Newsletter



March 2019

History of Pathology Society Officers

President: Susan Lester

President-Elect: Henry Tazelaar Past President: Gabriella Nesi

Secretary-Treasurer: Santo V. Nicosia

Trustees:

Daniel Kurtycz (2018-2021) Fabio Zampieri (2018-2021) Stephen A. Geller (2017-2020)

History of Pathology Society Meeting Gaylord Resort & Convention Center, National Harbor, MD, USA Sunday, March 17, 2019, 3:30-5:30 p.m.

United States and Canadian Academy of Pathology Meeting

Molecular Insights into Our Historical Past: Medical Museum Collections as Irreplaceable Biorepositories

Moderator, Susan Lester, MD, PhD, Brigham and Women's Hospital, Boston, MA

Course Description

Medical museum specimens provide a window into our historical past as revealed by information on human pathogens, inherited disease, and tumor biology. Unfortunately, the few surviving collections may be in peril due to challenges in maintaining specimens and a lack of appreciation of their value. This session will review the state of historical biorepositories in the United States, Canada, and Europe, discuss important studies on historical specimens, and suggest steps that can be taken to preserve these irreplaceable resources.

3:30	Overview of Historical Collections in the United States and Canada Julie Lemmon, MD, Sumner Regional Medical Center, Gallatin, TN
3:45	The 1918 Influenza Virus: How Understanding a Scourge of the Past Informs Our Future
	Jeffery Taubenberger, MD, PhD, National Institute of Health, DC
	European Historical Collections and their Role in Biomedical Research
4:15	Gabriella Nesi, MD, PhD, University of Florence, Italy
4:45	The Future of Our Past: A Call to Action to Preserve Our Medical Heritage
1,10	Susan Lester, MD, PhD, Brigham and Women's Hospital, Boston, MA
	Julie Lemmon, MD, Sumner Regional Medical Center, Gallatin, TN
5:00	Business Meeting

Molecular Insights into Our Historical Past: Medical Museums as Irreplaceable Biorepositories

History of Pathology Society – 2019 Moderated by President Susan C. Lester, MD, PhD







Schedule

- Overview of Historical Medical Museum Collections in the United States and Canada
 - · Julie Lemmon, MD
- The 1918 Influenza Virus: How Understanding a Scourge of the Past Informs Our Future
 - Jeffery Taubenberger, MD PhD- National Institute of Health
- European Historical Collections and their Role in Biomedical Research
 - Gabriella Nesi, MD PhD- University of Florence
- The Future of Our Past: A Call to Action to Preserve Our Medical Heritage
 - · Susan Lester, MD PhD- Harvard Medical School/Brigham and Women's Hospital

Overview of Historical Medical Museum Collections in the United States and Canada

Julie Lemmon, MD





The Rise of Medical Museums

- · Historical necessity
- · Scarcity of teaching materials
- Flexner Report- 1910



The Fate of Medical Museums?

- · Shifting focus of medical education
- Ability to reproduce and share images
- · Expense of maintenance and valuable real estate





#IAMUSCAP

Medical Museums Today- Pilot Study

- Identify existing US and Canadian biorepositories
- · Today's uses
- Future: increase accessibility, provide collaboration



Medical Museums Today- Pilot Study

- Historic museum specimens that retain biomolecules (pre-1970)
 - · Primarily wet specimens (tissue in fixative)
 - · Osteological specimens
 - Slides
 - Blocks



Medical Museums Today- Pilot Study

- 70 medical museums documented to exist prior to 1970s
 - · Noted in Flexner Report, Billings
- · Lester, Lemmon, Hall, and Wright investigated collections
- 13 still exist, at least partially catalogued

Medical Museums Today- Pilot Study

•80% discarded or lost to history





Medical Museums Today- Pilot Study

- Traditional uses
 - Teaching
 - Research
 - · Community engagement
- · Emerging use: historical biorepository



Medical Museums Today- Pilot Study

- · 12 of 13 available for research
- · 6 of 13 currently involved in modern biomedical research



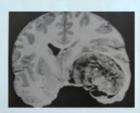




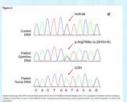
Harvey Cushing Treated the First Known Patient With Carney Complex

Cynthia J. Tsay,¹ Constantine A. Stratakis,² Fabio Rueda Faucz,² Edra London,² Chaido Stathopoulou,² Michael Allgauer,³ Martha Quezado,³ Terry Dagradi,⁴ Dennis D. Spencer,⁵ and Maya Lodish²

Tsay, CJ, et al, Journal of the Endocrine Society, 1:1312, 2017







Earliest documentation of a patient with Carney Complex by DNA sequencing.

Dr. Harvey Cushing Brain Collection - Yale University

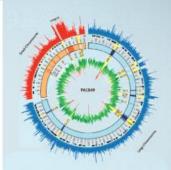


The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Second-Pandemic Strain of Vibrio cholerae from the Philadelphia Cholera Outbreak of 1849

Alison M. Devault, M.A., G. Brian Golding, Ph.D., Nicholas Waglechner, M.Sc., Jacob M. Enk, M.Sc., Melanie Kuch, M.Sc., Joseph H. Tien, Ph.D., Mang Shi, M.Phil., David N. Fisman, M.D., M.P.H., Anna N. Dhody, M.F.S., Stephen Forrest, M.Sc., Kirsten I. Bos, Ph.D., David J.D. Earn, Ph.D., Edward C. Holmes, Ph.D., and Hendrik N. Poinar, Ph.D.

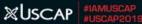


Devault AM, et al, New England Journal of Medicine 370:334-340, 2014.

Vibrio cholera DNA recovered from an intestinal specimen of a victim of the 1849 cholera epidemic demonstrated changes that could be associated with greater pathogenic capacity.

Mutter Museum









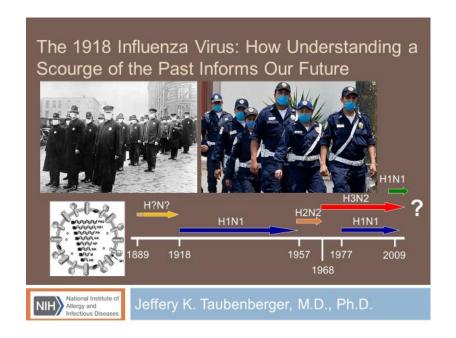
HISTORY OF MEDICINE

Influenza Cataclysm, 1918

David M. Morens, M.D., and Jeffery K. Taubenberger, M.D., Ph.D.

Morens DM, Taubenberger JK, NEJM 379:2285-2287, 2018.

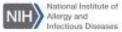






1918 Influenza Pandemic





1918 'Spanish' Influenza Mortality

- Total global deaths in the 9 months of the pandemic in 1918-1919 estimated to be 50-100 million^{‡,*}
- U.S. Deaths = 675,000
- Flu deaths in Philadelphia in October 1918 = 10,959.
 Total flu deaths = 15,785
- U.S. Military deaths to flu = 43,000 (out of ~100,000
 U.S. Troop casualties in WWI)
- Deaths in Virginia = 17,604; in Richmond = 1240 (~1% of population)



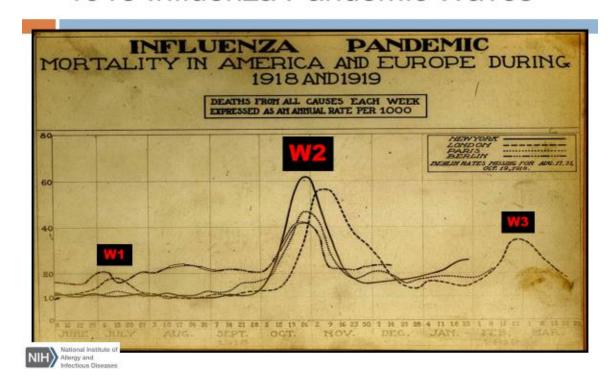
[‡]Johnson NP, Mueller J. (2002) *Bull Hist Med* 76:105-15 *Perspective: ~37 million AIDS fatalities in the last 36 years

US Soldiers with 1918 Influenza, Ft. Riley, KS

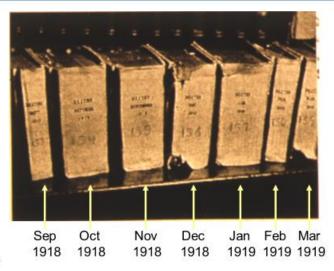




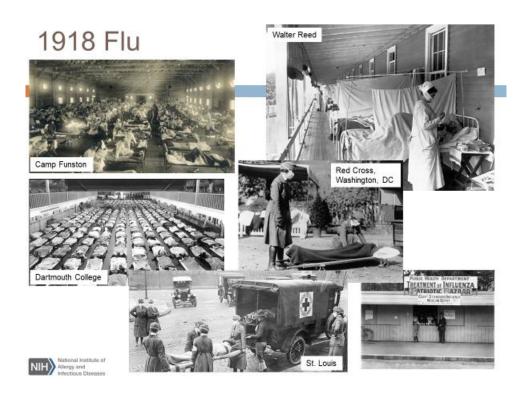
1918 Influenza Pandemic Waves



Death Registry, Oregon 1918-19

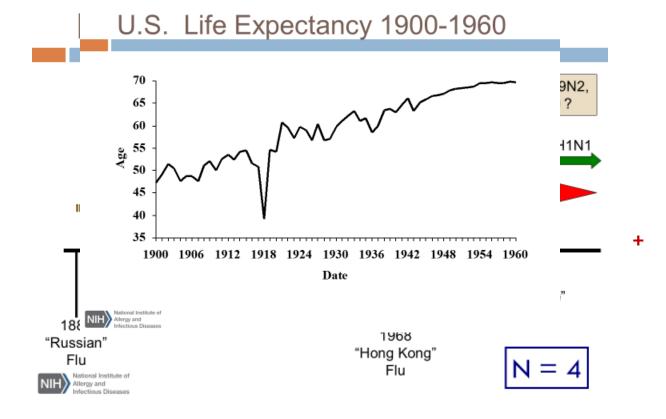




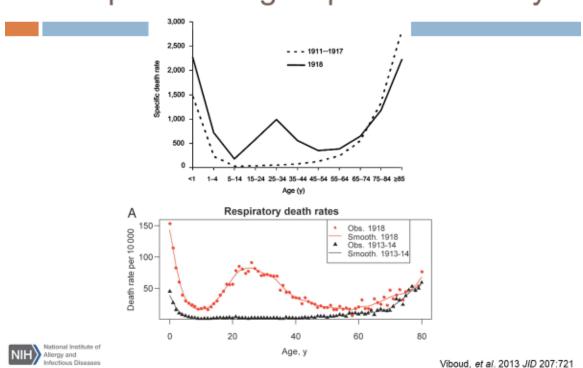






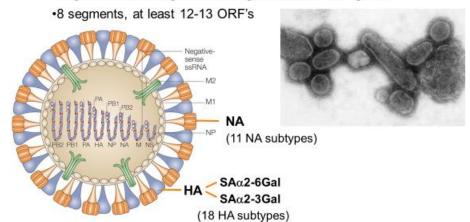


Unique 1918 Age-Specific Mortality



Influenza A virus

- # Family: Orthomyxoviridae
- •Negative sense, segmented, single-stranded RNA genome



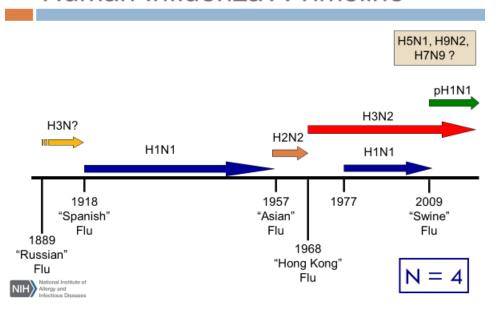
NIH) National Institute of Allorgy and Infectious Diseases

"Shift and Drift"

Influenza A Virus Host Range Quite Diverse

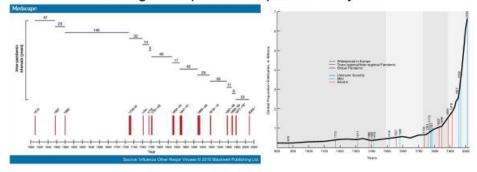


Human Influenza A Timeline



Influenza Pandemics in History

- ~14 pandemics in last 500 years
- · Average interpandemic period ~36 years



Hunting for the 1918 Influenza Virus

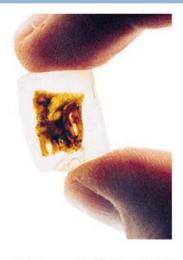
- Concept of viruses as infectious agents still new in 1918
- No isolates of virus made during pandemic
- Influenza A viruses first isolated from pigs in 1930 and from humans in 1933





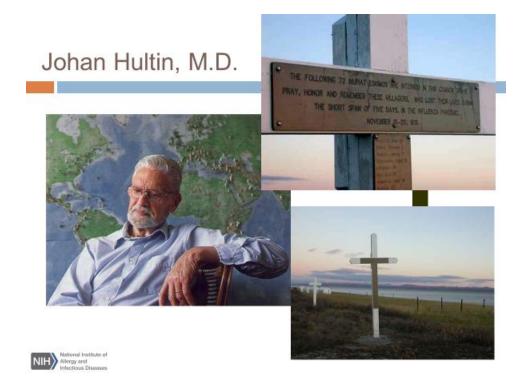
1918 Influenza Autopsy Cases







Taubenberger, et al. 1997 Science. 275:1793 Taubenberger, et al. 2005 Nature. 437:889



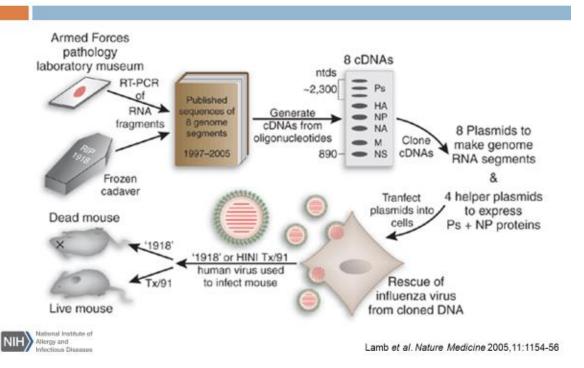
1918 Flu in Teller Mission, Alaska

- Teller Mission (now Brevig Mission) was an isolated Inuit village on the Seward Peninsula of Alaska
- Pandemic hit in November, carried by mail courier (traveling by sled dog)
- Local outbreak last 5 days
- 72 people killed (85% adult population), leaving dozens of orphans
- Johan Hultin performed an exhumation in 1951



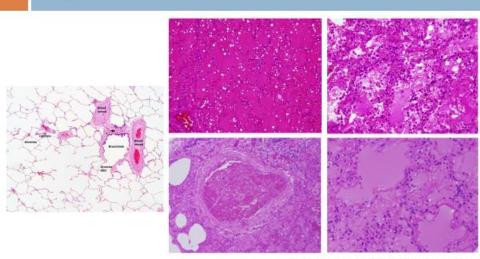


'Resurrecting' the 1918 Influenza Virus



1918 Lung Pathology

Primary Viral Pneumonia: DAD with edema, alveolitis, thrombi



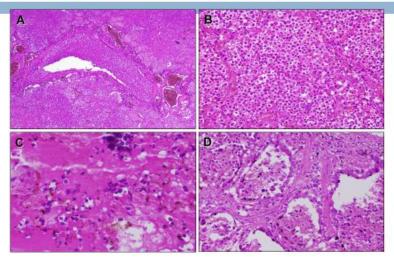
NIH

National Institute of
Allorgy and
Infectious Diseases

Taubenberger & Morens 2008 Ann Rev Path 3:499 Morens, Taubenberger & Fauci 2008 JID 198:962 Kuiken & Taubenberger 2008 Vaccine 26(S4):D59

1918 Lung Pathology

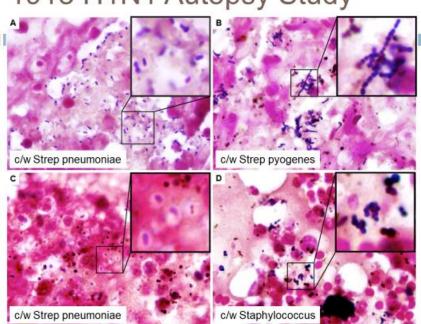
Secondary Bacterial Pneumonia and Repair





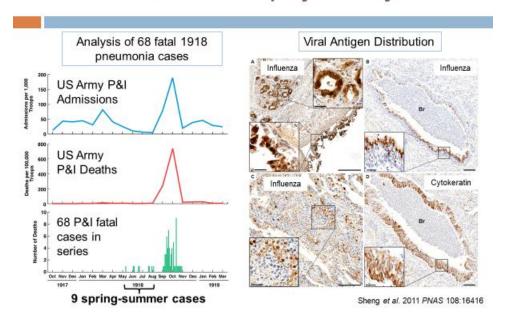
Taubenberger & Morens 2008 Ann Rev Path 3:499 Morens, Taubenberger & Fauci 2008 J/D 198:962 Kuiken & Taubenberger 2008 Vaccine 26(S4):D59

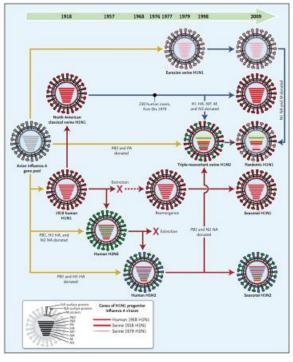
1918 H1N1 Autopsy Study





1918 H1N1 Autopsy Study

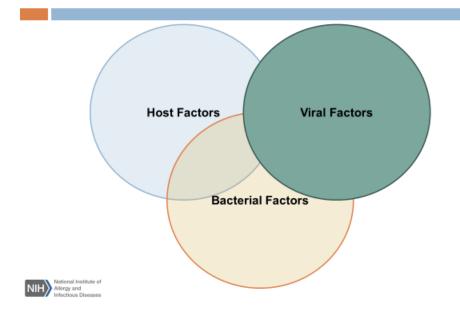




- NIH National Institute of Allargy and
- Since 1918 all pandemic and seasonal influenza viruses descended from the 1918 virus
- All influenza mortality in last 100 years ultimately due to one viral introduction
- Concept of 'pandemic era'

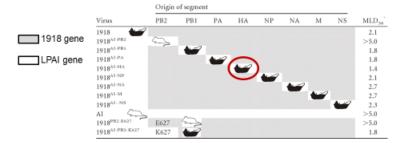
Morens, et al. 2009 NEJM. 361:225-229

Influenza Pathogenicity



Mapping Virulence of the 1918 Influenza Virus - 1918-Avian Single Gene Reassortants

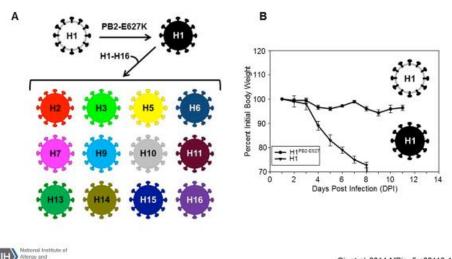
- 1918 HA is the main virulence factor in pathogenicity in mice, ferrets, NHP
- 1918 virus has a very avian-like genome
- Avian H1 HAs did not attenuate 1918 virus, and share virulence with 1918
- 1918 virus virulence therefore likely not pandemic virus-specific but inherited from a low path avian H1 ancestor



What about other low path avian influenza (LPAI) HA subtypes?



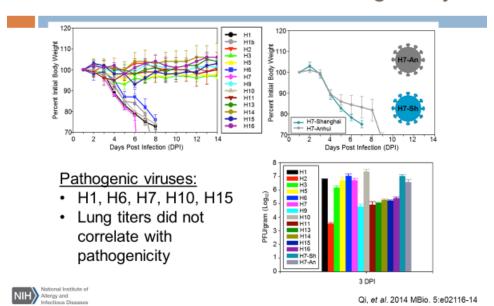
What about other LP Avian HA Subtypes?

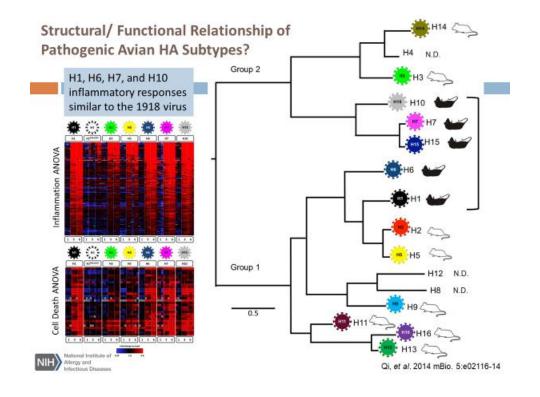


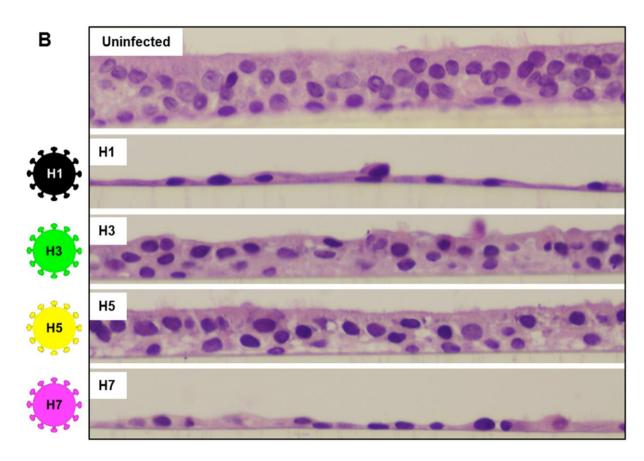
NIH National Institutional Ins

Qi, et al. 2014 MBio. 5:e02116-14

LP Avian Virus Mouse Pathogenicity

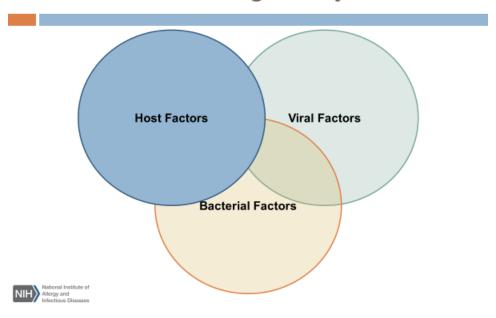




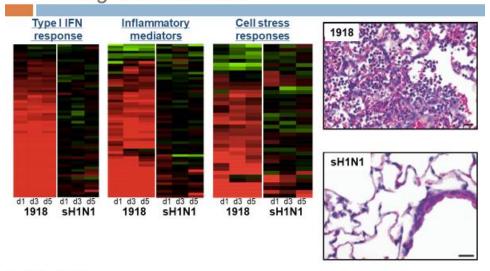




Influenza Pathogenicity



Upregulated Inflammatory Responses During 1918 Infection

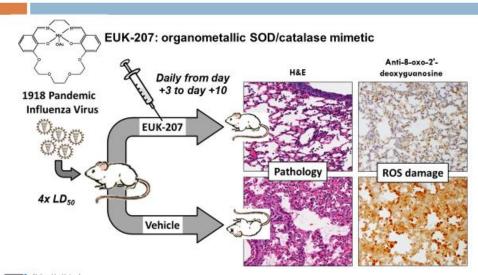


NIH

National Institute of
Allergy and
Infectious Diseases

Kash, et al. 2006 Nature 443:578

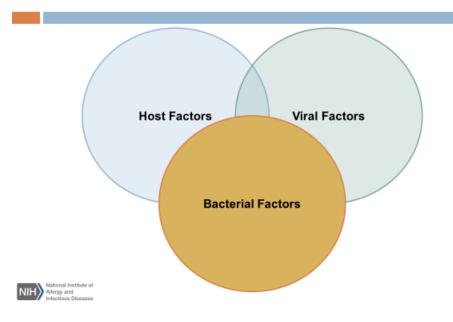
Treatment with a Catalytic ROS Scavenger Decreases Lung Damage and Increases Survival



NIH National Institute of Allergy and Infectious Diseases

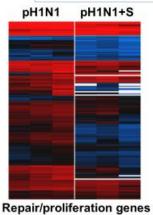
Kash et al. 2014 FRBM 67:235-47

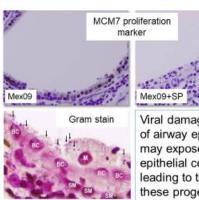
Influenza Pathogenicity



Viral & Bacterial Copathogenesis

pH1N1+SP infection associated with loss of basal cells and absence of re-proliferation and repair of airway epithelial cells



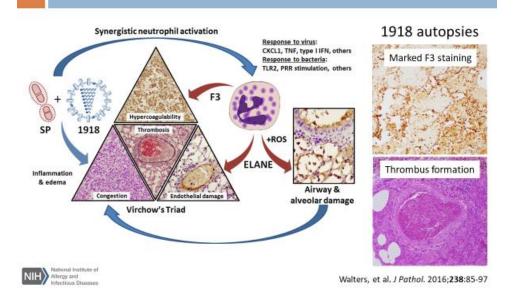


Viral damage to and loss of airway epithelial cells may expose basal epithelial cells to bacteria leading to the death of these progenitor cells, limiting reproliferation

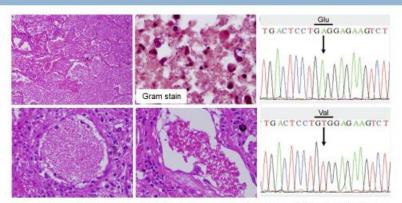


Kash et al. 2011 mBio 2:e00172

Model of Inflammation and Pulmonary Thrombosis during 1918 & SP Co-Infection



1918 Pneumonia Case with Prominent Erythrocyte Sickling



DNA sequence of the hemoglobin beta gene from the 1918 FFPE lung tissue showed **Glu6Val hemoglobin S mutation**, 4 years before term "sickle cell anemia" described

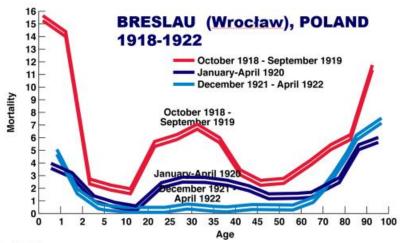


Outstanding 1918 Questions to be Addressed by Archaevirology

- Where and when did the 1918 pandemic virus emerge?
 - Identification of pre-1918 human influenza pnenumonia autopsy tissues
 - What subtype(s) of influenza circulated before 1918?
 - What was the nature of the 1889 pandemic virus?
 - Identification of spring-summer wave 1918 cases
- Studying early post-pandemic evolution of H1N1 viruses
 - Identification of post-1918 human influenza pnenumonia autopsy tissues



Flattening of the "W"





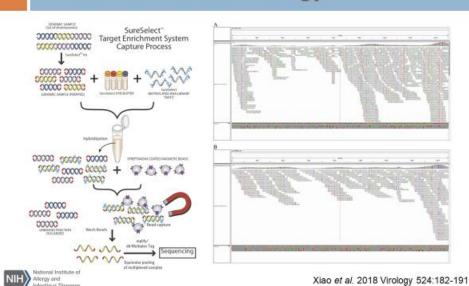
Next Generation Sequencing of 1918 cDNA

1918 sample library sequenced:

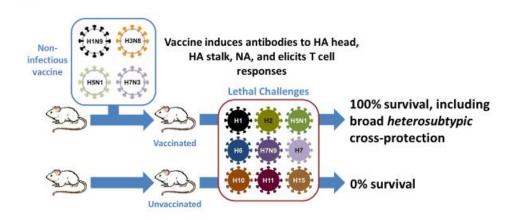
- Complete viral genome at 3000x coverage, including UTRs
- Host gene and bacterial genes well represented in library
- High bacterial representation of Streptococcaceae (Postmortem lung culture pos. for Strep pneumoniae) & Pasteurellaceae (H. influenzae)
- 1918 sample significantly enriched for genes related to host defense and cell death responses as compared to a 2009 pandemic autopsy sample

Xiao et al. 2013 J Pathol 229:535

Positive Enrichment Strategies for Influenza Archaevirology



Tetravalent Vaccine Provides Broad Protection





Park, et al. Unpublished - Confidential

Acknowledgements and Funding

Viral Pathogenesis and Evolution Section, Laboratory of Infectious Diseases, NIH/NIAID

Clinical Studies Unit Matt Memoli, MD, MS Rani Athota, PhD Rachel Bean, MD Adriana Cervantes-Medina Jason Cleath Lindsay Czajkowski, RN, NP Kristina Edwards Luca Giurgea Alison Han, MD Dana Neitzey Susan Reed

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Rodney Levine, NHLBI LB
David Morens, NIAID, OD Cecile Viboud, FIC

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Non-NIH Collaborators

Felice D'Agnillo, FDA Paul Digard, Univ. Edinburgh Susan Doctrow, Boston Univ Maryna Eichelberger, FDA Kevan Hartshorn, Boston Univ Emanuel Petricoin, GMU







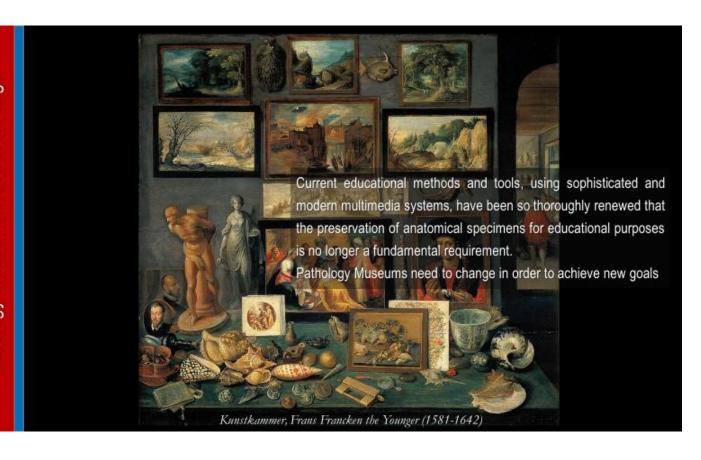








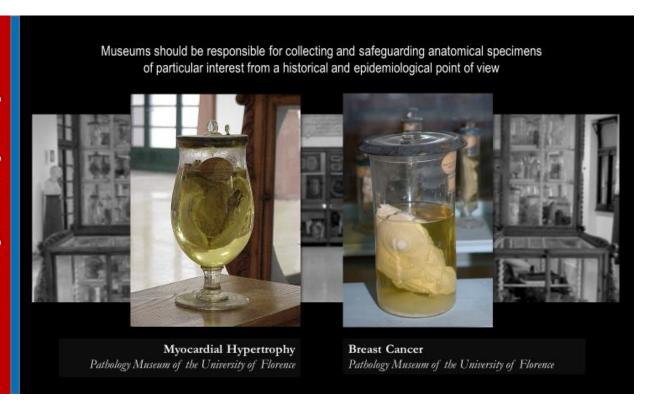






The creation as well as the revamping of a Museum should be based on the use of multimedia and interactive systems. These should include the possibility to offer to scholars collections of pictures of rare and peculiar cases together with historical-documentary information





The History of Pathology Working Group Survey



The results will be used to improve our knowledge of history, location, institutional status, audiences and policies of Pathology Museums across Europe

Preservation of anatomical specimens and facilities is neither easy nor uncostly, and calls for patronage. In order for it to develop, a European Pathology Museum Network should aim to promote the study, access and divulgation of antique collections

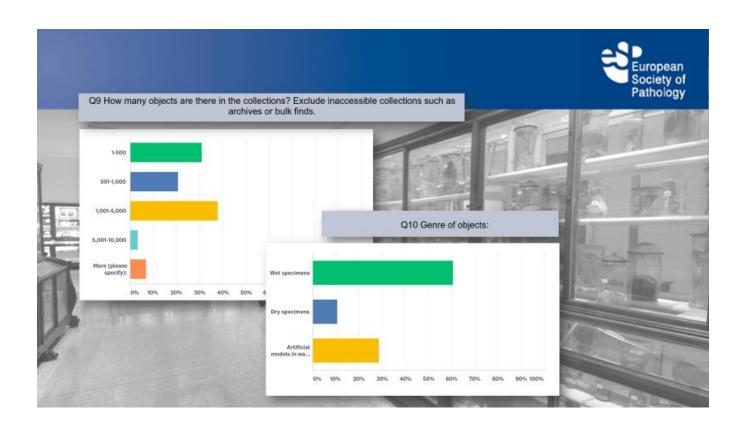


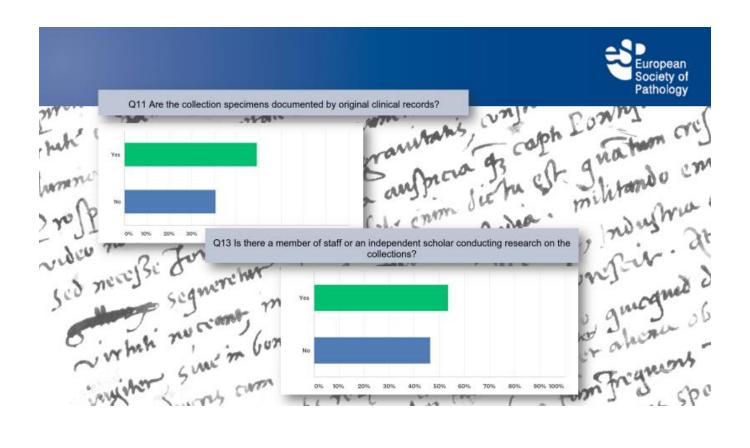
PRELIMINARY RESULTS

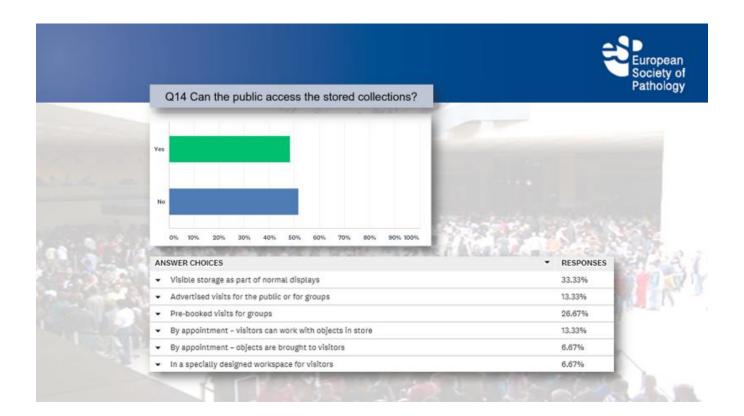


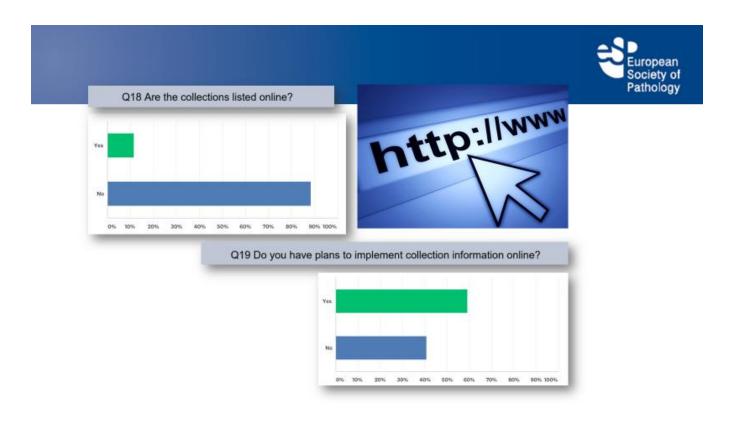


AUSTRALIA	
AUSTRIA	
AZERBAIJAN	
CZECH REPUBLIC	
GERMANY	
HUNGARY	
IRAQI KURDISTAN	
ITALY	
REPUBLIC OF MOLDOVA	
THE NETHERLANDS	
POLAND	
PORTUGAL	
ROMANIA	
SPAIN	
TURKEY	
UKRAINE	
UNITED KINGDOM	









On 15 June 1888, the German Emperor, Kaiser Friedrich III, died of laryngeal cancer. Three biopsies of his laryngeal lesion had been taken by the British laryngologist, Morel Mackenzie, in 1887 and diagnosed by Rudolf Virchow as "pachydermia verrucosa laryngis", confirming Mackenzie's assessment that the Kaiser's disease was benign. A fourth specimen coughed up by the patient was considered by Virchow to be nondiagnostic. A further specimen expectorated by the patient 3 months before his death was diagnosed as carcinoma by Wilhelm Waldeyer.

The autopsy revealed squamous carcinoma in the larynx with a cervical lymph node metastasis. The discrepancies between the initial diagnoses and the final outcome of the Kaiser's disease gave rise to a never-ending medical controversy. Our investigations on this historical case were limited to the official German documents and publications and their English translations and to subsequent literature sources of the time, after having received confirmation that the histological slides and Virchow's original reports had been lost. Based on current surgical pathology knowledge, we propose that the tumour that challenged the diagnostic skills of the founder of pathology was hybrid verrucous carcinoma (HVC), an extremely rare, metastasizing variant of verrucous carcinoma (VC) composed of pure VC mixed with clusters of conventional squamous cell carcinoma. As we see it now, Virchow was therefore not totally wrong. Our retrospective evaluation suggests that Virchow's detailed description of the Kaiser's cancer preceded the paper that contributed to the full understanding of HVC of the larynx by 110 years

The Kaiser's cancer revisited: was Virchow totally wrong?

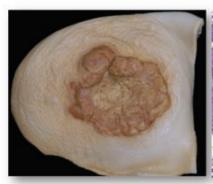
Antonio Cardesa - Nina Zidar - Llucia Alos -Alfons Nadal - Nina Gale - Günter Klöppel

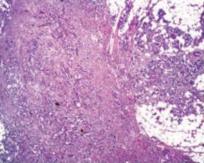


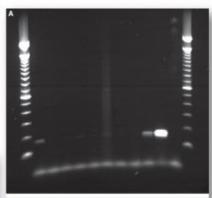
Virehows Arch 2011;458:649-57

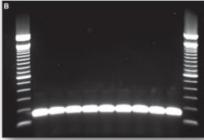
KRAS mutations in historical tumour specimens of the Viennese Museum of pathological anatomy

Sedivy R, Kalipciyan M, Patzak B, Mader RM

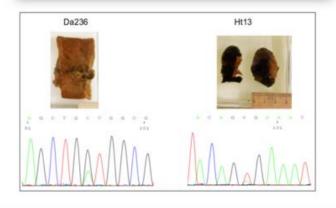


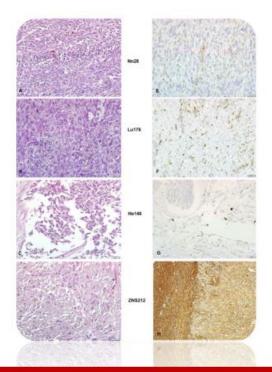






Molecular and Immunohistochemical
Characterization of Historical Long-Term
Preserved Fixed Tissues from Different
Human Organs
Maja Hühns*, Paula Röpenack, Andreas Erbersdobler





PLoS One 2015;10:e0135297





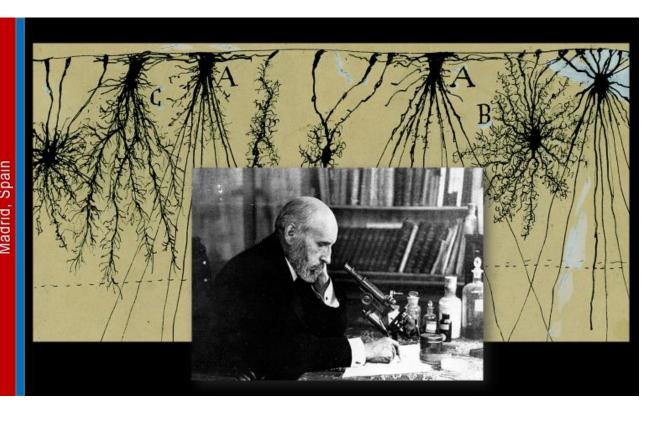




The Medical Historical Museum











"Norwegian scabies" in a wax model at the Pathology Museum of the University of Florence

Nesi G, Santi R, Sestini S, De Giorgi V, Taddei GL

The reproduction in wax of anatomic specimens is considered a glorious Italian tradition, particularly in Florence. Indeed, the work of wax masters which was cultivated for ex-votos and statuary models, together with the development of anatomic studies under the guidance of Paolo Mascagni at the end of the eighteenth century, gave origin to several collections of waxes, among which the collection of the Museum of Anatomic Pathology holds undoubted interest. The so-called "leper", a full-scale reproduction by Luigi Calamai of a man affected with Norwegian scabies, a rare skin disease, is considered the symbol of the Museum

«Impetigine scabida complicata da rogna» Wax Master: Luigi Calamai (1796-1851)

Med Secoli 2008;1:339-49



"N. Ordine 1881 Questo preparato eseguito dal Sig. Egisto Tortori sotto la direzione del prof. Augusto Michelacci è il ritratto fedele di una giovane di 25 anni che fu ricoverata nell'ospedale delle malattie cutanee di Firenze nell'anno 1865. Essa era da molti anni ammalata delle scrofulidi che sono rapprsentate nel preparato"

Text from the Original Catalogue of the Museum

"Scrofulide tubercolare verrucose e flemmonosa della facia", A Case of Cutaneous Tubercolosis, Wax Master: Egisto Tortori (1829-1893)



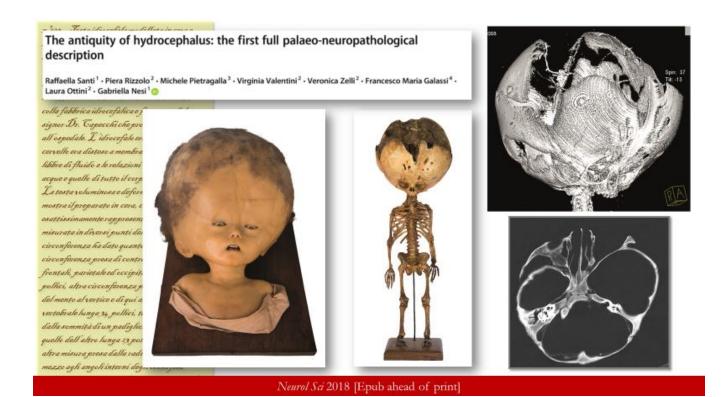
Art and the teaching of pathological anatomy at the University of Florence since the nineteenth century

Gabriella Nesi - Raffaella Santi - Gian Luigi Taddei

In 1840, the University of Florence was the first university in Italy to confer a Professorship in Pathological Anatomy. The origin of this teaching post is linked to the history of the Pathology Museum founded in 1824 by the Florentine *Accademia Medico-Fisica*. The Museum houses anatomical specimens and wax works depicting pathological conditions in the nineteenth century. Both the need to instruct medical students in pathology without resorting to corpse dissection and the difficulty of the lengthy preservation of anatomical preparations made it necessary to produce life-sized wax duplicates of diseased parts of the body. Through the history of the Pathology Museum of Florence, we describe how pathology developed and, in particular, how pathologists from a literary circle laid the foundations of modern surgical pathology in Italy. Museum visits for the medical students guided by lecturers are still today a component of the course of Pathological Anatomy

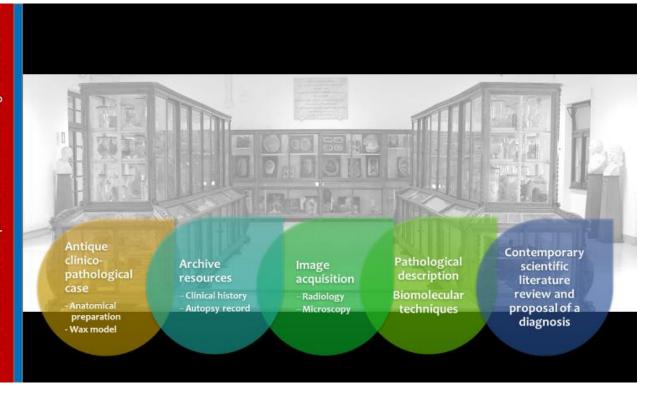


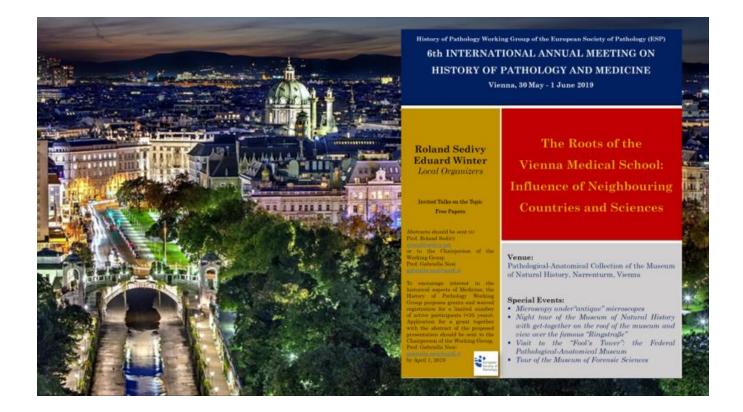
Univentricular Heart in a Newborn Infant Wax Master: Egisto Tortori (1829-1893)



Ancient DNA (aDNA) Extraction







The Future of Our Past: A Call to Action to Preserve our Medical Heritage

Susan C. Lester, MD PhD Julie Lemmon MD

UNLOCKING WUS

XUSCAP #IAMUSCAP



Outlook for existing collections

- · Funding at risk
- · Dedicated space difficult to maintain
- Underappreciated and underutilized





What can we do?

Identify

Support

Brainstorm

Join







Remaining Collections in United States

A		
Collection	Location	Contact
Warren Anatomical Museum – Harvard Medical School	Boston, MA	Dominic Hall MA ALM, Curator
The Mütter Museum	Philadelphia, PA	Anna Dhody, Curator
The National Museum of Health and Medicine	Silver Spring, MD	Brian Spatola, Curator
Mayo Clinic	Rochester, MN	Joseph J. Maleszewski, Director of Tumor Registry Gary L. Keeney, Chairman of Pathology
Dr. Harvey Cushing Brain Collection – Yale University	New Haven, CT	Melissa Grafe, Curator
Old Red Medical Museum – University of Texas	Galveston, TX	Paula Summerly, Research Project Manager
Gordon R. Hennigar Pathology Museum – Medical University of South Carolina	Charleston, SC	Evelyn T. Bruner, MD
University of Maryland	Baltimore, MD	Adam C. Puche
Indiana Medical History Museum	Indianapolis, IN	Sarah M. Halter, Executive Director
Monroe Moosenick Collection – Transylvania University	Lexington, KY	Jamie Day, PhD

Remaining Collections in Canada

Collection	Location	Contact
Maude Abbott Museum – McGill University	Montreal, QC	Richard Fraser, MD- Director
Boyd Pathology Museum – Manitoba Medical College	Winnipeg, MB	Gabor Fischer
William Boyd Collection – University of British Columbia	Vancouver, BC	Helen Dyck, Curator

IDENTIFY

If you know of other existing collections, let us know -

Julie.Lemmon@gmail.com





SUPPORT

Advocate - If you are associated with an institution with a historical tissue collection, take opportunities to show your support.

Visit - Many collections are open to the public.

Funding - Consider opportunities to help collections catalog and preserve their holdings.







BRAINSTORM

Are there other interesting research projects that could be done with historical specimens?

Are there researchers who may not be aware of existing specimens?

Are there are other ways to help preserve these collections?





JOIN

- · Coalition of curators, researchers, pathologists
 - North America
 - · Europe- European Society of Pathology History of Pathology Working Group
 - · All other locations- similar groups??
- Website to connect and serve as resource
- Collection description, scope, and point of contact
- Resource for research scientists
- · Increase visibility
- Send contact information to Julie.Lemmon@gmail.com



