



History of Pathology Society Officers

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History of Pathology Society Meeting
 Sunday, March 12, 2016, 3:30-5:30 p.m. CC 602-604
 Washington State Convention Center, Seattle, WA, USA
 United States and Canadian Academy of Pathology Meeting

Beginnings

Moderator: Stephen A. Geller
 Weill Cornell Medical College, New York, NY, US

3:30

Introductory Remarks

Stephen A. Geller, Weill Cornell Medical College, New York, NY, US

3:35

Time-Travelling to the Origins of Lung Cancer

Anthony A. Gal, Emory University School of Medicine, Atlanta, GA

4:05

~~Alfred's Morgagni Klemperer~~ Crohn Disease

Stephen A. Geller, Weill Cornell Medical College, New York, NY, US

4:35

How Neuropathological Observations Have Determined the Treatment of Neurological Disease: A Historical Perspective

Harry Vinters. David Geffen School of Medicine, University of California, Los Angeles, CA

5:05

Business Meeting

TIME TRAVELLING TO THE ORIGINS OF LUNG CANCER

Anthony A. Gal, M.D.

Professor Emeritus

Emory University School of Medicine, Atlanta, Georgia

Faculty Disclosures: **None**

LUNG CANCER IN THE EARLY 21st CENTURY

- Global epidemic
- Most common cause of cancer-related death in M & F
- Survival stage and histology dependent
- Majority (~80%) related to cigarette smoking

TIME TRAVELING

- Charles Dickens: A Christmas Carol (1843)
- H.G. Wells: The Time Machine (1895)
- Star Trek (1966–1969)
- Time Tunnel (1966–7)

TIME TUNNEL

- Irwin Allen producer
- 30 Episodes
- Project Tic-Toc

"Two American scientists are lost in the swirling maze of past and future ages, during the first experiments on America's greatest and most secret project, the Time Tunnel.

Tony Newman and Doug Phillips now tumble helplessly toward a new fantastic adventure, somewhere along the infinite corridors of time."

MID 20th CENTURY

- 52% men and 35% women cigarette smokers
- Targeted markets: Virginia Slims (1970's) & Menthols (1960's)
- Oscar Auerbach's "Smoking Beagles" (1967-1970)
- US Surgeon General Smoking and Health (1964)
- Epidemiological studies linking smoking to lung cancer (1950's)

WW II

- Highest consumption of cigarettes
- Mass marketing, advertising, sponsorship
- Cigarette smoking & lung cancer [Oshner/Debaquey (1939)]
- Nazi anti-smoking campaign

INTERWAR YEARS

- Increasing tobacco consumption
- Cigarette advertising and sponsorship
- German autopsies: more cases of lung cancer
- Small cell carcinoma [Barnard (1926)]
- 1st histological classification [Marchesani (1924)]

ETIOLOGIES OF LUNG CANCER IN EARLY 20th CENTURY

Industrial and occupational exposure

Air pollution
Benzene
Arsenic
Nickel
Chromium
Asbestos

Automobile related:

Motor vehicle exhaust
Asphalt
Tarred-roads

Latent exposure from toxic gas injury during WW I

Chronic irritation following 1918-9 influenza pandemic

WW I

- “Doughboys” tobacco rations
- Cigarettes given by philanthropic organizations
- Seductive and romantic advertising

ISAAC ADLER, M.D. (1849-1918)

- *Primary Malignant Growths of the Lungs: a Pathological and Clinical Study* (1912)
- First book dedicated to lung cancer
- “Among the rarest form of disease”
- Suggested a link between cigarette smoking & lung ca

TURN OF THE CENTURY

- Extremely rare: 140 cases [M. Kaminsky (1898)]
- “Polite smoking” in Victorian & Edwardian society
- Decline in pipe smoking
- Radiography (Roentgen 1895)
- Rigid bronchoscopy (Killian 1895)

1880's

- 1st rise in consumption of cigarettes
- Hand-rolled cigarettes: 3/min
- James Bonsack Cigarette Rolling Machine (1880): 200/min
- American Tobacco Company (1890-1994)
 - James B. Duke (1859-1924)
 - 90% of cigarettes
 - Monopoly: Sherman-Antitrust: dissolved into 4 companies (1911)

MID 19th CENTURY

- Johannes Müller / Carl von Rokitansky / Rudolf Virchow
- TB vs. lung cancer: very difficult to separate
- "Growths" arose in lymph nodes
 - Invaded into bronchi
 - Cicatric, sclerosing, ulcerating
 - Encephaloid, lymphosarcoma, sarcoma primitif

EARLY 19th CENTURY

- Papeete via Spain
- Cigarette: Honoré de Balzac (*Œuvres diverses*, 1831)
- René-Théophile-Hyacinthe Laënnec (1781-1826)
 - Encéphaloïdes du poumon (1815)
- Gaspard Laurent Bayle (1774-1816)
 - Phthisie cancéreuse (1810)

18th CENTURY

- Percival Pott (1714 -1788): scrotal cancer in chimney sweeps (1775)
- Giovanni Morgagni (1682 -1771): *Ulcus cancrosum* (1761)
- Bernadino Ramazini (1633 - 1714): *De Morbis Artificum Diatriba*
[Diseases of Workers] (1700, 1713)

16th CENTURY

- "Everything comes from the mine" (*Alles kommt vom Bergwerk her*)
- Ore Mountains (Erzgebirge) rich in ores: silver, iron, pitchblende
- Fatal pulmonary disease in miners
 - Mountain Disease, Bergsucht, Schneeberger Bergkrankheit
- "Marry early & leave when they die in their early 40's a large number of children"

GEORGIUS AGRICOLA (1494—1555)

- "Father of mineralogy"
- Town physician in St. Joachimsthal /Jáchymov (1527-1533)
 - Joachimsthaler coins→ taler→dollar
- Observed numerous diseases in miners
- Perhaps 1st to document lung cancer in miners

DE RE RE METALLICA (1556)

- 12 volumes: mining and metallurgy
- 270 woodcut images
- Described many diseases of the miners (Vol VI)
 - "Death pits"
 - "An angel choking old miners to death"
 - "If the dust has corrosive qualities, it eats away the lungs"
 - "Women have married 7 husbands....carried off to a premature death"

WHAT IS THIS MINERS' DISEASE?

- Lung Cancer
- Tuberculosis
- Silicosis
- Mesothelioma
- Toxic fume-related injury
- Others / Combinations

ORE MINERS & LUNG CANCER

- F. H. Härtling & W. Hesse (1878-9)
 - *Der Lungenkrebs, die Bergkrankheit in den Schneeberger Gruben*
- Autopsies of miners & pathology reviewed at Pathological-Anatomical Institute @ Leipzig University
- "Lymphosarcoma" & "endothelial" carcinoma
- The endemic lung disease is lung cancer
- Responsible for 75% of deaths in miners

RADIATION CONNECTION

- Radioactivity: Henri Becquerel (1896)
- Erzgebirge Pitchblende ore rich in uranium, polonium, and radium
 - Pierre and Marie Curie (1898)
- Radon gas: Friedrich Ernst Dorn (1900)
- $^{238}\text{U} \rightarrow ^{226}\text{Ra} \rightarrow ^{222}\text{Rn}$
- Connection between radon and lung ca (Rajewsky (1939))

RADIATION –RELATED LUNG CANCER

- USPHS: radiation studies in Colorado Miners (1949)
- Hiroshima Tumor Registry [Harada & Ishida (1960)]
- Geno Saccomanno (1915-1999) lung cancer in uranium miners (1960's)
- Waggoner: NEJM Article (1965)
 - "excessive occurrence of respiratory cancer among uranium miners as well as a dose-response relation between airborne radiation and the incidence of respiratory neoplasia."
- Radon-222 carcinogenic (International Agency for Research)
- Cancer WHO International Radon Project (2005)

CONCLUSIONS

- Lung cancer has been part of humanity
- Masked by other diseases
- Clues to pathogenesis in 16th C, but not until past 100 years
- 19th-21st C tobacco consumption
- Lung cancers in non-smokers

IN THE FUTURE “Mission Possible”

Next generation of pathologists and other time travelers



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Weber LW. Georgius Agricola (1494-1555): scholar, physician, scientist, entrepreneur, diplomat. *Toxicol Sci*. 2002;69:292-294.

United States Public Health Service. *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service*. 1964.

NOTES

Questions

1. The seminal paper by FH Härtling and W Hesse (1879) showed which of the following?
 - a. A link between atomic bomb blasts and lung cancer
 - b. A link between mining and lung cancer
 - c. A link between chimney sweeps and scrotal cancer
 - d. A link between snuff and nasal cancer
 - e. A link between asbestos and malignant mesothelioma
2. In the 1920's which of the following was not considered to be a risk factor for lung cancer?
 - a. Second hand smoking
 - b. Air pollution
 - c. Toxic gas injury during WW I
 - d. Motor vehicle exhaust
 - e. Post-influenza irritation
3. The association between radon gas and lung cancer was first suggested in which century?
 - a. 16th C.
 - b. 17th C.
 - c. 18th C.
 - d. 19th C.
 - e. 20st C.
4. Which famous French author introduced the term cigarette?

a. Marcel Proust



b. Alexandre Dumas



c. Victor Hugo



d. Honoré de Balzac

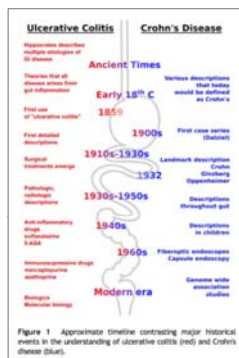
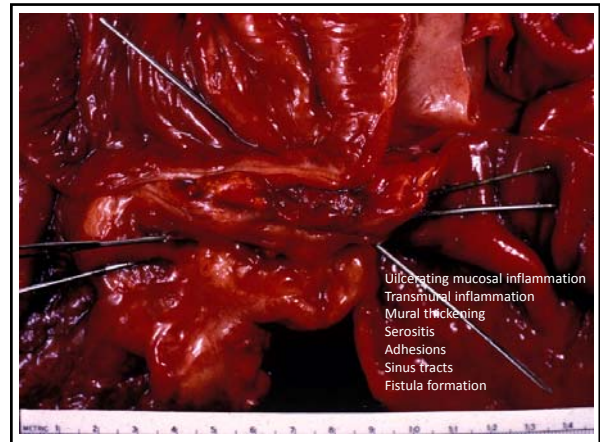


e. Voltaire



~~Alfred's Morgagni Klemperer~~ Crohn Disease

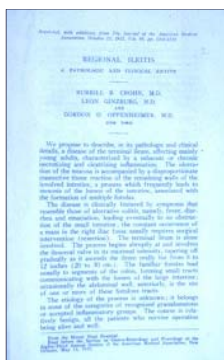
Stephen A. Geller, M.D.
Weill Cornell Medical College, New York
David Geffen School of Medicine, UCLA



Mulder et al: A tale of two diseases: The History of inflammatory bowel disease. J Crohn's Colitis 2014;8:341-348.



Burrill B. Crohn, M.D. (1884-1983)



Regional Ileitis 1932



Oppenheimer Crohn Ginzburg

The first case of Crohn disease ...



?? Aretaeus (Ἀρεταῖος) of Cappadocia (Καππαδόκη) – 1st C.C.E.



Alfred the Great (849-899)

Asser: Life of King Alfred

Alfred had married Ealhswith his Mercian bride, he participated in a grand feast that had lasted for a day and a night "he was struck without warning in the presence of the entire gathering by a sudden severe pain that was quite unknown to all physicians. Certainly it was not known to any of those who were present on that occasion, nor to those up to the present day who have inquired how such an illness could arise and - worse of all, alas! - could continue so many years without remission, from his twentieth year up to his fortieth and beyond. Many alleged that it happened through the spells and witchcraft of the people around him; others, through the ill-will of the

is reasonable to suppose that Asser used an everyday word to describe the king's perianal condition. The word that Asser used is 'ficus'. This word usually gets translated as 'haemorrhoids'. If this translation is accepted then we are either dealing with the familiar condition of haemorrhoids or some other externally visible perianal pathology. The alternative interpretation of this word is that it refers to the sexually transmitted disease of ano-genital warts. If the king's condition was that of ano-genital warts then it would not have helped any cause of Asser's to broadcast this as lay people were well aware of the connection between this highly contagious condition and sexual

Ficus
Before proceeding to the other symptoms I think it is worth dwelling on the possible nature of the perianal condition and the bearing of the translation of the word that I am using to mean 'piles'. I shall deal with the translation first. Asser wrote in Latin, he was a fairly well educated man who would have been exposed to the influence of other scholars in the court of King Alfred. It has been said that the list of works known and cited by Asser do not suggest exceptional learning and the quality of his writing does not reveal any mastery of Latin prose. He was a cleric without, we must assume, specialist medical knowledge, so it is reasonable to suppose that Asser used an everyday word to describe the king's perianal condition. The

Asser gives us a picture of a stricken monarch who suffers almost unrelentingly from his symptoms. Only a little further on in his account does he tell us that despite this, the king was able to pursue matters of state and the things that gave him pleasure with some energy. Thus the list runs that he contended with wars, Viking attacks and was still able to direct the governing of his kingdom, pursue all manner of hunting, give instructions to all his goldsmiths and craftsmen, direct his falcons, hawk trainers and dog keepers, as well as making his own designs for treasure. The king was able to fight, study, pursue his leisure interests, worship and govern, in short he lived a very full life. Either we are to understand that Alfred was of such fortitude that he continued doing all of this whilst very ill, is with all of his symptoms present, or more plausibly, that his illness was intermittent. The former seems quite incredible.

Craig G. Alfred the Great: a diagnosis. J Roy Soc Med 1991;84:303-305.

De Abditis Morborum Causis, 1507 (The Hidden Causes of Disease)

XCV.
" ... gripes in the intestines, called by the Greeks dysenteria ... apt to ulcerate the lining of the intestines and thus the excrement comes down bloodstained and mucous ..."

XCV.
Similar symptoms and also wasting and death with "entrails ... internally eroded."



Antonio Benivieni (1443-1502)



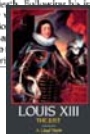
Louis XIII of France (1601-1643)

Attacks of diarrhea for decades, fever and rectal abscesses
1642 – bloody diarrhea, fever, abdominal pain, perianal abscess or fistula
1643 – autopsy showed ulcerated small and large bowel, perianal abscess or fistula, cavitary lesion of lung

292 Conclusion

down the king's strong constitution. His intestines were inflamed and ulcerated, making digestion virtually impossible; tuberculosis had spread to his lungs, accompanied by a tubercular cough. Either of these major ailments, or the accumulation of minor problems, may have killed him, not to mention psychological weaknesses that made him prone to disease or his doctors' remedies of emesis and bleedings, which continued right to his death.

Death came on 14 May 1643, the thirty-third anniversary of his father's death. He was buried in the Chapelle de la Vierge, the body in a lead casket covered with plain blue satin and gold embroidered coats of arms, a carriage to carry it by six horses in a day-long solemn funeral at St-Denis. Along the route, windows were lit with



WHEN he died 150 years ago, it threw his wife Queen Victoria, and the entire country, into a deep mourning.

And until recently it had been undisputed that Prince Albert's unexpected death in December 1861 was due to typhoid fever.

But thanks to a team of experts at the John Radcliffe Hospital and the tireless research of an Oxford historian, the theory is being put to the test for the first time.

Author Helen Rappaport has uncovered details about the death of Prince Albert which suggest he could have actually died from a more modern condition, Crohn's disease.





Dwight David Eisenhower (1890-1969)
34th President of the United States



June 5, 1944

Ailment's Discoverer Sees a Full Recovery:
EISENHOWER CASE WAS 'SAFEST TYPE' Dr. Crohn
Believes Patient May Resume Light Duties After 2
Weeks in Bed NO ILL EFFECT FORESEEN Expert Says
Disease Recurs in 30-35% of Cases but Usually in a Mild
Form

New York Times, June 10, 1956

Giovanni Battista Morgagni (1682-1771)

1682 – born, Forlì Italy, comfortable circumstances

1701 – University of Bologna M.D. (prosector for Valsava, who was a student of Malpighi)

1706 – *Adversaria anatomica* (total of 6 editions)

1712 – University of Padua – chair of theoretical medicine
(successor to Vesalius, Fallopio, Fabrizio, etc)

1713 – married – 3 sons and 12 daughters - poet

1761 – *De Sedibus et causis morborum per anatomen indagatis*

1771 – died, Padua



Some of Morgagni's contributions

angina pectoris, coronary atherosclerosis, vegetative endocarditis, aneurysm, aortic coarctation, mitral stenosis and insufficiency, tetralogy of Fallot, pulmonary stenosis, lobar pneumonia, cirrhosis, pulmonary tuberculosis, Stokes-Adams, cuneiform cartilages of Morgagni, hydatids of Morgagni, Morgagni's caruncle, Morgagni cataract, Morgagni concha, Morgagni columns, Morgagni foramen, Morgagni lacunas, Morgagni tubercles, Morgagni sinus, Morgagni ventricle, Morgagni-Turner-Albright syndrome, Morgagni-Stewart-Morel syndrome, femoral artery embolus, nephritis, syphilitic gumma, aortic syphilis, central nervous system syphilis, gastric carcinoma, colonic carcinoma, intestinal polyps, ulcerative colitis, Crohn disease, appendicitis, Richter hernia, pancreatitis, benign prostatic hypertrophy, Marfan's syndrome, post-mortem thrombi, stroke, etc etc etc



1761

De Sedibus et Causis Morborum
(The Sites and Causes of Disease)



Giovanni Battista Morgagni (1682-1771)

"20 year old man with mesenteric lymphadenopathy ... erosions, ulcerations and perforations of the extremity of the ileum and the nearest point of the colon to the extent of two hands breadth..."

Some post-Morgagni descriptions ...

1793 – Matthew Baillie – *Morbid Anatomy* - "intestine inflammation ... thickened mucosa ... ulcerated ... perforation or fistula ... thick-walled, ulcerated mucosa, narrowed lumen and dilated bowel cephalad ..."

1813 – Combe – "The lower part of the ileum as far as the colon was contracted, for the space of three feet, to the size of a turkey's quill. The colon had three constrictions ..."

1835- Cruveilhier – *Anatomie Pathologique* – strictured skip lesions from pylorus to rectum

1859 – Wilks – *Lectures on Pathologic Anatomy* – local acute ileitis with inflammation of the whole wall, "the whole tissue charged with pyoid corpuscles." (granulomas)

Samuel Wilks on Isabella Banks



"The intestines lay in a coil adherent by

a thin layer of lymph indicative of recent inflammation. The ileum was inflamed for three feet from the ileocecal valve, though otherwise the small intestine looked normal. The large intestine was ulcerated from end to end with ulcers of varying size, mostly isolated although some had run together ... inflammation was most marked at the proximal colon and the cecum appeared to be sloughing, causing the peritonitis."

1859

and more ...

1830 - Colles	1925 - Coffen
1889 - Fenwick	1925 - Horsley
1890 - Redmond	1926 - Cabot, Cabot
1901 - Lartigan	1930 - Bergen, Weber
1902 - Robson	1931 - Mock
1918 - Jones, Eisenberg	1932 - Golub

And, in these same years, Monsarrat, Mohnihan, Edwards, Proust, Lejars, Wilmanns, Braun, Schmidt, Lawen, Tietze, Bachlechner, Fröhlich, Verebly, Razzaboni, Goto, Nuboer, Lichtarowicz, Bergmann, Wilks, Dalziel, AND MORE – from England, France, Germany, Hungary, Italy, Japan, Netherlands, Poland, Russia, Scotland, United States

But few if any clearly identified the unique “pathological and clinical entity” as did the Mount Sinai authors.

E. Hurry Fenwick, 1889

27 year old woman with a history of diarrhea and weight loss - “ ... many of the coils of intestine were adherent and communication existed between the cecum and a portion of the small intestine adherent to it. Whilst the sigmoid flexure was adherent to the rectum and a communication also existed between them, the lower end of the ileum was much dilated and hypertrophied and the ileocecal valve was contracted to the size of a swan’s quill.”

Chronic Interstitial Enteritis



Thomas Kennedy Dalziel (1861-1924)



1913

The Mount Sinai Hospital papers

Lilienthal H. Hyperplastic colitis: extirpation of the entire colon, the upper portion of the sigmoid flexure and four inches of the ileum. Mt Sinai Hosp Rep 1901-1902;2:409-413.

Wiener J. Ileocecal tuberculosis. Ann Surg 1914;59:699-714. (no tubercle bacilli found in 10 cases).

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Berg AA. An operative procedure for right-sided ulcerative colitis. Ann Surg 1936;91-96

Eli Moschkowitz, M.D.



1882-1964

Internist and pathologist

1911 – first association of eosinophils and allergic reactions (NY Med J, 93:15-19)

1923 – “Nonspecific granulomata of the intestine” (Am J Med Sci, 166:48-66)

1925 - thrombotic thrombocytopenia purpura TTP; Moschkowitz disease (Arch Int Med, 36:89-93)

Why not Berg disease?



1899 – joins Surgery department after studying with Billroth

1914 – Department of Surgery organized into four divisions: Neurosurgery (Charles Ellsberg) Thoracic (Howard Lilienthal) Genitourinary (Edwin Beer) Gastrointestinal (A.A. Berg)

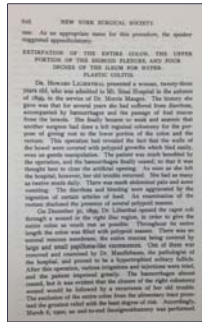
1922 – Berg performs first gastrectomy in United States for peptic ulcer disease



(Berg only publishes papers with his name alone)



Howard Lilienthal



1900

What about Ginzburg and Oppenheimer?



And how does Paul Klemperer fit into our story?



... in 1926 ... I was Associate Pathologist at the hospital ... running the department of morbid anatomy, without salary, earning my living by the practice of medicine in ... moments ... I could escape from the laboratory.

... Dr. Fred Mandelbaum took ill with a fatal illness ... I knew that I couldn't run both departments and perhaps also bacteriology and immunology and everything else ... time had come when the laboratory should be put on a full-time basis.

They agreed and we secured a director of pathology, Dr. Paul Klemperer ...

George Baehr, M.D.

My source...

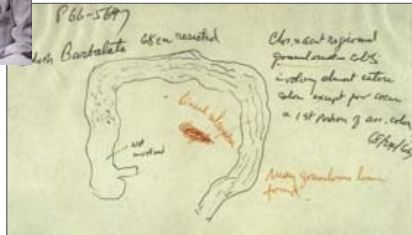


Sadao Otani (1892-1969)



Sadao Otani, M.D.

- 1892 Born, Kuwana-mie, Japan
- 1918 M.D., Chiba Medical College
- Assistant Pathologist
- 1920 Obstetrics-gynecology, Kyoto
- 1923 Anatomic pathology, Freiburg (Aschoff)
- 1925 Postgraduate Medical School, New York (now NYU)
- 1927 The Mount Sinai Hospital
- 1969 Dies, emphysema, gastric ulcers (steroids)



Paul Klemperer - 1

- 1887 Born, Vienna
- 1906 Enters University of Vienna, faculty of law
- 1906 Attends lectures by Sigmund Freud, joins psychoanalytic society, transfers to medical school
- 1911 Joins Alfred Adler, breaking with Freud
- 1912 M.D., University of Vienna
- 1912 Studies Pathology with Karl Sternberg (student of Virchow), University of Brunn
- 1915 Drafted into Austrian army, World War I
- 1918 Pioneering studies on pathology of influenza

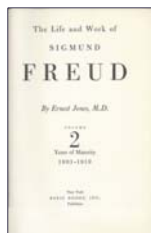
"... in 1906, when Freud was but a voice crying in the wilderness, Klemperer became one of his first disciples ..."

Eli Moschkowitz, M.D.

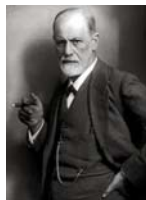
76 E. Mollateiner and J. Reissner 191 Forum Psychoanal 6, 1997

Table 2. Acceptance of members (men and women)

1902	1903	1904	1905	1906	1907	1908	1909	1910
Adler Freud Kubler Kurtz Sachal	Freud Bakke Mori	Grat	Hochstein	Bach Bach A. Deutsch Fro Hofner Hofner Kam Kam Schneider Wach	Adler Bach A. Deutsch Sachal L. Harnisch Hofner Kam Kam Schneider Wach	Froesch Juchas Rit	Freudberg Furtmüller Furtk	Gitter Grüner Hofner Hofner Hofner Kam Kam Schneider Wach



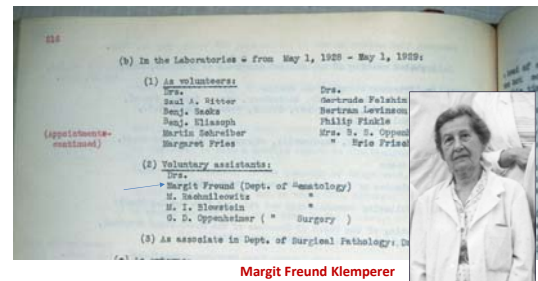
Freud continued his University lectures during these years. We happen to possess a list of those attending in the year 1906. They were seven in all: Carl Furtmüller, Franz Grüner, Gustav Grüner, Paul Klemperer (who kindly gave me this information), H. Oppenheim, Emmy Pisko (Sach's future wife), Hanns Sachs and Richard Wagner. Four years later all these, except Emmy Pisko, became members of the Vienna Society, but in October of the same year (1910) four of them resigned with Adler, all except Sachs and Wagner.



Sigmund Freud (1856-1939)



Alfred Adler (1870-1937)



Margit Freund Klemperer

"It is fascinating that both Klemperers saw no ideological incompatibility between pathology and psychiatry".

Stanley M. Aronson, M.D.

Paul Klemperer - 2

1919	Rejoins Sternberg
1921	Arrives in New York, refused Mount Sinai position
1922	Assistant Professor, Loyola Medical School, Chicago
1923	Assistant → Associate Professor, New York Post-graduate Medical School (now NYU)
1927	Pathologist-in-chief, The Mount Sinai Hospital
1942	"Pathology of disseminated lupus erythematosus"
1955	Retires
1964	Dies, ruptured aneurysm

- Systemic lupus erythematosus
- Concept of 'collagen diseases'
- Lymphomas
- Spleen
- Myoblastoma
- Benign pleural neoplasms
- Mesothelioma
- Lipoid nephrosis
- Shock
- Malignant hypertension (with Otani)
- Immunopathology
- ?? Crohn disease
- others ...

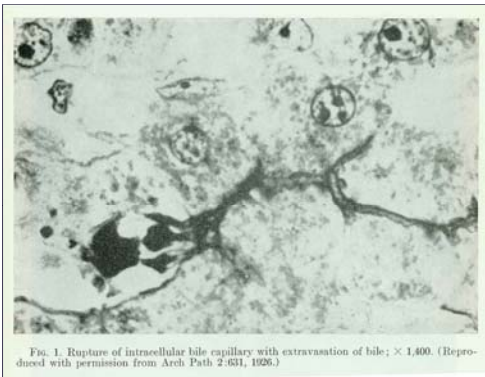
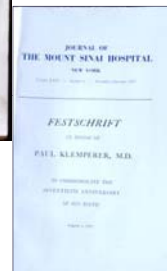
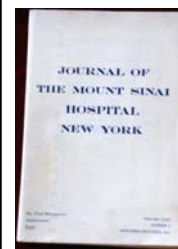


FIG. 1. Rupture of intercellular bile capillary with extravasation of bile; $\times 1,400$. (Reproduced with permission from Arch Path 2:631, 1926.)

(1931 – Knoll and Ruska invent electron microscope)



729 pages
80 articles
128 authors
48 Klemperer students
46 centers
8 countries

"Dr. Klemperer would never say that pathology residents were in a training program; he would say that you don't train pathologists, you teach them and they learn."

Lotte Strauss, M.D.

Was it Paul Klemperer who really identified what we now call Crohn disease?

A.A. Berg, Leon Ginzburg, his associate, and Gordon Oppenheimer, then a resident in surgical pathology, studied five of Berg's patients.

Burrill B. Crohn had under his care another two or three patients.

The two groups united at the suggestion of Paul Klemperer who provided them with additional cases ("a new disease") to make up the 14 patients in the 1932 article on "terminal ileitis."

The alternate versions

- AA Berg recognizes the disease and instructs Ginzburg and Oppenheimer to study ?14 cases of 'atypical ulcerative colitis'
- Ginzburg collects data on ?12 cases
- Crohn collects data on 2 or 3 cases, appropriates Ginzburg's data and presents at AMA meeting
- Ginzburg and Oppenheimer present data at American Gastroenterologic Association 2 weeks later
- Crohn, Ginzburg, Oppenheimer publish paper

Would Crohn, Ginzburg, Oppenheimer have allowed/encouraged Klemperer to join the paper?

Yes (but the eponym would still be 'Crohn' since the journal only used alphabetical order)

Would Klemperer have allowed his name to be affixed to the paper if he did not participate in the actual study and the writing?

No!

What if Berg had not been so peculiar (writing papers with his name alone)?

We probably would be talking about Berg disease!

Paul Klemperer embodied the virtues and triumphs of both the new and the old world pathology. He was dedicated to medical science as a whole but considered pathology to be the central theme and the role of the pathologist to be that of an orchestra conductor directing the instruments of many artists. He combined humility and wisdom with a pervading devotion to the stimulation and development of young people.

Hans Popper, M.D., Ph.D., 1964

He was the hospital's conscience and principal intellectual guide.

Saul Jarcho, M.D.

An Imaginary Conversation with the Gang of Three:

A Ghostly Interview With Burrill B. Crohn, Leon Ginzburg, and Gordon Oppenheimer

HENRY D. JANOWITZ, M.D.

THROUGHOUT THE COON OBJECTS OF Drs. Kowitza and Prostera, this unusual dialogue with these three physicians "on the other side" allowed me to discuss some aspects of "Regional Ileitis" with its original discoverers.

Henry D. Janowitz (HJD): Good evening, Burrill, Leon, and Gordon. It has been a nearly a quarter of a century since I had the pleasure of seeing you all, in 1960, at a meeting of the National Foundation of Ileitis and Colitis of which you all were honorary chairmen.

Gordon Oppenheimer (GO): Someone joked that this was the first time we had been together again since we wrote the original paper.

Leon Ginzburg (LG): Like most jokes, it was

raised by the term. Yes, Leon, although you are smiling, that's true.

Now that I have got you all here together, there are several things I want to get straight. It was early in 1960 that Lockhart-Mummery and Morson put regional enteritis of the colon definitively into the literature and on the map.

New Leon and Gordon, you had described the colonic involvement of granulomatous disease in your first independent paper in the surgical world in 1953 after the joint paper in New Orleans in 1952. Why didn't you follow up on that?

LG: The idea seemed clear enough to me and obvious. Gordon was interested in urology and I was born to be a surgeon. Pathologists and medical

Janowitz HD. An imaginary conversation with the gang of three: a ghostly interview with Burrill B. Crohn, Leon Ginzburg and Gordon Oppenheimer. Mt Sinai J Med 1996;63:61-65.

So, when all is said and done – what do we call this chronic, distinct, still incompletely understood pathophysiologic entity?

**Alfred's Louis' Benivieni, Morgagni
Wilks, Dalziel-Moschkowitz-Klemperer-Ginzburg
Crohn Disease**



Giovanni Battista Morgagni (1682-1771)



Burrill B. Crohn, M.D. (1884-1983)

Morgagni-Crohn disease?

however ...

- Eponyms are almost gone from medical use
- History does not seem to matter very much
- Change of any kind, including changing disease names, is not so easy
- The Crohn, Ginzburg, Oppenheimer paper was the first to clearly describe the pathophysiologic features of the disease
- Therefore, until the specific etiology is determined and an appropriate scientific name is developed, it is still

Crohn disease

Had Paul Klemperer given this presentation – and it would have been a far more learned presentation than mine – he would end by saying:

It is not so great an honor to speak to a medical audience ... but to be listened to by a medical audience, there's the honor.



Paul Klemperer (1887-1964)

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NOTES

Questions

1. Which of the following national leaders most likely suffered from Crohn disease?
 - a. Alfred the Great of England, Louis XIII of France, Otto von Bismarck of Germany
 - b. Alfred the Great of England, Louis XIII of France, Dwight D. Eisenhower of the United States
 - c. Alfred the Great of England, Louis XIII of France, Franklin D. Roosevelt of the United States
 - d. Prince Albert of England, Louis XVI of France, Mary, Queen of Scots
 - e. Louis XVI of France, Prince Albert of England, Dwight D. Eisenhower of the United States
2. The first clinicopathologic description of Crohn disease was made in which of the following centuries?
 - a. 3rd century BCE (Hippocrates)
 - b. 1st century CE (Aretaeus of Cappadocia)
 - c. 16th century (Benevieni)
 - d. 18th century (Morgagni)
 - e. 20th century (Crohn *et al*)
3. Names for Crohn disease used in the past include which of the following?
 - a. Chronic interstitial enteritis, nonspecific granulomata of the intestine, pseudolymphoma
 - b. Nonspecific granulomata of the intestine, chronic interstitial enteritis, regional ileitis
 - c. Nonspecific granulomata of the intestine, chronic interstitial enteritis, ulcerative colitis
 - d. Hyperplastic colitis, chronic interstitial enteritis, intestinal Hodgkin granulomatosis
 - e. Ileocecal tuberculosis, chronic interstitial enteritis, ulcerative colitis
4. Paul Klemperer began his career as a student of which of the following?
 - a. René-Théophile Hyacinthe Laennec
 - b. Rudolf Virchow
 - c. Theodor Billroth
 - d. Sigmund Freud
 - e. Carl von Rokitansky

How neuropathologic observations have determined the diagnosis and treatment of neurologic diseases: Emphasis on *Dementia*

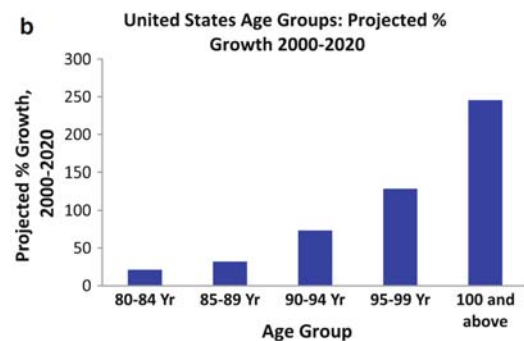
Harry V. Vinters, M.D.
Professor of Pathology and Laboratory Medicine
Chief of Neuropathology
David Geffen School of Medicine, UCLA

HV Vinters financial disclosures/conflicts:

- HVV is involved in studies aimed at optimizing ligands for amyloid imaging in the brain, which may be of commercial value
- Through a rev living trust, HVV owns shares in, & receives dividends from, companies that are developing diagnostic biomarkers (including neuroimaging methods) for AD, and novel treatments. These include *General Electric, Teva Pharma, Pfizer Pharma, and Glaxo SmithKline Beecham*

Neurodegenerative diseases.....USA Prevalence

Alzheimer's disease (SDAT)	5.3 million
Parkinson's disease	400,000-1,000,000
Amyotrophic lateral sclerosis (ALS/MND)	16-17,000
Frontotemporal lobar degeneration(s)	? 50-100,000



Coined the term 'dementia praecox (schizophrenia)'; worked with Nissl & Alzheimer



Figure 3. Emil Kraepelin (1856-1926).

Father of modern psychiatry; believed in the 'physical/morphologic' basis of psychiatric diseases

**History of the study of neuropsychiatric and neurodegenerative diseases—
from a *morphologic* perspective**

- A history that is relatively brief (begins late 1800s)
- AD first described in 1906, public'n in 1907
- By 1909, only 5 additional cases published— between ages 45 & 67; first subject (Auguste D.) almost certainly a familial case
- *Staining methodology (esp. silver stains) crucial in evolution of our understanding of AD*

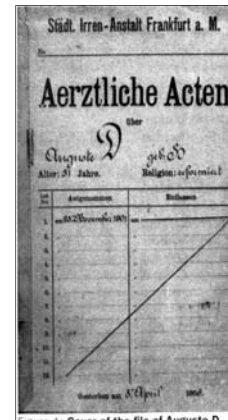
First description of AD

Clinicians by day, histopathologists by night...



Figure 1. Alois Alzheimer (1864-1915).

Various academic posts in Germany (Frankfurt, Heidelberg, Munich)

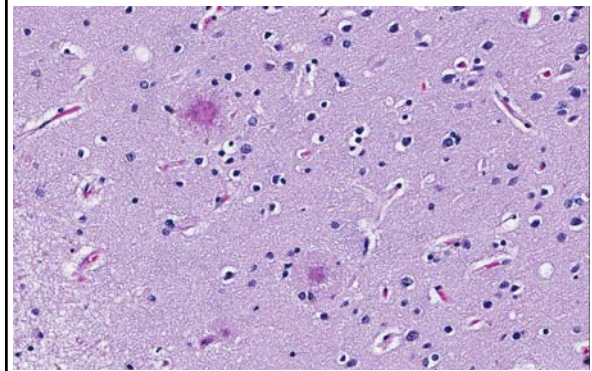
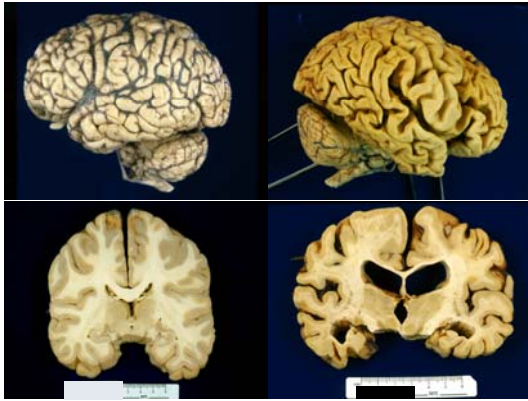


Clinical record...of the first AD patient, 1906

Figure 1. Cover of the file of Auguste D

Normal Aging

AD



X20

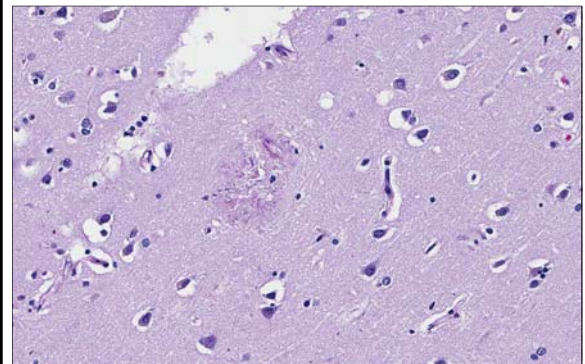
Figure 1. Georges Marinco, 1863-1938



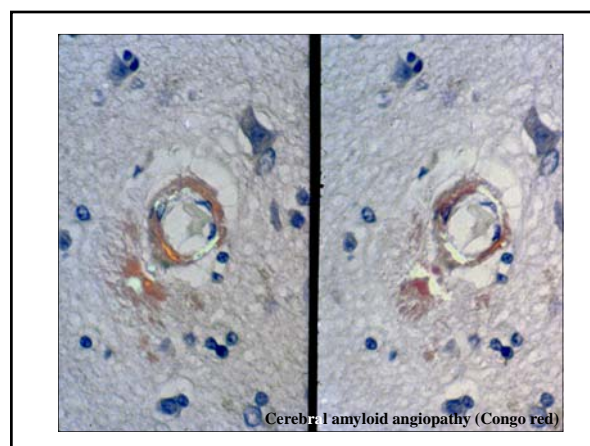
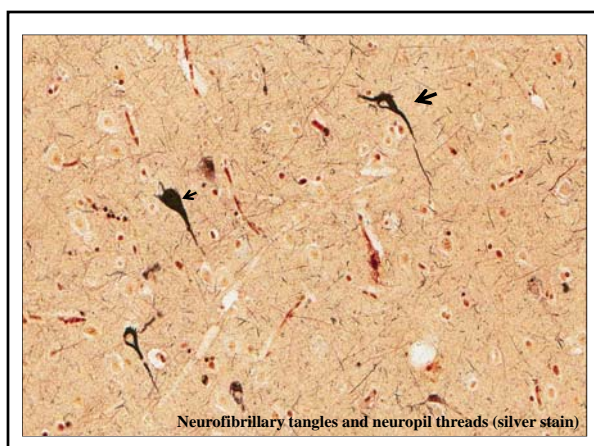
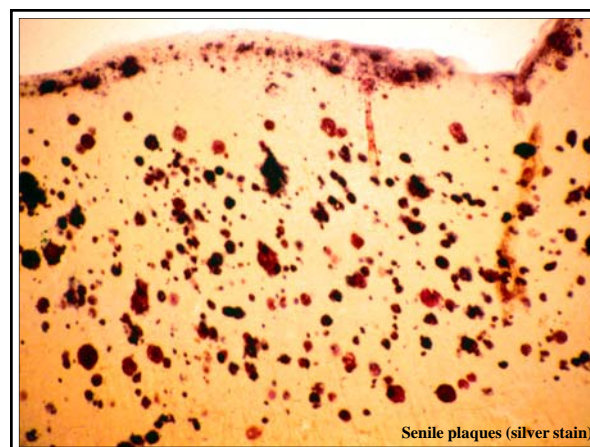
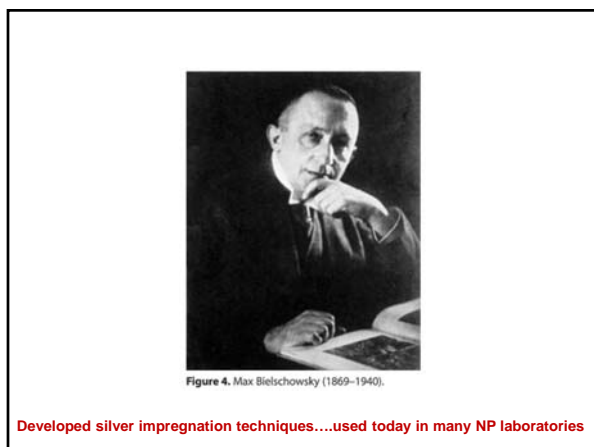
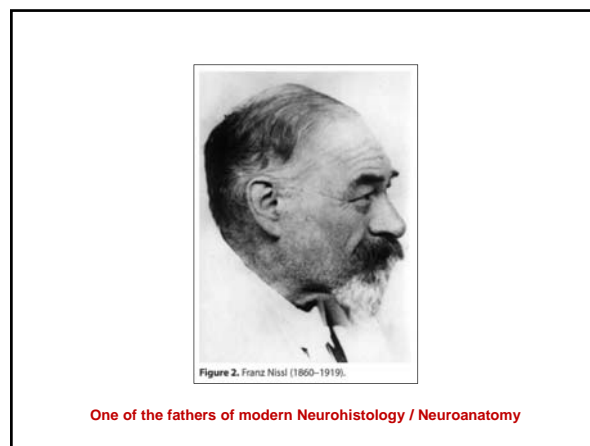
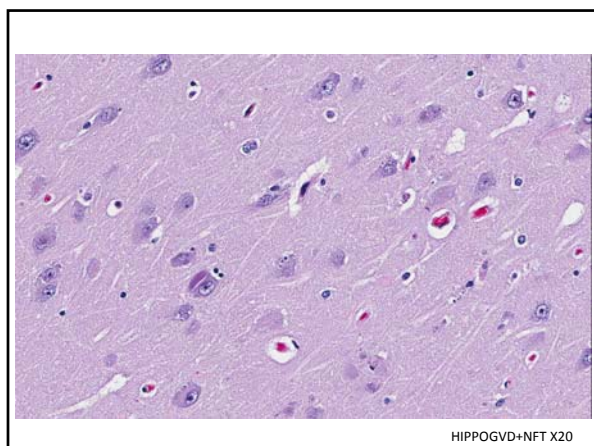
Figure 2. Paris Medical Weekly, November 12, 1882

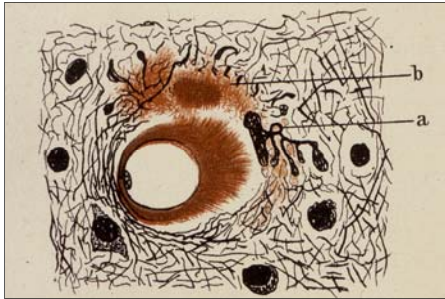
TRAVAUX ORIGINAUX
Sur les lésions, et le pathogénie de l'épilepsie
de l'adulte.
Il est que l'existence et la physiologie pathologique de l'épilepsie ont été l'objet de nombreuses recherches, et que les auteurs ont pu constater, dans les cas les plus importants, la présence de lésions importantes, et que les auteurs ont pu constater, dans les cas les plus importants, la présence de lésions importantes.

First observation of senile plaques—in the brains of deceased epilepsy patients...



SP X20





CONTRIBUTIONS of NEUROPATHOLOGY to DEMENTIA RESEARCH - 1

Early 1900s: Classic descriptions of AD neuropathology—routine & silver stains
SPs, NFTs, CAA all characterized

1960s-1970s: Correlative clinicopathologic studies established AD as
commonest cause of dementia (*Blessed-Tomlinson-Roth 1968, 1970*)

Empirical cyto/immunohistochemical (IHC) & E/M approaches to
looking at AD lesions

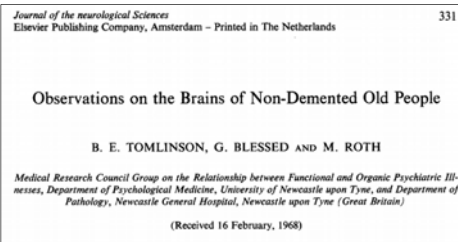
1980s-1990s: Isolation of AD lesions and the proteins that constitute them—
Glennner & Wong, 1984—characterized *A4/Beta-amyloid* from
isolated meningeal CAA; Masters *et al* characterized SP core protein

'Rational' IHC using primary antibodies to AD proteins (ABeta, p-
Tau, others)—Terry *et al*, importance of synaptic loss in disease
progression

Characterizing neuropathologic component of AD Tg animal models

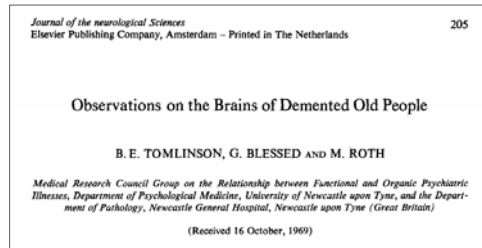
J Neurol Sciences 7: 331

Cited 660+ times (WOS)

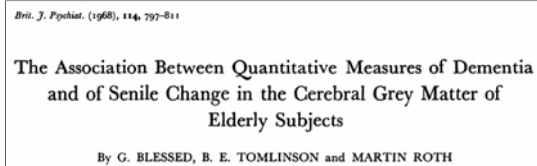


J. Neurol. Sci. 11:205

cited 1300+ times



Cited 3194 times (per WOS)



Established clin-path correlation.....imperfect though it remains !!

Key
AD
lesions

LESION	AMYLOID	NEOCORTEX	HIPPOCAMPUS
Granulovascular degeneration (intraneuronal)	NO	NO	+++
Neurofibrillary tangle (intraneuronal)	YES	++	+++
Senile 'neuritic' plaque (extraneuronal)	YES & NO	+++	+++
Amyloid angiopathy (extraneuronal)	YES	+++	+

CONTRIBUTIONS of NEUROPATHOLOGY to DEMENTIA RESEARCH - 1

Early 1900s: Classic descriptions of AD neuropathology---routine & silver stains SPs, NFTs, CAA all characterized

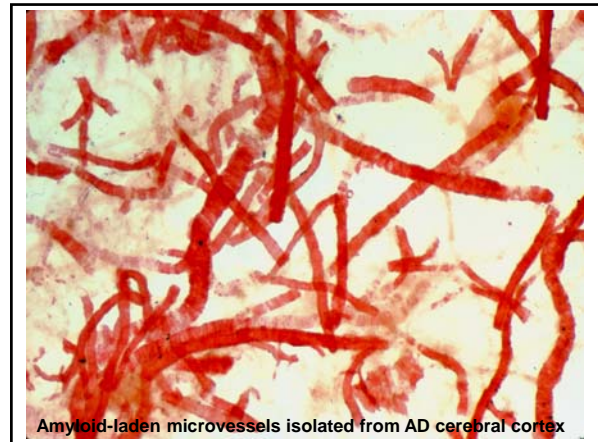
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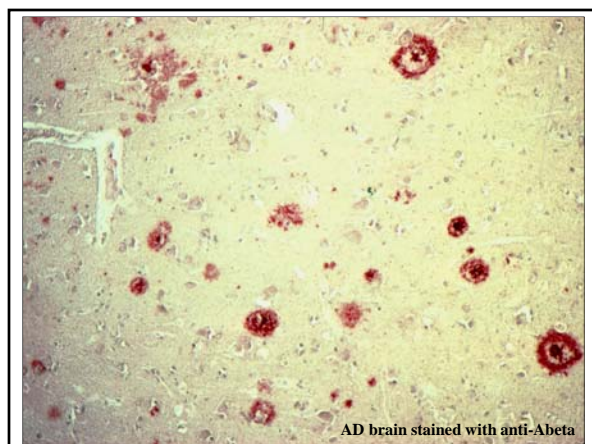
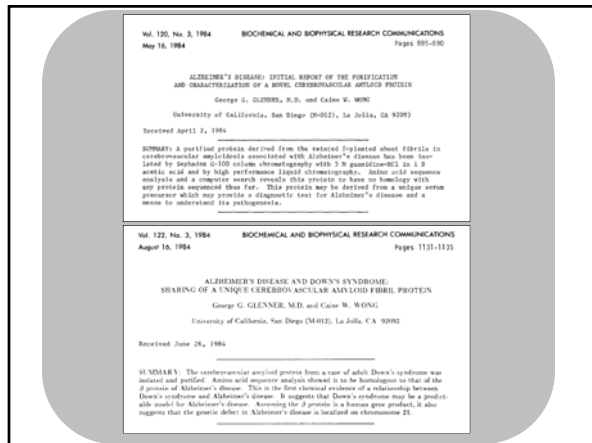
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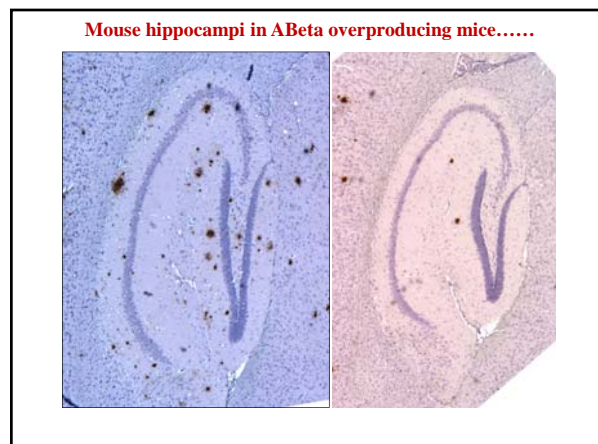
Characterizing neuropathologic component of AD Tg animal models



Amyloid-laden microvessels isolated from AD cerebral cortex



AD brain stained with anti-ABeta



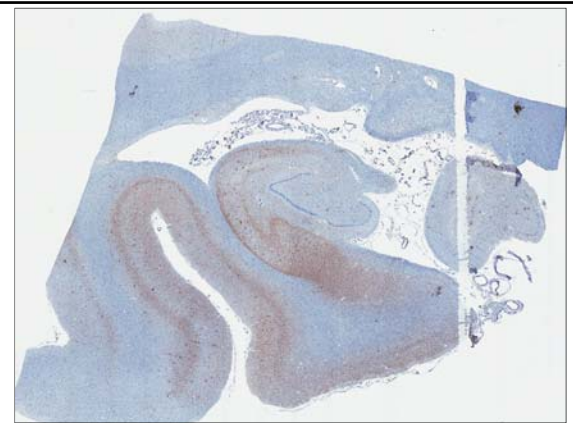
Mouse hippocampi in ABeta overproducing mice.....

Discoveries of Tau, abnormally hyperphosphorylated tau and others of neurofibrillary degeneration: A personal historical perspective

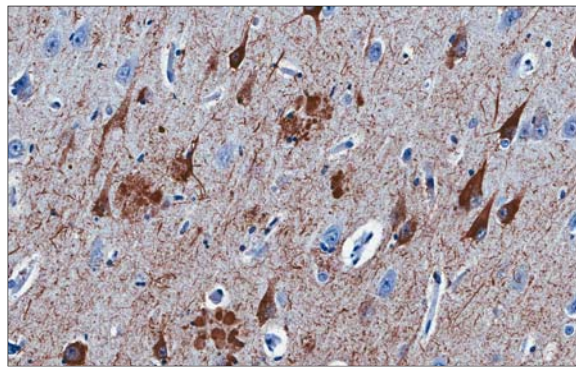
Khalid Iqbal^a and Inge Grundke-Iqbal^a
 New York State Institute for Basic Research in Developmental Disabilities, Department of Neurochemistry, 1659
 Route 90B Road, Staten Island, New York 10314-4299, USA
 E-mail: iqbal@worldnet.att.net, i.g.iqbal@nybb.org



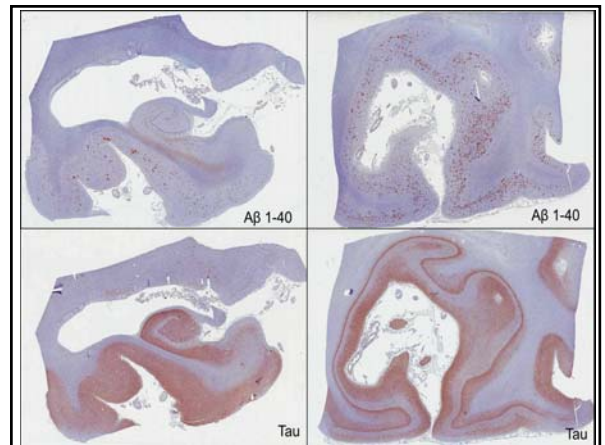
Abstract. Alzheimer disease was described by Alois Alzheimer in 1907, but it was not until ~60-70 years later that any new significant developments were reported on the pathology of this disease. The discoveries that laid down the foundation for the exciting research that has been carried out during the last ~20 years and that have significantly enhanced our understanding of the disease are the discovery of neurofibrillary tangles and neuritic (senile) plaques, the clinical-pathological correlation of these lesions to the presence of dementia, and the bulk isolation and protein characterization of paired helical filaments and plaques. We discovered tau as the major protein subunit of paired helical filaments/neurofibrillary tangles, the abnormal hyperphosphorylation of this protein in this lesion and in Alzheimer brain, and the gene of tau. Since then, our laboratory has been involved in the discovery of tau and its abnormal hyperphosphorylation in paired helical filaments and Alzheimer brain cytosol. This article also describes several major findings which subsequently resulted from the discovery of tau and its abnormal hyperphosphorylation of tau and in a large part account for the current understanding of the role of this lesion in Alzheimer disease and other tauopathies.



TauWMTHippo



NFTsHippoTauX20.0



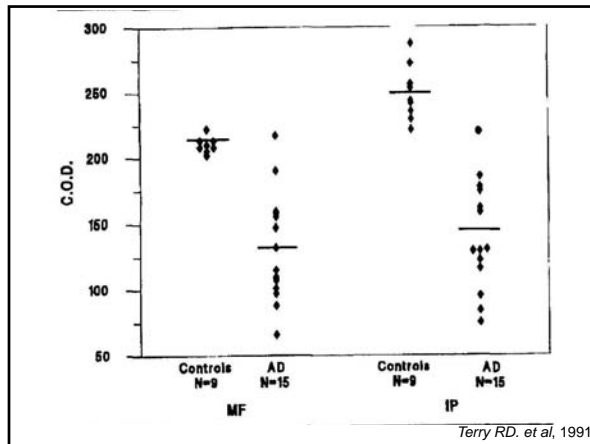
Physical Basis of Cognitive Alterations in Alzheimer's Disease: Synapse Loss Is the Major Correlate of Cognitive Impairment

Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, Hansen LA, Katzman R.
 Department of Neurosciences, University of California-San Diego, La Jolla 92093-0624.

Department of Neurosciences, University of California-San Diego, La Jolla 92093-0624

Abstract

We present here both linear regressions and multivariate analyses correlating three global neuropsychological tests with a number of structural and neurochemical measurements performed on a prospective series of 15 patients with Alzheimer's disease and 9 neuropathologically normal subjects. The statistical data show only weak correlations between psychometric indices and plaques and tangles, but the density of neocortical synapses measured by a new immunocytochemical/densitometric technique reveals very powerful correlations with all three psychological assays. Multivariate analysis by stepwise regression produced a model including midfrontal and inferior parietal synapse density, plus inferior parietal plaque counts with a correlation coefficient of 0.96 for Mattis's Dementia Rating Scale. Plaque density contributed only 26% of that strength.

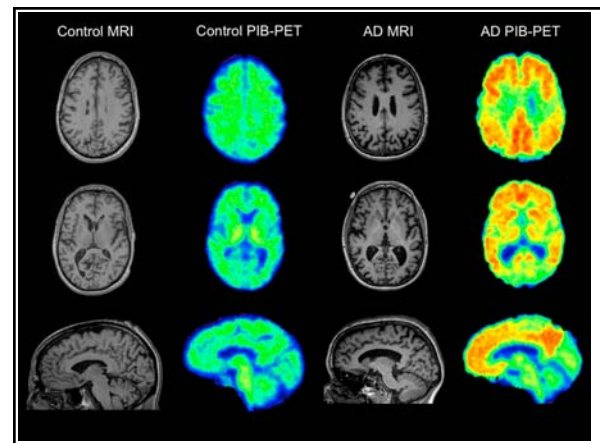


Diagnostic criteria for staging AD Neuropathology

- Khachaturian (1985)
- CERAD (1990s)—stress *neuritic plaques*
- Braak & Braak (1990s)—stress *NFT distribution*
- NIA-Reagan Institute (1998)—“probabilistic”
- NIA-Alzheimer’s Association Guidelines, published in 2012 (T. Montine et al, *Acta Neuropathologica*)

CONTRIBUTIONS of NEUROPATHOLOGY to DEMENTIA RESEARCH -2

- 2000s:** Recognition of the ‘universe’ of non-AD dementias—including DLBD, FTL spectrum
- New diseases ‘caused by/related to’ new genes and proteins: Tau, TDP-43, FUS, alpha-synuclein, progranulin, C9ORF (FTD-ALS)
- Importance of AD-parenchymal-vascular co-morbidity in dementia pathogenesis—role of *hippocampal ischemic injury*?
- Validating neuroimaging data (PiB, FDDNP, etc.)
- 2000s+++:** Disease-modifying approaches—will they lead to structural ‘footprints’ in the brain ?



CLINICAL SYNDROME

- Memory impairment
- Cognitive decline
- Focal motor/sensory deficits
- Personality change

(Autopsy) ↓ ↑

NEUROPATHOLOGIC FEATURES

- Cortical atrophy, synapse and dendrite loss
- SPs, NFTs, CAA
- Microglial, astrocyte activation
- Microvessel-mediated ischemic changes

- 1907: First neuropathologic description by Alzheimer
- 1907-1915: Description and characterization of AD-related lesions (e.g. by Alzheimer, Fischer)
- 1960-70's: Recognition of the high incidence of AD (vs. vascular dementia) and the similarity/identity of AD and SDAT (e.g. Blessed, Tomlinson, Roth et al.)
- 1960-70's: Description of detailed cellular/ultrastructural pathology of AD/SDAT by Kidd, Wisniewski, Terry and many others
- 1970-80: Evolution of immunohistochemistry (e.g. in study of AD-specific lesions (NFT's, amyloids))
- 1984: Isolation (G. Glenner) of brain microvascular amyloid (from AD patients) and characterization of beta/A4 protein—subsequent evidence that A4 protein is identical in AD/SDAT and DS and SP and microvascular amyloid are +/- identical
- 1987: Cloning of beta peptide/A4 precursor (A4P, APP)
- 1988--: In vitro studies of A4, A4P and transgenic mouse models of AD??

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Montenigro PH, Corp DT, Stein TD, Cantu RC, Stern RA. 2015. Chronic traumatic Encephalopathy: Historical origins and current perspective. *Annual Review of Psychology* 11: 309-330.

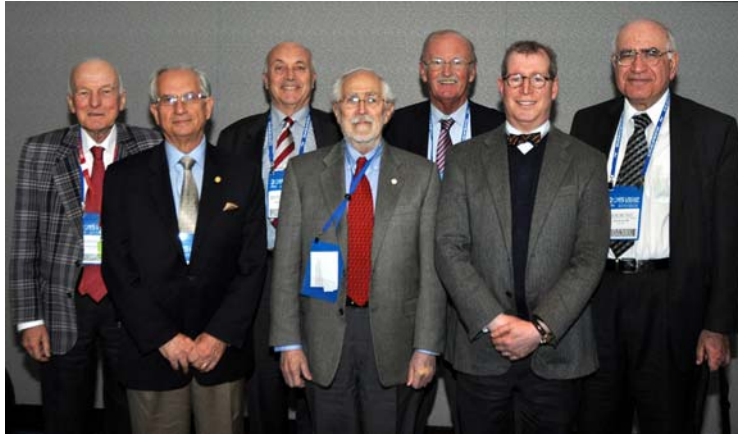
Tomlinson BE, Blessed G, Roth M. 1968. Observations on the brains of non-demented old people. *Journal of the Neurological Sciences* 7: 331-356.

Tomlinson BE, Blessed G, Roth M. 1970. Observations on the brains of demented old people. *Journal of the Neurological Sciences* 11: 205-242.

NOTES

Questions

1. The clinical and neuropathologic features of Alzheimer's disease were first described in _____ and published the following year?
 - A. 1698
 - B. 1856
 - C. 1906
 - D. 1916
 - E. 1930
2. Silver impregnation techniques, effective in demonstrating (within brain parenchyma) the cortical senile plaques and neurofibrillary tangles characteristic of Alzheimer disease, were first developed by which of the following?
 - A. Max Bielschowsky
 - B. Franz Nissl
 - C. Georges Marinesco
 - D. Bernardino Ghetti
 - E. Alois Alzheimer
3. Until the late 1960s, Alzheimer disease was thought to be a rare or unusual cause of dementia. Which of the following two papers co-authored by the following individuals established the high frequency of AD in elderly individuals known to be demented prior to death?
 - A. Ghetti-Gambetti-Selkoe
 - B. Hardy-Tanzi-Trojanowski
 - C. Steele-Richardson-Olszewski
 - D. Dickson-Cohen-Richardson
 - E. Tomlinson-Blessed-Roth
4. In 1984, Glenner & Wong published two seminal papers which changed the course of AD research. They isolated a protein A4 (subsequently known as beta-amyloid) from which of the following components of autopsy brains originating in Alzheimer patients?
 - A. Synaptosomes
 - B. Brainstem
 - C. Subcortical white matter
 - D. Meningeal blood vessels involved by amyloid angiopathy
 - E. Hypothalamus



Presidents– History of Pathology Society

Back row:

Robin A. Cooke (2000-01), Gaetano Thiene (2012-13), Robert H. Young (2008-09), Samir S. Amr (2011-12)

Front Row:

Santo V. Nicosia (2005-06), Stephen A. Geller (2015-16), David N. Louis (2014-15)

USCAP 2015, Boston, Massachusetts
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2015 Speakers – History of Pathology Society
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Robert H. Young, David N. Louis, Michael J. `Obrien
Companion Meeting - USCAP 2015
Boston, Massachusetts (photo courtesy of Robert A. Cooke)