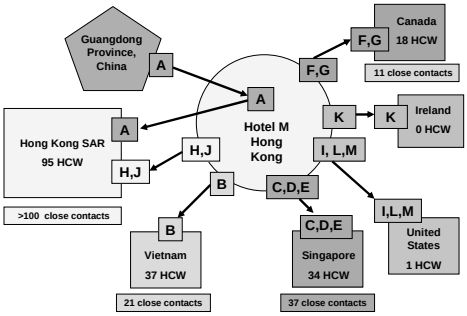
Coronavirus



- Member of the Coronaviridae family
- Pleomorphic 100-150 nm particle with characteristic surface projections
  - Single stranded, (+) sense RNA genome (27-32 kb)
  - Cytoplasmic replication
  - Viral assembly in Golgi apparatus and endoplasmic reticulum
- Infects multiple species
  - Chickens, turkeys, mice, rats, cats, dogs, rabbits, cattle, pigs and humans
- In humans
  - Before SARS – clinical expression was mild respiratory disease in healthy persons
  - Gastrointestinal disease?
- Respiratory illness has been seasonal
  - Peaks in winter and spring
- In volunteer studies
  - Virus shed for 48 h after inoculation and continues for approx. 5 d

Spread from Hotel M

Reported as of March 28, 2003



SARS - 2003

- Human cases date back to November 2002 in China
- Local chains of transmission reported in mainland China, Hong Kong, Taiwan, Hanoi, Singapore, Toronto, UK and US
- 8,096 cases in 29 countries
- 774 deaths
  - Case fatality rate 9.6%

SARS: ?Origin

Guangzhou Food Market

Civet

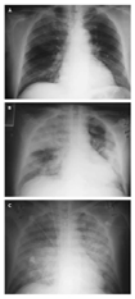
SARS: Clinical Description

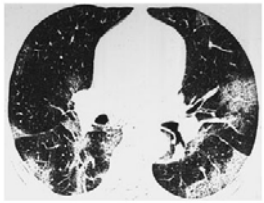
- Incubation period 2 – 7 days
  - Maybe as long as 10 days
- Illness begins with prodrome of fever
  - Chills, headache, malaise, myalgia, diarrhea may also be present
- Next phase: dry cough and/or shortness of breath
- In 10-20% disease may be rapidly progressive and require mechanical ventilation
- Chest films: normal → focal interstitial infiltrates → more generalized infiltrates → consolidation and ARDS
- Lymphopenia, thrombocytopenia, elevated CPK and hepatic enzymes may be seen
- Treatment is supportive
- Full spectrum of disease unknown

SARS: Diagnosis

- **Clinical suspicion**
  - **Particularly in a traveler from an endemic region or someone exposed to a possible/probable case**
- **Laboratory**
  - **Still investigational**
  - **Sputum, blood and body fluids for viral cultures and PCR**
  - **Antibody**
    - **May not be positive for up to 28 days**

SARS: Radiographic Characteristics





NEJM: 2003

SARS Coronavirus Excretion

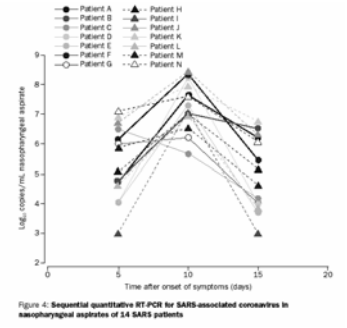


Figure 4: **Sequential quantitative RT-PCR for SARS-associated coronavirus in nasopharyngeal aspirates of 14 SARS patients**

Peiris et al: Lancet, May 24, 2003

Example #4: Avian Influenza

Known Disease in New Host

Avian Influenza

- **Only influenza A infects birds**
  - **H5, H7 and H9 most common**
    - **Potentially 9 different subtypes for each (N1-N9)**
    - **H5 and H7 can vary in pathogenicity**
    - **H9 typically low in pathogenicity**
- **Transmission to humans**
  - **Directly from birds or contaminated environment**
  - **Via an intermediate host – e.g., pig**
- **Human cases reported since 1997**

Avian Influenza in Humans: History

- **1997: H5N1 – Hong Kong**
- **1999: H9N2 – China and Hong Kong**
- **2002: H7N2 – Shenandoah Valley, VA**
- **2003: H5N1 – China and Hong Kong**
- **2003: H7N7 – Netherlands**
- **2003: H9N2 – Hong Kong**
- **2003: H7N2 – New York**
- **2004: H5N1 – Thailand and Vietnam → Ongoing**
- **2004: H7N3 – Canada**

Avian Influenza: Cumulative Human Cases 12/26/03 – 11/29/06

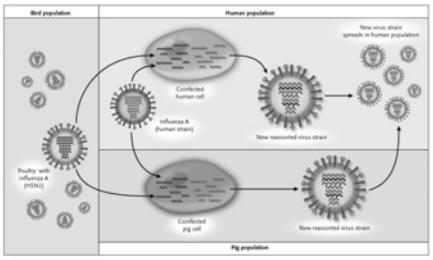
Country	Cases	Deaths
Vietnam	93	42
Thailand	25	17
Indonesia	74	57
Cambodia	6	6
China	21	14
Egypt	15	7
Turkey	12	4
Azerbaijan	8	5
Iraq	3	2
Djibouti	1	0
TOTAL	258	154

Source: www.who.int

Avian Influenza H5N1 in 2004

- Poultry outbreaks in 8 countries in Asia
  - 100 million birds died or culled
- Human cases
  - 17 cases and 12 deaths in Thailand
  - 27 cases with 20 deaths in Vietnam
  - One human-to-human case reported
- Movement into other species
  - Pigs in China; tigers and leopards in Vietnam
- Antiviral and vaccine possibilities
  - Resistant to amantadine and rimantadine
  - Generally sensitive to zanamivir and oseltamivir
    - Oseltamivir resistance in H5N1 strains reported, however
  - Vaccine under development
- The big question: Is a global pandemic on the horizon?

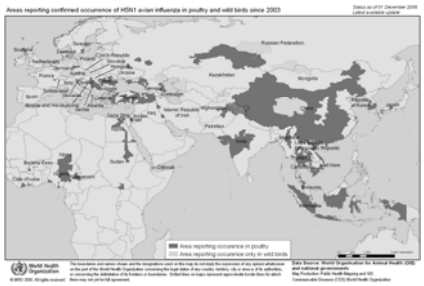
Generation of a Potentially Pandemic Strain of Influenza through Reassortment



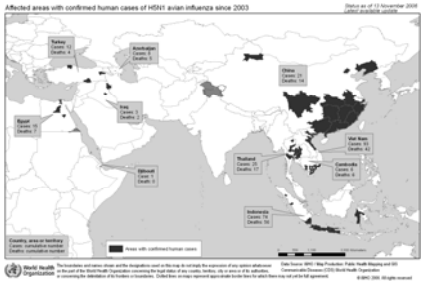
Hien, T. T. et al. N Engl J Med 2004;351:2363-2365

The NEW ENGLAND JOURNAL of MEDICINE

H5N1 Avian Influenza in Poultry and Wild Birds Since 2003



H5N1 Avian Influenza in Humans Since 2003



Avian Influenza: Challenges to Control

Science 2004;306:392-399

Example #5:
Variant Creutzfeldt-Jakob Disease (vCJD)
(Bovine Spongiform Encephalopathy)

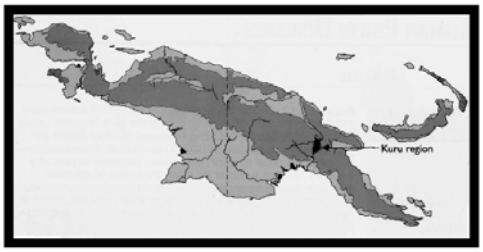
Known Disease in a New Form

Prions

- ***Pro*teinaceous *in*fectious particles**
- ***NOT* viruses**
- **Responsible for the transmissible spongiform encephalopathies (TSE's)**
  - **Pathologic hallmark**
    - **Spongiform changes in brain**
    - **Absence of inflammation**

Kuru

Papua New Guinea



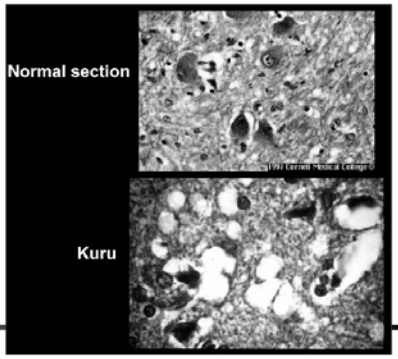
Kuru

Disease strikes children

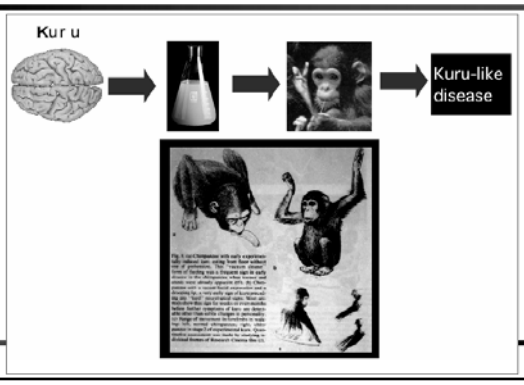
Clinical features of Kuru

Transmission	Autoinoculation/ingestion of infected brain material
Prevalence	Fore linguistic group of Papua New Guinea
Clinical features	Cerebellar ataxia, tremor, movement disorders
	Mental impairment, emotional lability, frontal release signs (snout, suck, root, grasp reflexes)
Course	Fatal 9-24 months after onset

Spongiform Encephalopathy - Histology



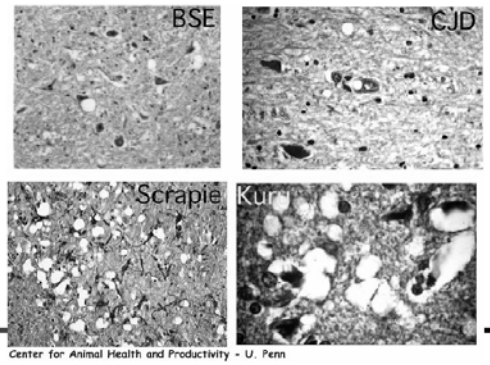
Linking Kuru to an Infectious Agent (Gajdusek)



Prion Diseases

Disease	Natural Host	Prion	Pathogenic PrP Isoform
Scrapie	Sheep and goats	Scrapie Prion	$OvPrP^{Sc}$
Transmissible mink encephalopathy (TME)	Mink	TME Prion	$MkPrP^{Sc}$
Chronic wasting disease (CWD)	Deer and elk	CWD Prion	$MdePrP^{Sc}$
Bovine spongiform encephalopathy (BSE)	Cattle	BSE Prion	$BoPrP^{Sc}$
Feline spongiform encephalopathy (FSE)	Cats	FSE Prion	$FePrP^{Sc}$
Exotic ungulate encephalopathy (EUE)	Nyala & greater kudu	EUE Prion	$UngPrP^{Sc}$
Kuru	Humans	Kuru Prion	$HuPrP^{Sc}$
Creutzfeldt-Jakob disease (CJD)	Humans	CJD Prion	$HuPrP^{Sc}$
Gerstmann-Staussler-Scheinker syndrome (GSS)	Humans	GSS Prion	$HuPrP^{Sc}$
Fatal familial insomnia (FFI)	Humans	FFI Prion	$HuPrP^{Sc}$

Spongiform Encephalopathies



Center for Animal Health and Productivity - U. Penn

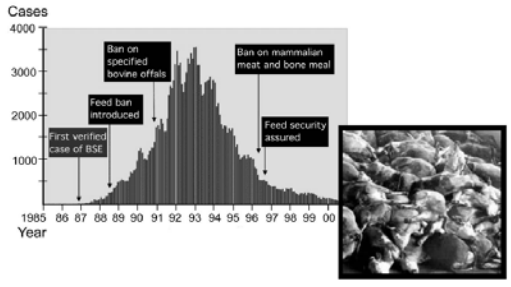
Human Prion Diseases

DISEASE	SYMPTOMS	ACQUISITION	DISTRIBUTION	DISEASE COURSE
Kuru	Loss of coordination followed by dementia	Infection (Cannibilism)	2000cases identified in Papua New Guinea	3 mo - 1 yr
Creutzfeldt-Jakob Disease	Dementia followed by loss of coordination	Usually unknown (Sporadic disease) 15% of cases involve an inherited mutation in the PrP gene Rarely infection through contaminated surgical instrument or organ transplant	Sporadic 1/1,000,000 Inherited 100 extended families identified Infectious 80 cases identified	Usually 1 yr but as short as 1 mo and as long as 10 yrs
Gerstmann-Straussler-Scheinker disease	Loss of coordination followed by dementia	Inheritance of a mutation in the PrP gene	50 extended families identified	2-6 yrs
Fatal familial insomnia	Trouble sleeping and disturbance of the autonomic nervous system. Followed by dementia and loss of coordination	Inheritance of a mutation in the PrP gene	9 extended families identified	About 1 yr

Creutzfeldt-Jakob Disease

- Most common human TSE - about 1 case/million/yr
- Three forms traditionally recognized
  1. sCJD - sporadic, about 85% of cases
  2. fCJD - familial, about 10% of cases
  3. iCJD - iatrogenic, about 5% of cases
- In 1996 a new variant emerged in the U.K. - vCJD
  - Associated with eating beef infected with BSE agent (Mad Cow)
  - In contrast with traditional forms of CJD, vCJD strikes young adults
  - Crossed species barrier

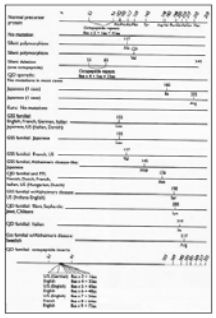
BSE Epidemic in UK

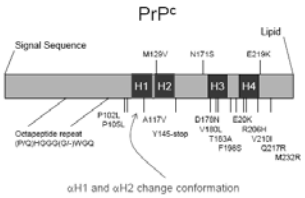


Search for the Agent (Prusiner Lab)

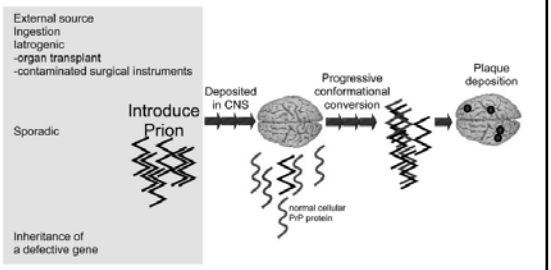
- Extremely small, proteinaceous infectious particle
- Resistant to DNAse and RNAse
- Resistant to limited proteolysis
- Resistant to chemical agents that inactivate conventional viruses

Genetic mutations in CJD and other Prion Diseases

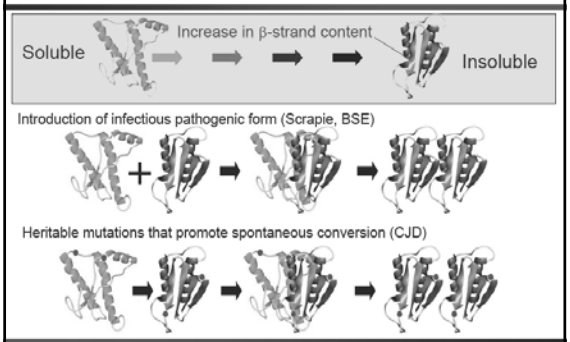




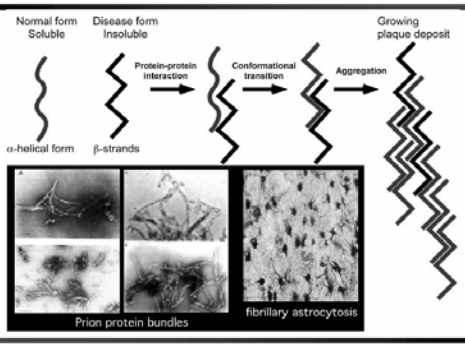
Prion Disease



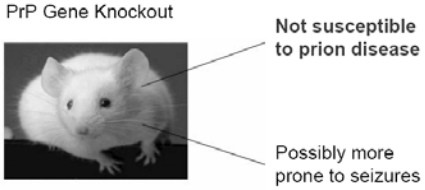
How Does Conformational Conversion Occur?



Prion Disease - Amyloid Deposition



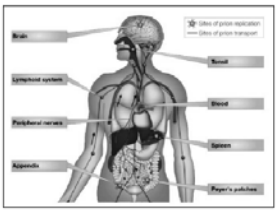
Normal PrPC Required for Disease Progression



What is Normal PrP^C?

- Glycoprotein ~250 amino acids
- Membrane associated through a C-terminal glycosyphosphatidylinositol (GPI) linkage
- Role in membrane trafficing has been proposed - possibly involved in some endocytic pathways
- Knockout mice develop and behave normally, but perhaps prone to seizures
- Interacts with laminin, which plays a role in cell adhesion and neurite formation
- Also interacts with the laminin receptor resulting in internalization of membrane-bound PrP^C
- Binds Cu^{++} - may have an antioxidant function that promotes neuron survival
- Abundant in brain - also detected in: spleen, lymph node, lung, heart, kidney, skeletal muscle, uterus, adrenal gland, parotid gland, intestine, and mammary gland.

Current View of Prion Disease Development



- Prions ingested and absorbed by intestines (Peyers Patches)
- Gains access to lymphoid fluids and blood
- Deposited in lymphoid tissues where it amplifies through conformational conversion
- Amplified prions deposited in brain - perhaps crosses blood-brain barrier or migrates by axonal transport
- Replicates in brain - toxicity resulting in neuronal cell death

Characteristic	Classic CJD	Variant CJD
Median age at death	68 years	28 years
Median duration of illness	4-5 months	13-14 months
Clinical signs and symptoms	Dementia; early neuro signs	Prominent psychiatric/behavioral symptoms; painful dysesthesiasis; delayed neurologic signs
Periodic sharp waves on electroencephalogram	Often present	Often absent
"Pulvinar sign" on MRI*	Not reported	Present in >75% of cases
Presence of "florid plaques" on neuropathology	Rare or absent	Present in large numbers
Immunohistochemical analysis of brain tissue	Variable accumu-lation	Marked accumulation of protease-resistance prion protein
Presence of agent in lymphoid tissue	Not readily detected	Readily detected
Increased glycoform ratio on immunoblot analysis of protease-resistance prion protein	Not reported	Marked accumulation of protease-resistance prion protein

www.cdc.gov

Emerging Infectious Diseases

- **AIDS worldwide**
  - **5 cases → 65-70 million cases with 25-30 million deaths in 25 years**
- **Hantavirus Pulmonary Syndrome**
  - **453 laboratory confirmed cases reported in the U.S. since 1993 from 30 states; majority in Southwest; 35% mortality**
- **Severe Acute Respiratory Syndrome**
  - **0 cases → 8,096 cases with 774 deaths (case fatality 9.6%) from 11/1/02 – 7/31/03**
  - **2004: 9 cases with 1 death**
    - **Linked to laboratory-associated cases occurring at Institute of Virology in Beijing**
  - **2005-06: no cases**
- **Avian influenza**
  - **258 cases with 154 deaths 12/26/03-11/29/06**
  - **What's next?**
    - **??Pandemic with 10-100 million deaths??**
- **vCJD**
  - **200 cases from 1996 – 2006**
    - **164 in UK, 21 in France, 4 in Ireland, 3 in the U.S., 2 in the Netherlands and 1 each in Canada, Italy, Japan, Portugal, Saudi Arabia and Spain**
    - **What's next?**

Emerging Infectious Diseases: Website Resources

- **www.cdc.gov**
- **www.idsociety.org**
- **www.promedmail.org**