

Etiology of Human Disease

- Malnutrition
- Infectious Agents
- Mutagens and Carcinogens
- Occupational and Environmental Toxins and Teratogens
- Auto and industrial accidents
- War
- Old Age

How do we identify etiology of disease?

- Pathology - Smallpox, Cholera, Ricketts
- Identification of agent - Lead, Pneumonia, Arsenic
- Epidemiology - Black Lung, Cancer, Mercury poisoning
- But for many conditions, etiology never identified.

Disease of Malnutrition and Poverty

- Scurvy
- Ricketts
- Beri-beri
- Pellagra
- Kwashiokor

Ricketts

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Abnormal skeletal development among child laborers due to vitamin D deficiency or other form of calcium deficiency.

Ricketts



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- During industrial revolution in UK, children in factory towns worked 15 hours a day, six days a week; not enough sunshine for skin to make vitamin D:
- First form of prevention was Child labor laws; passage of “ten hours bill”, over intense opposition of factory owners.
- Subsequently cod liver oil recognized as curative.

Prevention of malnutrition in US: 1965 War on Poverty

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- School breakfast/school lunch programs
- Food stamps
- WIC (women, Infants, Children) programs

Disease from infectious agents

- **Bacteria;** Cholera, typhus, tuberculosis, meningitis (Neisseria), gonorrhoea
- **Viruses;** Smallpox, polio, influenza, Herpes, HIV, hepatitis, SARS, rotavirus
- **Fungi:** Candida, coccidiomycosis, histoplasma
- **Protozoans;** Toxoplasmosis, malaria
- **Worms:** Nematodes, filariasis

19th Century Cholera Epidemics

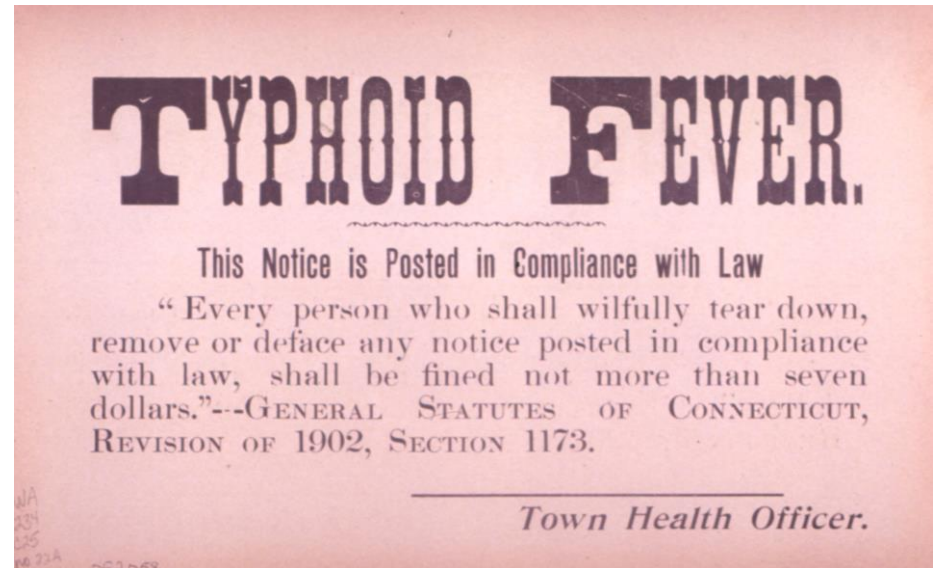
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<http://www.homeoint.org/books5/clarkecholera/cholera5.gif>.

Average annual Death Rate from Typhoid Fever in England and Wales

- 1871-1880 332
- 1881-1890 198
- 1891-1900 174
- 1901-1910 91
- 1911-1920 35
- 1921-1925 25



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Prevention of Cholera

- Biomedical advances in identifying causative agent waterborne *Vibrio cholera*
- Provision of sanitation and clean water supplies

20th Century Debate: Two General Policies on How to Respond

1) Disease carried by “unclean” (read ‘poor’) individuals.

Solution: Quarantine them >> build sanitoriums.

2) Infection due to absence of clean water supply;

Solution: Construct aqueducts and sewers, public sanitation systems.

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Origin of Public Health Boards

- Led to Development of State Boards of Health
- Sanitary Codes
- Protected water sources
- Restaurant inspections

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Large Scale Production of Penicillin

Responding to the serious problems of wound infections among the Armed Forces, the federal government initiated a publicly financed cooperatively organized large program to mass produce penicillin, with Merck as the primary contractor. In less than two years after its initiation penicillin was available for treating wound infections.

We have detailed and often tragic knowledge of the effects of formerly endemic pathogens

- Diphtheria
- Cholera
- Tetanus
- Syphilis
- Tuberculosis
- Yellow fever
- Smallpox

Progress in Controlling Infectious Disease

- Improved sanitation
- Scientific understanding of microbial agents
- Biomedical advances > antibiotics
- Biomedical advances > vaccines
- Universal public education
- Increased access to health care

Some pathogens continue to plague humans

- Influenza
- HIV virus
- SARS virus
- Marburg virus
- Ebola virus
- Antibiotic resistant bacteria
- Mad Cow disease

Some Sources of Community Infections

- Travelers
- Hospitals - Nosocomial infections
- Kitchens and food processing facilities
- Research institutions
- Biowarfare facilities

The SARS Outbreak

- By May 2003 7956 documented cases.
- 666 deaths.
- Source was small number of infected individuals.
- Spread corona virus to unsuspecting contacts.
- Hong Kong outbreak - cluster of 125 ill in Prince of Wales Hospital.
- Toronto outbreak -375 case and 44 deaths, initiated by a single individual returning from Hong Kong
- Infections in high containment labs in Singapore, Taiwan and Beijing

Occupational Diseases of Known Etiology

- Black Lung from coal dust
- Brown lung from cotton dust
- Silicosis from tunneling, mining
- Lung cancer from exhaust fumes
- Bladder cancer from aniline dyes
- Bone cancer from nuclear weapons isotopes

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Mercury Poisoning

- Felt for hats – “Danbury Shakes >> “Mad Hatter”
- Anti-fouling paints
- Silvering mirrors
- Photoengraving
- Disinfectants

Minamata Disease

Neurological disorder in children and adults occurring from 1950's onward in Southern Japan

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Please see the image on page,

<http://www.terradaily.com/images/congenial-minamata-disease-children-bg.jpg>

Mercury poisoning from Chisso Chemical Corporation

- Company dumped Hg catalyst into Minamata Bay
- Accumulated in fish
- Fisherman's families and local residents affected
- Decades of suffering before etiology admitted

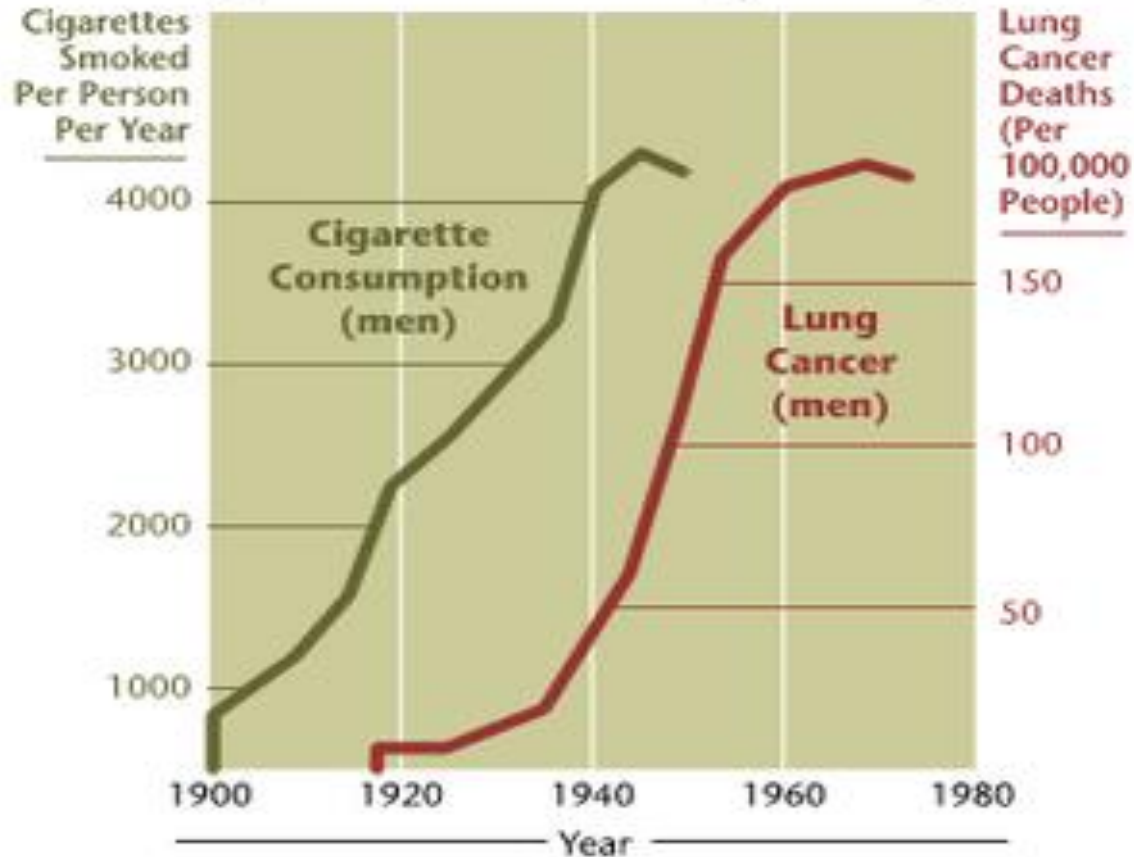
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<https://www.env.go.jp/en/chemi/hs/minamata2002/images/fig01.jpg>

Epidemiology of Lung Cancer and Tobacco Smoke

20-Year Lag Time Between Smoking and Lung Cancer



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Current Disease Burden

- Heart disease
- Vascular disease
- Cancer
- Neurodegenerative disease
- Arthritis

NUMBER OF PERSONS 65+, 1900 - 2030 (Numbers in Millions)

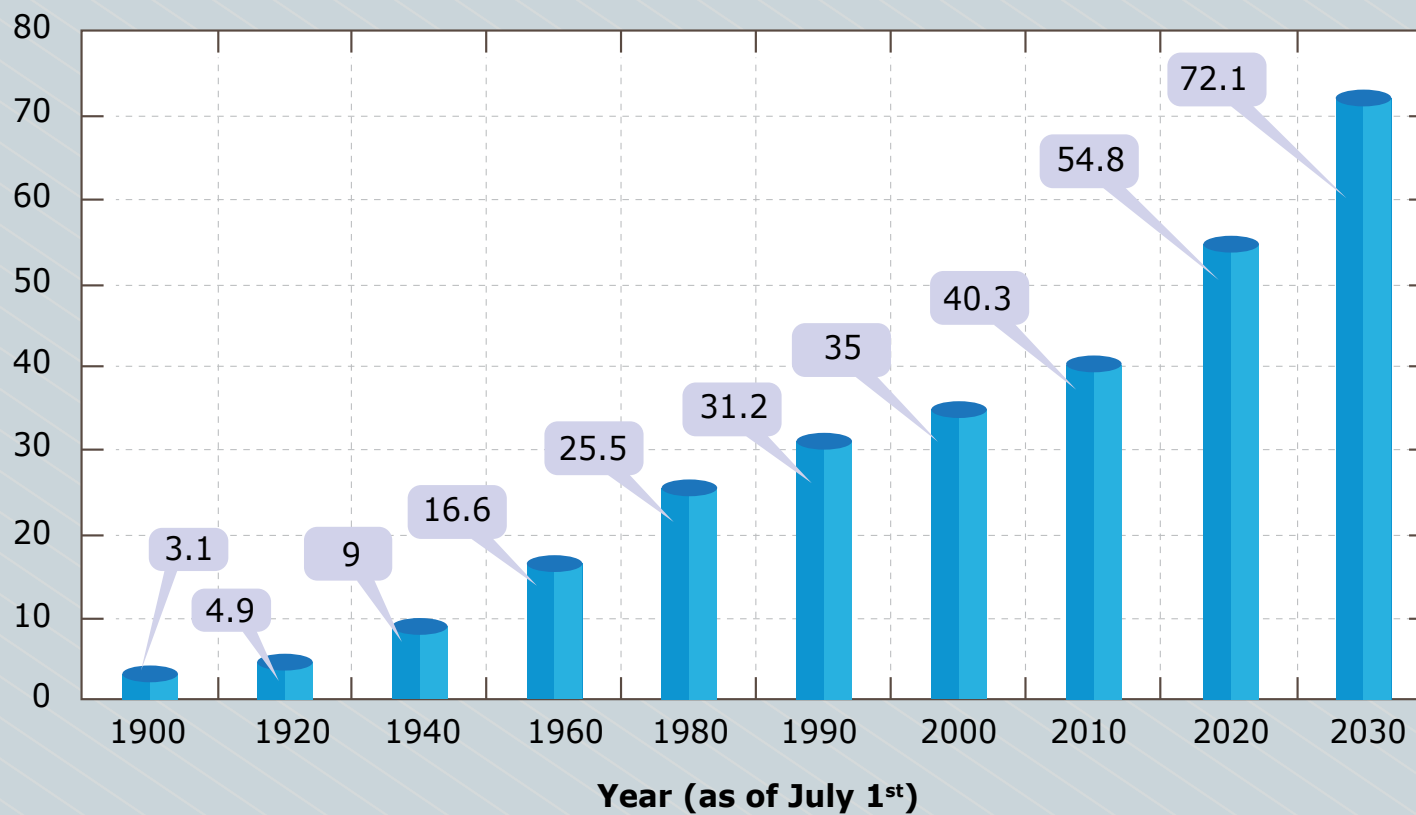
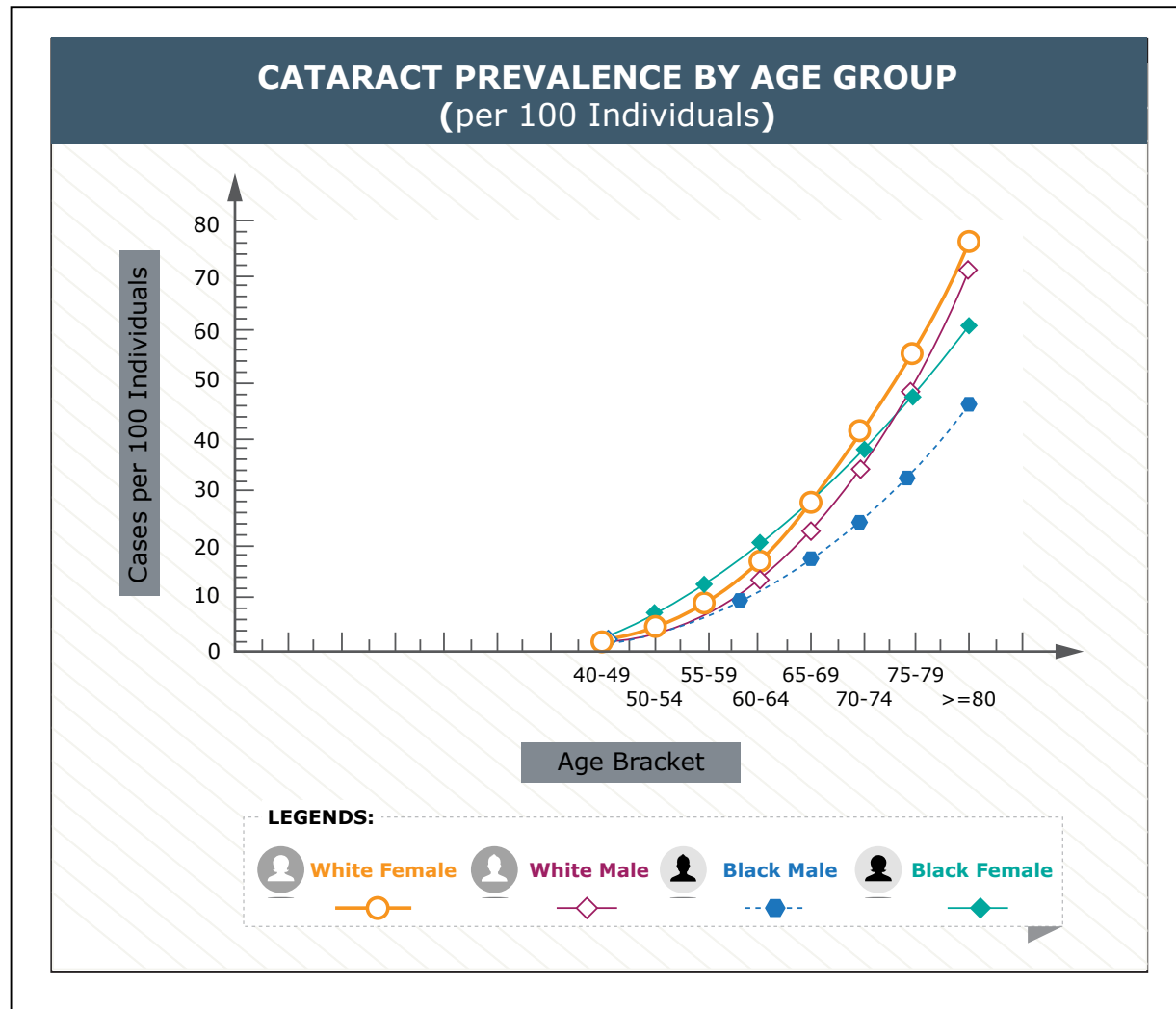


Image by MIT OpenCourseWare.

Mature Onset Pathology Associated with Protein Aggregation

- Alzheimer's Disease ~5.4 million cases
- Cataract ~ 2 million cases
- Parkinson's disease ~ 1 million cases
- Huntington's disease ~30,000 cases
- ALS ~30,000 cases

Cataract Prevalence: Rare in Youth, Sharp Increase with Age



Diseases Associated with Aging

- Often treated as “natural” or “spontaneous” or “inevitable”;
- Heart disease, Alzheimer’s, Cataract;
- No search for etiology or causation;
- A form of “Blaming the victim”;
- In fact many diseases due to environmental toxins show similar profiles with age!

Parkinson's Disease

- Neurodegenerative disease reflecting damage to a particular part of the brain, the Substantia Nigra, which controls motor functions.
- Movement and neuromuscular abnormalities easily diagnosed.
- Afflicts more than 500,000 Americans and is eventually lethal.
- Substantial body of evidence that plentiful presynaptic neuronal protein α -synuclein is involved in pathology.
- Brain cells from diseased patients accumulate a morphological feature known as Lewy bodies which appear to be dominated by α -synuclein polymerized into amyloid fibrils.

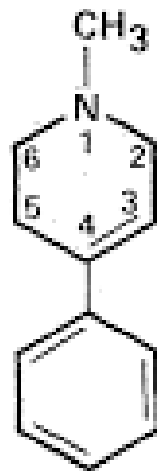
Parkinson's Disease Biochemistry

- α -Synuclein is a 140 amino acid natively unfolded protein that is plentiful in nerve cell terminals but of unknown function.
- Both truncated and ubiquitinated synuclein have been recovered from Lewy bodies.
- Rare mutations A30P, E46K, A53T in humans lead to early onset Parkinson's.
- Introduction of the A53T mutation into transgenic mice also results in Parkinson's like symptoms in mice, though wild type transgene does not have this effect.
- Also evidence that raising α -synuclein levels enhances rate of aggregation, development of pathology. (Human triplication)
- Other mutations affect ubiquitin-3-ligase Parkin gene) and a ubiquitin C-terminal hydrolase.

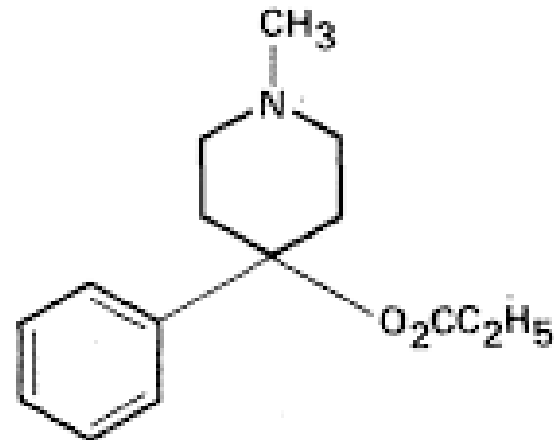
Known agents that have caused Parkinson's disease

- MPTP (1-methyl-4-phenyl 1,2,3,6-tetrahydropyridine)
- Contaminant in home made heroin and angel dust, caused Parkinson's in young users.
- MPTP is commercial chemical used in synthesis of other drugs;
- Active species that causes brain damage is believed to be charged metabolic product;
- Herbicide paraquat is very similar.

MPTP and MPPP (Demerol)



MPTP



MPPP

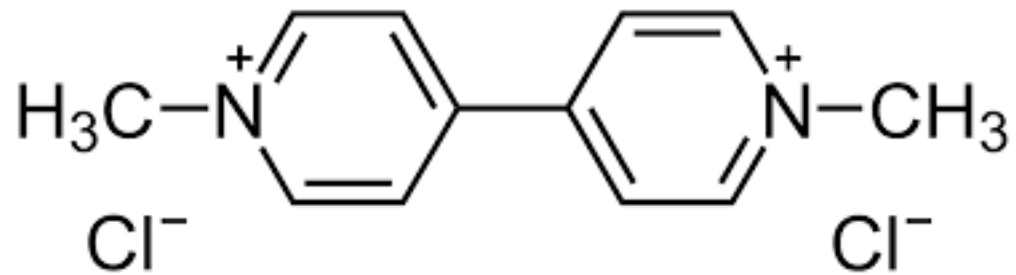
MPTP-induced animal model for PD

- Treated animals exhibit loss of muscular control as in humans;
- Alteration of Substantia Nigra;
- Widely accepted as authentic animal model for PD

Detailed Account of MPTP Discovery

The Case of the Frozen Addicts, by J. William Langston and Jon Palfreman, 1995, Pantheon Books, New York.

Paraquat



Paraquat and Parkinson's

- Produced in hundreds of thousands of tons on the world scale.
- Packed and shipped to retailers and wholesalers throughout many countries.
- Not limited to farms but is also used in domestic gardens and weed control.
- Acutely toxic to humans, and is often the agent used in suicides in rural areas.
- Use and misuse associated with thousands of deaths and many more nonfatal poisonings; acute and chronic health consequences such as respiratory and kidney damage, skin ailments, and eye injuries (Isenring, Madeley et al. 2006).

Some Key PD References

- Langston, J. W., P. Ballard, J. W. Tetrud and I. Irwin (1983). "Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis." Science **219**(4587): 979-980.
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- Tanner, C. M., F. Kamel, G. W. Ross, J. A. Hoppin, S. M. Goldman, M. Korell, C. Marras, G. S. Bhudhikanok, M. Kasten, A. R. Chade, K. Comyns, M. B. Richards, C. Meng, B. Priestley, H. H. Fernandez, F. Cambi, D. M. Umbach, A. Blair, D. P. Sandler and J. W. Langston (2011). "Rotenone, paraquat, and Parkinson's disease." Environ Health Perspect **119**(6): 866-872.
- Wolf, L. K. (2013). "The Pesticide Connection." Chemical & Engineering News **91** (47): 11-15.

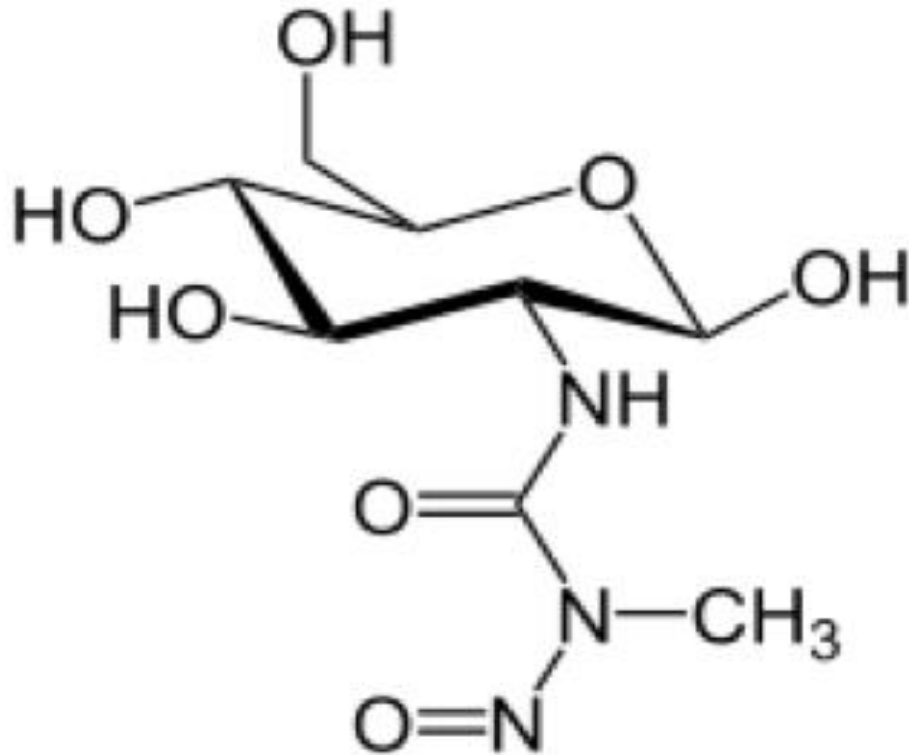
Streptozotocin and Type I Diabetes

Exploring evidence for an
environmental etiological agent
inducing Type I diabetes

Type I Diabetes

- Insulin insufficiency due to pancreatic beta cell death;
- 5-10% of worldwide cases;
- High geographic/cultural variation - e.g. 0.1/100,000 a year in Venezuela and 36.5/100,000 in Finland.
- Not highly heritable – many studies.

Streptozocin



Streptozocin Animal Model for Type I Diabetes

- First reported in 1963
- Induces human-like type I disease in mice, rats, dogs, sheep and baboons.
- Mechanism is damage to pancreatic islet beta cells as in humans.
- More than 100 studies, but never suggested as clue to etiology of human type I disease.

Streptozocin as an Anti-Tumor Agent

- Early investigators of antibiotic potency recognized toxicity due to islet cell death;
- Oncology team pickup up on that and initiated trials of anti-cancer activity for islet cell tumors.
- Streptozocin chemotherapy approved by FDA in 1982.
- Induction of diabetes disappears from anti-tumor reports.

Diabetes/Medical/Pharmaceutical Triangle

- Multi-billion dollar market for decades.
- Lilly intimately connected to every organization of patients, physicians, researchers.
- Despite evidence that it is a toxicity disease, no consideration of external etiology.
- Most models blame the patient.
- Some hope from emerging focus on diet.

Models for Type I Etiology

- Wider distribution of *Streptomyces achromogenes* than expected;
- Microbial contamination of foodstocks by related strains (Thus the strain that makes streptozocin colonizes herbage in silos, and presumably other stored plant food stocks such as grains, corn;.
- Modification of sugars during food processing, cooking, frying, baking, broiling;
- Physiological transformation of glucose into a toxic species, such as AGE.

Truncated forms of alpha-synuclein accumulate in human and mouse brain homogenates

- Human and mouse transgenic brain homogenates reveal presence of C-terminal alpha-synuclein truncations (10-30% of full length);
- PD brain homogenates had much higher levels of truncated species than controls. These species present in high salt soluble, SDS soluble and urea soluble fractions.
- In transgenic mice concentrated in SDS soluble, after onset of symptoms. Young mice have less. (Though TG mice do not produce urea soluble forms of alpha- Synuclein)
- Aggregated α -syn truncations are unique to PD/DLB patients, as fragments in age-matched controls are present only insoluble forms.

A truncated form of alpha-synuclein promotes aggregation and perhaps pathology

Methods:

- Use human and mouse brain homogenates, PD and controls:
- Rabbit antibodies;
- Thioflavin T and centrifugation for aggregation;
- Co-aggregation by His tag grabbing!!?
- 20 S proteasome from red blood cells:
- hs= high salt soluble; s= SDS soluble' u = urea soluble;
- Chang-Wei Liu, Benoit I. Giasson, Karen A. Lewis, Virginia M. Leek, George N. DeMartino and Philip J. Thomas (2005). A Precipitating Role for Truncated α -Synuclein and the Proteasome in α -Synuclein Aggregation: Implications for Pathogenesis of Parkinson's disease (J. Biol Chem., 280, #24, 22670-22678.)

Alpha-synuclein (not ubiquitinated) is cut by 20S Proteasome

- 26S proteasome degrades p21 and α -synuclein, but not Gfp.
- Construct fusions: 20 S and 26S degrades p21 and α -syn moieties, but not GFP at C-terminus.
- If they put GFP at N-terminal, p21 and α -syn moieties degraded at same rate as C-terminal constructs.
- Made sandwich constructs; Gfp still protected, but α -syn cleaved. So cleavage can be internal in a loop
- Liu CW, Corboy MJ, DeMartino GN, Thomas PJ. (2003) “Endoproteolytic activity of the proteasome” Science. Jan 17; 299 (5605): 408-11. Epub 2002 Dec 12.

Assessing potential risks from the BU Bioterror agent facility

- Ecological considerations
- Experience with infections within institutions
- Mission of the facility
- Political and economic pressures

Once introduced, novel organisms are not easily removed

- Chestnut blight
- Dutch elm disease
- Purple loosestrife
- Zebra mussels

Dangers of Bioweapons/Bioterror Research

- New source of extremely dangerous pathogens.
- Characterization requires growth of infectious organisms.
- Vaccine development requires challenge of animals and humans with infectious agent.
- Homeland security rules prevent real safety, which requires broad community knowledge of activities.

WHICH ONE DOES NOT BELONG?

Compare the location of the proposed BU bioterrorism BSL4 lab to the location of the three existing BSL4 labs:



BU Bioterrorism Lab (proposed)
SouthEnd/Roxbury, Boston, MA



Centers for Disease Control
Atlanta, GA



Southwest Foundation for Biomedical
Research, San Antonio, TX



US Army Research Institute on Infectious
Diseases, Ft. Detrick, Frederick, MD

Why is BU claiming that other BSL4 labs are in densely populated urban neighborhoods?

| People per square mile (per 2000 census data): | | |
|--|--------|--------|
| | Local | County |
| BU proposed lab: | 16,721 | 11,788 |
| Atlanta lab | 3,478 | 2,484 |
| San Antonio lab | 2,592 | 1,117 |
| Ft. Detrick lab | 2,036 | 294 |

The county population per square mile for the other proposed new BSL4 labs is: Galveston, TX: 627; and Hamilton, MT: 15.

March 12, 2004
Prepared by ACE/Safety Net
For more information, visit www.ace-ej.org

Some high containment accidents

- 60 documented in Pike Report
- Plum Island infections
- Tularemia outbreak at BU
- Probable Anthrax deaths (2) of Ft. Detrich employees.
- SARS infections in Taiwan and Singapore
- Underestimates due to national security constraints against reporting such accidents

The BU Tularemia Cover-Up

- **PROBE CITES LAG BEFORE BU LAB WORK WAS HALTED**
- **FORMER CHIEF DEFENDS PROCESS**
- Stephen Smith, GLOBE STAFF
- “An internal Boston University investigation into how three researchers were exposed to life-threatening tularemia and fell ill last year has concluded that the senior scientist in charge waited at least a month longer than he should have to halt the project.”

Bush Admin Prevents BW Inspections!?

The Washington Post

Thursday, September 19, 2002

“U.S. Drops Bid to Strengthen Germ Warfare Accord”

By Peter Slevin, Washington Post Staff Writer

Security from Bioterrorism?

- Strengthen Biological Weapons Convention through enforcement!
- Sharply limit Bioterrorism/Bioweapons research programs.
- Replace secrecy with transparency.
- End the war on Iraq.

Where did the weapons-grade anthrax come from?

- Identified as Ft. Detrick strain:
- Most likely one of the US bioweapons laboratories: Read et al (2002) Science vol 296, 14 June pp2028- 2033.
- Absent such programs, material would not have been produced.

Some Sources

- Cole, Leonard A. (1988) *Clouds of Secrecy: The Army's Germ Warfare Tests over Populated Areas*. Rowman & Littlefield, Totowa, New Jersey,.
- Cole, Leonard A. (1997) *The Eleventh Plague: The Politics of Biological and Chemical Warfare*. W.H. Freeman & Co, NY, NY.
- Guillemin, Jeanne (2005) *Biological Weapons: From the Invention of State-sponsored Programs to Contemporary Bioterrorism*. Columbia University Press, NY, NY.
- Wright, Susan (1990) *Preventing a Biological Arms Race*. The MIT Press, Cambridge, MA.

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