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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

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

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<td>Anthony A. Gal, Emory University School of Medicine, Atlanta, GA</td>
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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)
- 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/Debakey (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 1918-19 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 cancer

## 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 Virchov
• TB vs. lung cancer: very difficult to separate
• "Growth" arose in lymph nodes
  • Invaded into bronchi
  • Cicatric, sclerosing, ulcerating
  • Encephaloid, lymphosarcoma, sarcoma primitif

EARLY 19th CENTURY
• Papelate 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 Bergekrankheit
• "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. Härting & 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

References


NOTES


Morgagni GB. De Sedibus et Causis Morborum per Anatomam Indagatis. Venice: Typographia Remondini; 1761.


Questions

1. The seminal paper by FH Härting 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


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

Regional Ileitis 1932

Oppenheimer, Crohn, Ginsburg

The first case of Crohn disease ...
Aretaeus (Ἀρεταῖος) of Cappadocia (Καππάδοξ) – 1st C.E.

Aretaeus, believed to have been a physician, wrote about abdominal pain that was quite unknown to all physicians. Certainly he was not known to any of those who were present on that occasion, nor to those of the present day who have enjoyed such as these could imagine. The word that Aretaeus used is "diarrhea." This word actually gets translated as "hemorrhoids." If this translation is not correct, we are dealing with the belief that if hemorrhoids or some other externally visible part of the body is involved, then this disease condition was that of a serious or even fatal disease. It seems that the people were well aware of the connection between this highly external condition and severe illness.

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

"... gripe 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 ..."

Antonio Benivieni (1443-1502)

Aretaeus: Life of King Alfred

A young man named Edward, later to become Edward the Elder, was born into a family that could trace its lineage back to King Alfred. It has been said that the list of events known to be true of Alfred were not exaggerated. He would be considered a remarkable man who led the nation through hard times. In the case of King Alfred, it has been said that the list of events known to be true of Alfred were not exaggerated. He would be considered a remarkable man who led the nation through hard times.


Asser: Life of King Alfred

As far as our knowledge goes, the possible connection to the patient condition and the imaging of the material that was examined, he would have been classified as a diagnostician who would have been considered a remarkable man who led the nation through hard times.

Roche Before proceeding to the other symptoms I think it is important for understanding the possible connection to the patient condition and the imaging of the material that was examined, he would have been classified as a diagnostician who would have been considered a remarkable man who led the nation through hard times.


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. Similar symptoms and also wasting and death with "entails ... internally eroded."

Antonio Benivieni (1443-1502)

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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

Louis XIII of France (1601-1643)

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Louis XIII of France (1601-1643)
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, hydratides 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 etc

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 Bankes

“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.”

Giovanni Battista Morgagni (1682-1771)

1682 – born, Forli Italy, comfortable circumstances
1701 – University of Bologna M.D. (prosector for Vesalius, 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 anatomiam indigatis
1771 – died, Padua

“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 . . . .”
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

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.


Why not Berg disease?

1882-1964
Internist and pathologist
1911 – first association of eosinophils and allergic reactions (NY Med J, 93:15-19)
1925 - thrombotic thrombocytopenia purpura (TTP; Moschkowitz disease [Arch Int Med, 36:89-93]

1899 – joins Surgery department after studying with Billroth
1914 – Department of Surgery organized into four divisions: Neurosurgery (Charles Ellisberg) 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)
... 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.

What about Ginzburg and Oppenheimer?

And how does Paul Klemper fit into our story?

My source...

Sadao Otani (1892-1969)

Sadao Otani, M.D.

1892  Born, Kuwana-mie, Japan
1918  M.D., Chiba Medical College
1920  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.

Table 1: Acceptance of modern drugs and surgery

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

Stanley M. Aronson, M.D.

Sigmund Freud (1856-1939)

Alfred Adler (1870-1937)

Margit Freud Klemperer
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 Postgraduate 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 ...

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

"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.
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 714 cases of ‘atypical ulcerative colitis’
- Ginzburg collects data on 712 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

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

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.

Hod Paul Klemperer (1887-1964)

References


Questions

1. Which of the following national leaders most likely suffered from Crohn disease?
   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

How 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

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

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

Figure 3. Emil Kraepelin (1856–1926)

First description of AD

Clinicians by day, histopathologists by night...

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

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

Normal Aging

AD

First observation of senile plaques—in the brains of deceased epilepsy patients...
One of the fathers of modern Neurohistology / Neuroanatomy

- Developed silver impregnation techniques…..used today in many NP laboratories
- Senile plaques (silver stain)
- Neurofibrillary tangles and neuropil threads (silver stain)
- Cerebral amyloid angiopathy (Congo red)
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—
Glenner & 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 Sci. 11:205 cited 1300+ times

Cited 660+ times (WOS)

Established clin-path correlation.....imperfect though it remains !!
CONTRIBUTIONS of NEUROPATHOLOGY to DEMENTIA RESEARCH - 1

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Characterizing neuropathologic component of AD Tg animal models
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”

CONTRIBUTIONS of NEUROPATHOLOGY to DEMENTIA RESEARCH -2

2000s: Recognition of the ‘universe’ of non-AD dementias---including DLBD, FTLD 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, Fieder)
1965-70’s: Recognition of the high incidence of AD (with vascular dementia) and the similarity in dementia caused by AD and CVD (e.g. Blessed, Tollefsen, Roth et al.)
1965-70’s: Description of detailed cellular/structural pathology of AD/HDAC by Ellis, Warriner, Terry and many others
1970-80’s: Evolution of immunohistochemistry (e.g. in study of AD-specific lesions (NFTs, amyloid)
1984: Isolation (G. Glenner) of brain microvascular amyloid from AD patients and characterization of beta/tau protein—subsequent evidence that beta protein is identical to NFTs and CAA and tau and microvascular amyloid are +/- identical
1993: Cloning of beta propertin/k4 precursor (APP, APP)
1985-90’s: In vitro studies of k4, APP and transgenic mouse models of AD
References


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
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USCAP 2015, Boston, Massachusetts
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“Boston Pathology: The Founders and Their Descendants”

Robert H. Young, David N. Louis, Michael J. O'Brien

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