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History of Pathology Society Companion Meeting
Vancouver Convention Center, Vancouver, BC, Canada
Sunday, March 18, 2018, 3:30-5:30 p.m.

United States and Canadian Academy of Pathology Annual Meeting

Disease and Environment: Relevant Achievements throughout History
Moderator, Gabriella Nesi, MD, PhD
University of Florence, Italy

Course Description
A recent report by the World Health Organization recognizes that environmental risk factors are associated with approximately 25% of the global disease burden. Therefore, environmental hazard prevention and control could effectively help in improving public health. While living in healthy surroundings is still a challenge, scientific knowledge of environment-related illnesses can boast an impressive background. The session will focus on the complex interaction between disease and the environment in historical contexts, highlighting specific (lung, liver, urinary bladder) tumors.

<table>
<thead>
<tr>
<th>Time</th>
<th>Presentation</th>
</tr>
</thead>
</table>
| 3:30 | An All-Pervading Enemy: Environmental Causes of Disease Through the Ages  
Gaetano Thiene, MD, University of Padua, Italy |
| 4:00 | Lung Cancer
Henry Tazelaar, MD, Mayo Clinic, Scottsdale, Arizona |
| 4:20 | Liver Cancer
Stephen Geller, MD. Weill Cornell Medical Center, New York, NY |
| 4:40 | Urinary Bladder Cancer
Gabriella Nesi, MD, PhD, and Raffaella Santi, MD, University of Florence, Italy |
| 5:00 | Business Meeting |
An All-Pervading Enemy: Environmental and Behavioral Causes of Cardiovascular Disease

Gaetano Thiene
Emeritus Professor, Cardiovascular Pathology – University of Padua, Italy

The natural history of human body is featured by pathological events, which account for organ and tissue remodeling, morbidity and eventually death. Evolution dictated that we should be mortal to ensure human turnover. Medicine, which is the “Guardian of life and health against death and disease” (1), is able nowadays to guarantee optimal life span and welfare in the Western Countries.

Health- and life-threatening causes may be classified as environmental, malnutrition, infections, trauma, toxic, genetically determined, neoplasms, and cardio-cerebro-vascular. Atherosclerosis represents the “malignant” disease of the cardiovascular system (2). Behavior and life-style play a not so minor role.

Elucidation of human anatomy, physiology and pathology, as well as of cells, substructures and biological chemistry; development of anesthesis; discovery of bacteria and viruses; clarification of inheritance and genetics as another way to transmit disease; knowledge of immune system and invention of vaccination; discovery of antibiotics; heating, food, development of body imaging and electrocardiography; molecular pharmacotherapy; surgical/interventional procedures, all have extended life expectancy, reduced morbidity and improved quality of life, well beyond the most optimistic hopes (3).

In the last 30 years life expectancy increased 6 years. The “shares” of this extraordinary gain belongs to achievements in Cardiovascular Medicine (3.8 years), followed by decrease of injuries (0.7), perinatal fatalities (0.5), treatment of neoplasms (0.3), others (0.8), whereas chronic obstructive pulmonary disease (-0.2) and AIDS (-0.1) played an adverse trend (fig. 1) (4).

As far as determinants of premature death, behavioral patterns (40%) and genetic predisposition (30%), social circumstances (15%), poor health care (10%) and environmental exposure (5%) represent the main factors (fig. 2). Among behavior patterns, smoking and obesity/inactivity ranked first, followed by sex habits, alcohol, motor vehicle accidents, guns, drugs (fig.3), thus indicating that life expectancy largely depends from individual life style (5).

In USA (1980-2000), the number of deaths due to coronary artery disease, prevented or postponed as a result of changes in population risk factors, was not negligible (about 150,000): 20% due to systolic blood pressure and 24% for serum cholesterol decrease, 12%
with smoking cessation, 5% with increased physical activity, whereas mortality augmented by 10% for diabetes and 6% for obesity (fig.4) (6).

On the other hand, the percentage of prevented or postponed deaths in USA (#159.330), thanks to medical or surgical treatments, were due to care of acute myocardial infarction/coronary syndromes (10%), post infarction, chronic angina, coronary artery bypass/ percutaneous angioplasty follow up (16%), heart failure including heart transplantation (9%) up, drug control of hypertension (7%), serum cholesterol reduction by statins (5%) (fig.5) (6).

The decrease of deaths due to coronary artery disease, whether for treatment or risk factor changes, differed from country to country. In USA (1968-1976) treatment held 40% of shares vs 54% of prevention, whereas in Finland 76% of decrease was explained by prevention vs 24% by treatment (fig. 6) (6). However, despite these indisputable results, there is an alarming trend of increase in coronary artery disease mortality in the age interval 35-44 years, both in male and female (fig. 7) (7).

It is predictable that in the next 20 years drugs and technological development will still play a key role in improving health- life expectancy, whereas preventive medicine, pointing to risk factors including genetics, will be the protagonist thereafter (fig. 8) (8).

REFERENCES

**FIGURES**

Figure 1. The fight against cardiovascular disease accounted for 3.8 years gain of life expectations in the last 30 years (4).

Figure 2. Factors accounting for premature death. Behavior plays the major role (5).
Figure 3. Behavioural risk factors for death: smoking and obesity rank first (5).

<table>
<thead>
<tr>
<th>Causes</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>39,925</td>
<td>12%</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>68,800</td>
<td>20%</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>82,830</td>
<td>24%</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>17,445</td>
<td>5%</td>
</tr>
<tr>
<td>Body mass index</td>
<td>-25,905</td>
<td>-8%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-33,465</td>
<td>-10%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>149,635</strong></td>
<td><strong>44%</strong></td>
</tr>
</tbody>
</table>

Figure 4. In the time interval 1980-2000 the number of deaths by coronary artery disease decreased by 44%. Control of systolic blood pressure, smoking and physical activity were the protagonists, whereas death due to obesity and diabetes increased (from Ford ES et al., N Engl J Med 2007) (6).
<table>
<thead>
<tr>
<th>Condition</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myocardial infarction – Unstable angina</td>
<td>35,145</td>
<td>10%</td>
</tr>
<tr>
<td>Secondary prevention after myocardial infarction</td>
<td>28,565</td>
<td>8%</td>
</tr>
<tr>
<td>Chronic angina</td>
<td>17,730</td>
<td>5%</td>
</tr>
<tr>
<td>Secondary prevention after CABG or PTCA</td>
<td>7,435</td>
<td>3%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>30,235</td>
<td>9%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23,845</td>
<td>7%</td>
</tr>
<tr>
<td>Statin for lipid reduction, primary prevention</td>
<td>16,580</td>
<td>5%</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>159,330</strong></td>
<td><strong>47%</strong></td>
</tr>
</tbody>
</table>

*Figure 5.* The success of medical/surgical treatment accounted for a decrease of cardiovascular death by 47%: less mortality of acute myocardial infarction (10%), medical and surgical treatment of chronic ischemic heart disease (17%), heart failure treatment (9%), hypertensive therapy (7%), primary and secondary prevention of coronary artery disease including lipid reduction (6).

*Figure 6.* Overall decrease in death (prevented or postponed) in USA was due almost equally by medical/surgical treatment (40%) and control of risk factor (54%) whereas in Finland the intervention on risk factors (76%) prevailed vs treatment (24%) (6).
Figure 7. After 2000, there is a trend of increase in coronary artery disease interval, both in male and female (7).

Figure 8. Prediction of the impact of intervention vs prevention in the next decades (from Braunwald E, J Am Coll Cardiol, 2003) (8).
AN ALL-PERVADING ENEMY: ENVIRONMENTAL CAUSES OF DISEASE THROUGH THE AGES

Gaetano Thiene
University of Padua, Italy

Disclosure of Relevant Financial Relationships

The faculty, committee members, and staff who are in position to control the content of this activity are required to disclose to USCAP and to learners, any relevant financial relationship(s) of the modules or narratives that have occurred within the last 12 months with any commercial interest(s) whose products or services are related to the USCAP content. USCAP has reviewed all disclosures and resolved or managed all identified conflicts of interest, as applicable.

The following faculty reported no relevant financial relationships: Gaetano Thiene.

USCAP staff associated with the development of content for this activity reported no relevant financial relationships.

The fight against cardiovascular disease accounted for 3.8 years gain of life expectations in the last 30 years

Factors accounting for premature death. Behaviour plays the major role.

In the time interval 1980-2010 the number of deaths by coronary artery disease decreased by 44%. Control of systolic blood pressure, smoking and physical activity were the protagonists, whereas death due to obesity and diabetes increased

<table>
<thead>
<tr>
<th>Factors</th>
<th>% Change</th>
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</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>-12%</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>-20%</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>-24%</td>
</tr>
<tr>
<td>Physical activity</td>
<td>-5%</td>
</tr>
<tr>
<td>Body mass index</td>
<td>-8%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-10%</td>
</tr>
<tr>
<td>Total</td>
<td>-44%</td>
</tr>
</tbody>
</table>
The success of medical/medical treatment accounted for a decrease in cardiovascular death by 47%. The mortality rate of acute myocardial infarction (1.9%), medical and surgical treatment of chronic ischemic heart disease (1.7%), heart failure (1.5%), hyperlipidemia (1.3%) primary and secondary prevention of coronary artery disease including lipid reduction (1.2%) decrease as a result of the treatment of primary prevention of coronary artery disease.

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke arterial infarction</td>
<td>31,945</td>
<td>10%</td>
</tr>
<tr>
<td>Non-ST infarction</td>
<td>22,055</td>
<td>8%</td>
</tr>
<tr>
<td>Venous infarction</td>
<td>7,730</td>
<td>5%</td>
</tr>
<tr>
<td>Primary prevention</td>
<td>7,235</td>
<td>3%</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>16,580</td>
<td>5%</td>
</tr>
<tr>
<td>Total</td>
<td>170,284</td>
<td>47%</td>
</tr>
</tbody>
</table>

(From Robitaille et al., R.Engl Med. 2008:356:2388)

(Overall decrease in death (prevention=to posthospitalization) in USA was due to a reduction in the use of secondary prevention of coronary artery disease including lipid reduction (1.2%) and control of risk factor (1.4%) whereas in Europe due to the intervention on risk factors (1.5% primary and secondary prevention of coronary artery disease including lipid reduction (1.2%)).

After 2000, there is a trend of increase in coronary artery disease interval, both in male and female.

(From Robitaille et al., R.Engl Med. 2008:356:2388)

Prediction of impact of interventions on prevention in the next decades

(From Robitaille et al., R.Engl Med. 2008:356:2388)

REFERENCES

Major Environmental Causes of Lung Cancer throughout the Ages

Henry D. Tazelaar, MD
Geraldine Zeiler Colby Professor of Cytopathology, Mayo Clinic Arizona

While cigarette and other forms of smoking could be considered environmental causes of lung cancer in that patients choose to smoke and create an environment around them which is unhealthy, there are other major environmental causes of lung cancer which were known prior to conclusions regarding the association of smoking and lung cancer.

Perhaps the earliest scientific information we have on risks comes from the medieval period. A skeleton exhumed in Schleswig, Germany from a 40-50-year-old man showed the presence of multiple osteolytic bone lesions and high levels of antimony in his bones. The patient may have been a sailor exposed to coal tar in the building and maintaining of boats, which are rich in carcinogenic polyaromatic hydrocarbons (PAH), or a metal worker/blacksmith.

During the Renaissance at least 27 physicians are known to have written about diseases of miners. “Schneeberg lung disease” was described in the Saxony region of Germany associated with mines being established in 1410 (silver, nickel, cobalt, bismuth, arsenic). It was thought to be due to a combination of COPD and pneumoconiosis. But in the late 1800s, radiation in and around mines began to be measured (radon-222 released from uranium), and it was ultimately confirmed to be the cause of the deadliest cases of “Schneeburg lung disease”. The Third Reich recognized this and made improvements in mine ventilation through the “First Ordinance on Occupational Diseases of the German Reich” (1925). When the Soviets took over the region they camouflaged these mines as containing bismuth, and ignored the safety precautions made by the Germans, leading to an excess 9000 deaths in the race to build an atomic bomb and nuclear power plants. A similar story took place in Western Colorado in the development of the nuclear bomb under the guise of the Manhattan project. Uranium mine companies did not protect their workers in the U.S. either, leading to an excess of 4000 deaths. Dr. Geno Saccomanno used material from these Colorado patients to describe the cytologic changes which occur during the progression from squamous metaplasia to squamous cancer and that both squamous and small cell carcinoma were most closely associated with radiation exposure.

Diseases due to silica exposure, specifically silicosis, have been known for centuries, the earliest records we have coming from the Greeks. The association of silica exposure to lung cancer, however, is a hotly disputed topic. Most of the evidence suggests that there is an association particularly when silicosis is present.
The association between asbestos exposure and lung cancer was researched in England, Germany and the United States between 1935 and 1953, with the Germans again out ahead determining that there was a causal relationship as early as 1943. Dr. R. Doll (United Kingdom) studied the link among workers at the Turner Brothers Asbestos Company, published his results over the objections of the company, but unfortunately for many workers it took years for asbestos to be banned. In the USA, it took until 1989 for the United States Environmental Protection Agency to ban most asbestos containing products. In 1991, however, after a legal battle, some of the forms of asbestos were once again allowed to be used.

There are numerous other environmental and occupational causes of lung cancer well outlined in the Field WR and Withers BL article published in 2012.

Associations between environmental and occupational exposures in the development of lung cancer are often difficult to prove and companies as well as countries have been masters at camouflage. Much work continues today, and pulmonary pathologists continue to contribute to the field.

REFERENCES


Major Environmental Causes of Lung Cancer Through-Out the Ages

Henry D. Tazelaar, M.D.
Geraldine Zeiler Colby Professor of Cytopathology
Chair, Department of Laboratory Medicine and Pathology
Mayo Clinic Arizona

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Outline

- Introduction
- Medieval risks
- Renaissance risks
  - Uranium-radon
  - Modern Risks
    - Asbestos
    - Others (too many to name!)
- Conclusions

Introduction

- Lung cancer in never smokers is the 7th leading cause of cancer mortality
- A top ten killer in the US

RM 42

- Medieval skeleton from Schleswig, Germany
- Among 250 exhumed well preserved bodies, 11th–12th century cemetery
- Not as well preserved as some bodies from the cemetery in part due to disease

RM 42

- Gross exam
- Radiographs
- Microscopy
- Trace element analysis and comparison to others
- Hypotheses
**RM 42 - Occupational Theory #1**

- Sailor?
- Exposed to coal tar building and maintaining boats
- Coal tar rich in polyaromatic hydrocarbons (PAH)

**Sailor?**
- Exposed to coal tar building and maintaining boats
- Coal tar rich in polyaromatic hydrocarbons (PAH)

**Tarring the Boat**
1873
Edouard Manet
– In the public domain

- Could he have been a metal worker?

**Vulcan Forging the Thunderbolts**
Peter Paul Rubens, 1638
– In the public domain

- May be the first autopsy of a patient with an occupationally induced lung cancer

**Renaissance period**

- At least 27 physicians write about diseases of miners from 15-17th century ("Bergsucht")
- 1567: On the Miner’s Plague and Other Illnesses (Paracelsus)

**Schneeberg Lung Disease**

- Saxony region: Schneeberg, St. Joachimsthal (thaler)
- First mines 1410
- Silver, nickel, cobalt, bismuth, arsenic
- Initially described a combination of COPD and pneumoconiosis

**RM 42 - Trace Elements mg/gm**

<table>
<thead>
<tr>
<th>Element</th>
<th>All Adult</th>
<th>Aged Adult</th>
<th>Males</th>
<th>RM 42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co</td>
<td>0.528</td>
<td>0.486</td>
<td>0.289</td>
<td></td>
</tr>
<tr>
<td>Cs</td>
<td>0.035</td>
<td>0.011</td>
<td></td>
<td>1.584</td>
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<tr>
<td>Mg</td>
<td>1.533</td>
<td>1.629</td>
<td>1.151</td>
<td></td>
</tr>
<tr>
<td>Sb</td>
<td>0.186</td>
<td>0.119</td>
<td>13.940</td>
<td></td>
</tr>
<tr>
<td>Sc</td>
<td>0.002</td>
<td>0.002</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Zn</td>
<td>165.3</td>
<td>119.4</td>
<td>111.3</td>
<td></td>
</tr>
</tbody>
</table>

**Grupe G. Am J Phys Anthropol 1988:75;369-74**

- RM 42
- Trace Elements mg/gm

- Element
- All Adult
- Aged Adult
- Males
- RM 42

- Co: 0.528 (0.486), 0.289
- Cs: 0.035 (0.011), 1.584
- Mg: 1.533 (1.629), 1.151
- Sb: 0.186 (0.119), 13.940
- Sc: 0.002 (0.002), 0.001
- Zn: 165.3 (119.4), 111.3

- In the public domain
Schneeburg Lung Disease

- Saxony region: Schneeburg, St. Joachimsthal (thaler)
- First mines 1410
- Silver, nickel, cobalt, bismuth, arsenic
- Initially described a combination of COPD and pneumoconiosis

- Early 19th century mine shafts were going deeper
- Young aged men, cough, expectoration, SOB
  - 60-80% of miners died of lung cancer

Schneeburg Lung Disease - A multidisciplinary discovery

- FH Harting, miners’ doctor at Schneeburg
- W Hesse, physician in neighboring Schwarzenberg
  - Autopsies on miners 1860’s
- K Schiffner, Freiberg Mining College
  - Measured radiation in and around mines (1890)
- HE Muller, “union rep” suspected lung cancer in miner while he was still alive

- Uranium emits Radon-222 (α particles)
- “A single bronchial epithelial cell that has sustained genetic damage can initiate lung cancer”
- Silicosis necessary?
- Led to some improvements in mine ventilation
  - 1925: “First Ordinance on Occupational Diseases of the German Reich”
Camouflage

- USSR
  - Wismut (Bismuth) Corporation 1946-1990
  - 100,000 workers, 400 shafts, 15 mills
  - > 9000 deaths

Uranium Mineral Belt

Four Corners region of southwest USA

The Manhattan Project

"Ventilating the mines is unnecessary and too expensive." Witschi H. Toxicol Lett 2001;164:4-6.

Development of Carcinoma of the Lung as Reflected in Exfoliated ratios


Chimney Sweeps

- Exposed to soot, carbon, other inorganic material and PAH's
- Standardized incidence ratio of 1.49
- Also in Firefighters, masons, heating and ventilation workers


Holding ponds at Uranium processing mill in Uravan, Montrose County, Colorado (in the public domain)
Silica and Lung Cancer
- Sandblasters
- Glass manufacture
- Construction
- Denim
- Oil and gas extraction
- Agriculture

Relationship of Silica Exposure to Carcinoma of the Lung
- Disputed topic
- There most likely is an association when silicosis is present
- Whether silica exposure without silicosis causes lung cancer is unresolved but attribution of a cancer to silica exposure in an individual case is dubious
- There may be dust type (e.g., cristobalite) and industry specific associations

Asbestos Associated Lung Cancer
- 1935-1953
  - England, Germany and US
  - 1943 - German consensus was that there was causal relationship
  - 1953 Dr. R Doll (UK) studies the link among workers at Turner Bros. Asbestos, publishes over objections of the company
  - 1989 EPA ban most asbestos containing products somewhat overturned in 1991 court case

Other Environmental/Occupational Causes of Lung Cancer
<table>
<thead>
<tr>
<th>Toxic</th>
<th>Environmental/Occupational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diesel exhaust</td>
<td>Drivers, loaders</td>
</tr>
<tr>
<td>PAH</td>
<td>Coal gasification, coke production, foundry workers</td>
</tr>
<tr>
<td>Benzene, lead, phthalates, chromium, Ni</td>
<td>Painters</td>
</tr>
<tr>
<td>Nitrosamines, asbestos contaminated samples, PAH phthalates</td>
<td>Rubber workers</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Glass and ceramic workers, fireworks manufacturing, textile production</td>
</tr>
<tr>
<td>Beryllium</td>
<td>Aircraft, space vehicles and defense industries</td>
</tr>
</tbody>
</table>

Conclusions- Environmental Causes of Lung Cancer
- Associations between environmental and occupational exposures often difficult to prove
- Companies and countries have been masters at camouflage and cover-ups
- Earliest occupation assoc with lung cancer may be builders of pyramids but little surviving proof
- Much work continues today
- Pulmonary pathologists continue to contribute
Rudimentary discussions of cancers involving the liver have been found in the Rigveda (~4000 BCE), the oldest Indo-European book, written in Hindu Sanskrit, which alludes to malignant tumors in general and in the Ramayana (~2000 BCE), an Indian epic poem which similarly considers malignant tumors. The first unequivocal reference to liver cancer is in the writings of Aretaeus (1st or 2nd century) who suggested that liver cancer follows hepatitis. Galen (129-210) described liver tumors. More than 1500 years later, Morgagni (1682-1711) described "steatomata" or "hard" tumors of the liver and provided the first autopsy description of cancers of the liver, which were almost certainly metastatic. Matthew Baillie (1763-1829) extended Morgagni's work, describing "large white tubercles" in the liver and comparing them with "scirrhous" of other organs, but did not definitely distinguish neoplasia from tuberculosis, syphilis and other conditions. Gaspard Bayle (1774-1816) gave the first clear descriptions of liver cancer and affirmed that the lesions described by Morgagni were true cancers and that they resembled breast cancer.

The earliest attempt to classify liver cancers based on macroscopic features was by Hanot and Gilbert in 1888. This was modified by Eggel in 1910. Soon after, in 1911, Yamigawa proposed a microscopic classification for liver tumors. In the same year, Goldzicher and Bokay also classified liver cancers based on their histopathology. The modern classification of liver tumors is primarily based on the work of Edmondson and Steiner in 1954.

Primary liver cancer, including hepatocellular carcinoma is the second most common cause of cancer mortality worldwide, accounting for 9% of all reported cancer deaths. Its incidence is increasing and is currently the most rapidly rising solid tumor in the United States.

There are many hundreds of environmental agents incriminated in liver injury, with many of them, including aflatoxin, anabolic steroids, arsenicals, hepatitis B and C, thorotrast (thorium dioxide), monomeric vinyl chloride and others clearly associated with the development of primary malignant tumors.

Aflatoxin is a fungal contaminant of foods, including peanuts, corn, rice and others and, in the laboratory, is the most potent of hepatocarcinogens. In some regions of the world it is responsible for significant numbers of cases of hepatocellular carcinomas (HCC).
hepatitides, hepatitis B and C, are also significant cause of HCC although the development of specific vaccines and effective therapies will likely lead to marked reduction in the incidence of occurrence of these conditions, if not eradication.

Hepatic angiosarcoma is a relatively rare malignancy that is strongly associated with exposure to arsenicals, thorium dioxide (thorotrast) and vinyl chloride. Landmark studies of the pathobiology of hepatic angiosarcoma in the 1970s and '80s contributed to greater understanding of carcinogenesis in general.

Dozens of "internal environmental factors," metabolic/genetic, also predispose to the development of liver cancers. In many patients, however, a specific etiology may not be clinically identified.

Continuing improvement in our ability to identify the molecular and immunohistochemical markers of hepatic cancers themselves, as well as their precursor states, will allow for even greater precision in diagnoses as well as more effective therapies and preventive measures.

REFERENCES

Disease and Environment: Liver Cancer

History of Pathology Society
March 18, 2018

Stephen A. Geller, M.D.
Weill-Cornell Medical College, New York

Understanding of cancer
Hippocrates (460-370 BC): introduced the word “cancer” or “cancrum”

Galen (130-201 AD): “Scirrhus is a hard, heavy, immobile, and painful tumor; cancer is a very hard malignant tumor, with or without ulceration. Its name comes from the ancient word for rock.”

Vicarious (1821-1902): cancer arises as metaphasia of connective tissue, from cells into cells

Retzius (1794-1858): skin cancer arises from the epithelium, not the connective tissue

Waldeyer (1836-1921): carcinomas of internal organs arise from the epithelium, carcinoma spreads by direct extension and by embolus through veins and lymph channels

Ewing (1866-1948): “Neoplastic Diseases”

Malignant epithelial liver tumors

- Primary
  - Hepatoblastoma
  - Hepatocellular carcinoma (HCC)
  - Fibrolamellar carcinoma (FL-HCC)
  - Intrahepatic cholangiocarcinoma
  - Hepatobiliary cystadenocarcinoma
- Secondary (metastatic)

Liver tumors and etiologic associations

Liver cancer, including hepatocellular carcinoma (HCC), accounts for 9.1% of all reported cancer deaths.

Liver cancer is the second most common cause of cancer mortality worldwide.

HCC incidence is the most rapidly rising of solid tumors in the United States.

Overall there >750,000 new cases/year with >250,000 deaths/year in China.
Don’t forget the **internal environment:**

Worldwide, liver cancer is more common in men (~55,000/year) than women (~22,800) year.

In experimental models of aflatoxin carcinogenesis male rats have an earlier onset and higher incidence of cancer when compared to female rats.

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**Primary carcinoma of the liver - historical background**

- Rigveda (1500 BC): oldest Indo-European book: Hindu Sanskrit - alludes to malignant tumors
- Ramayana (200 BC): Indian epic poem alludes to malignant tumors
- Haeusler-Smitty papers (1881-1883)
- Hirschsprung (1879): introduced the word “tumor” as "carcinoma" as a descriptive term for all new tissue formations which could not be cured - distinguished "scirrhous," a hard type of tumor, from soft "carcinoma" - clinical description of breast and skin cancers
- Averan stones (1907): regarded liver cancer as result of hepatitis
- French (1280-1350): early description of liver cancer
- Morgagni (1811): founder of pathologic anatomy - described "scirrhous" as "broad" tumors of the liver - first cataloged description of cancers of the liver, almost certainly metastatic.

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**Primary carcinoma of the liver - Morgagni forward**

- Matthew Baillie (1761-1823): extended Morgagni's work - described "large white infiltrated" in the liver, comparing them with "scirrhous" in other organs - could not distinguish neoplasms from tuberculosis, cirrhosis, and other diseases
- Guillard Baillie (1794-1875): first clear description of cancer of liver - showed that "scirrhous" of Morgagni (and "white infiltrated") of Baillie were true cancers, similar in cancer of breast - thought that metastasis represented a constitutional cancerous diathesis
- Thomas Hodgkin (1798-1866): understood nature of cancer, including metastasis.

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**Primary carcinoma of the liver - histopathology**

- Rudolf Virchow (1821-1902): defined primary and metastatic
- Leblanc and Krous (1874): two types of primary liver cancer
- Sabourin (1876): design primary liver tumors from malignant
- Hauser and Gilbert (1896): classification of primary liver cancer - early "carnaracters"
- Linch (1909): "carnaracters" - important malignancy of liver cancer
- von Haeckelin (1909): incidence of primary liver cancer
- von Haeckelthorpe (1911): in the differential diagnosis of primary liver cancer
- Lloyd (1919): modified Hauser/Gilbert/TVH "divide" - separated into two histologic types of primary liver cancer ("primary adenocarcinoma")
- Kunitoh and Mimura (1930): "hepatic" and "cholangiocarcinoma" types of liver cancer
- Goldblatt and von Foerster (1959): "hepatic ductal carcinoma" and "cholangiocarcinoma"
- Edmondson and Water (1954): grading of hepatobiliary carcinoma
- Hugh Edmondson (1958): first AFIP fascicle on liver tumors

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**Environment: Aflatoxin**

From fungal contaminant of peanuts, corn, rice, cottonseed, and other foods.

Geographical distribution in regions high in hepatocellular carcinoma.

The most potent experimental hepatocarcinogen.
### Biomarkers

**Biomarker of exposure** – measurement of a specific compound of interest, its metabolite(s) or its specific interactive products in a body compartment or fluid, indicative of the presence of a biological response from exposure to an environmental agent. 

**Biomarker of susceptibility** – indicator or metric of an inherent or acquired ability of an Individual to respond to the challenge of exposure to a specific toxic agent.


### Incidence and mortality rates for HCC are increasing in the United States - why?

- HCV infection
- Influx of immigrants from HBV endemic areas (e.g., China, Taiwan, Korea, Vietnam)
- Increase in numbers of persons living with cirrhosis
- Increase in environmental carcinogens (e.g. aflatoxin)
- HIV
- Obesity epidemic and diabetes mellitus

### Hepatic angiosarcoma

- Rare
- 200-300 new cases worldwide annually
- Peak age 6th and 7th decades
- Exceedingly rare in children
  - Type 2 infantile hemangioendotheliomas
  - Androgens/steroid steroids
  - 7 arsenic exposure
- M:F = 3:1
- Very poor prognosis – no effective therapy
- k-ras mutation ~85%

### Etiology of hepatic angiosarcoma

<table>
<thead>
<tr>
<th>Etiology of hepatic angiosarcoma</th>
</tr>
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<tbody>
<tr>
<td>Exposure/Genetic factor</td>
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<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>Radon</td>
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<tr>
<td>External radiation</td>
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<tr>
<td>Vinyl chloride</td>
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<tr>
<td>Inorganic arsenic</td>
</tr>
<tr>
<td>Copper</td>
</tr>
<tr>
<td>Arsenic</td>
</tr>
<tr>
<td>Thoracic (diaphragm)</td>
</tr>
</tbody>
</table>
Macroscopic features:

- Variegated
- Gray, tan and/or white tissue alternating with small and/or large hemorrhagic areas
- Blood-filled cystic spaces sometimes
- Reticulated pattern of fibrosis with vinyl chloride, thorotrast
- Cirrhosis uncommon (<20%)
Microscopic features - 1:
- Malignant spindle-shaped or irregular endothelial cells with irregular borders
- Lightly eosinophilic cytoplasm
- Hyperchromatic elongated and/or irregular nuclei
- CD31, CD34, F VIII, ulex, etc

Microscopic features - 2:
- Tumor cells grow along preformed vascular channels
- Sinusoidal growth leads to liver plate atrophy and disruption
- Liver cell hyperplasia
- Larger vascular channels ("peliotic") and cavitory spaces develop
- Spaces lined by tumor cells – may have papillary/polyloid projections

Microscopic features - 3:
- Vein (THV, portal) invasion → obstruction
  - hemorrhage, infarction, necrosis
- Solid pattern resembles fibrosarcoma
- Hematopoiesis (especially Thorotrast related)
- May have simultaneous hepatocellular carcinoma or cholangiocarcinoma
Hepatic angiosarcoma - etiologic associations

- Arsenic (villunteers, Fowler's solution for postural hemorrhage)
- Thorotrast (Thorium dioxide)
- Vinyl chloride (monomer)
- Radiation - external, implanted
- T Divin
- T Copper-containing vineyard sprays
- T Iron
- T Steroids
  - T contraceptive pills
  - T anti-estrogen/endorse steroids
  - T diethylstilbestrol
- T Phenacetin (MAG inhibitor)
- T Urlophans
- Idiopathic

- Fibrosis
  - Portal
    - Portal vein wall
  - Intrahepatic
  - Capsular (most characteristic)
- Cholestasis, with bile plugs
- Hepatocyte proliferation
  - Nodules
- Endothelial cell atypia
- Sinusoidal dilation

Constitutional genetic diseases leading to liver tumors

<table>
<thead>
<tr>
<th>Name</th>
<th>Tumor type</th>
<th>Chromosome(s)</th>
<th>Gene(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>von Hippel-Lindau</td>
<td>Hepatocellular carcinoma</td>
<td>3p25-26</td>
<td>VHL</td>
</tr>
<tr>
<td>Hereditary hemorrhagic telangiectasia</td>
<td>Hepatocellular carcinoma</td>
<td>12p11.2</td>
<td>SMAD4</td>
</tr>
<tr>
<td>Cowden syndrome</td>
<td>Papillary thyroid carcinoma</td>
<td>10q23.3</td>
<td>PTEN</td>
</tr>
<tr>
<td>von Hippel-Lindau-like liver disease</td>
<td>Hepatocellular carcinoma</td>
<td>3p25-26</td>
<td>VHL</td>
</tr>
<tr>
<td>Lesch-Nyhan syndrome</td>
<td>Hepatocellular carcinoma</td>
<td>Xq28</td>
<td>HPRT1</td>
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</tr>
</tbody>
</table>

Future directions

- Continuing identification of molecular and immunohistochemical biomarkers
  - predict response to chemotherapeutic agents
  - identify targets, including metabolites (biomarkers) for new in vitro therapies, including preventative
- Increasing use of genetic studies for diagnosis and prognosis
- New forms of non-invasive evaluation (e.g., spectral and other assays)

Thank you for your attention
Environment and Urinary Bladder Cancer: A Historical Perspective

Gabriella Nesi and Raffaella Santi
University of Florence, Florence, Italy

Cancer is not a recently discovered disease and has afflicted people since ancient times. Besides ageing and inherited predisposing conditions, environmental exposure to carcinogens plays a major role in cancer promotion. Known carcinogens include lifestyle habits (e.g. cigarette smoking), natural elements (e.g. ultraviolet light), infective agents, drugs, and pollution (Faguet, 2015). Prevention of exposure to toxins is one of the main goals in the fight against cancer. Multiple environmental factors are considered causative of urinary bladder cancer. A historical perspective of this disease highlights how unveiling the potentially involved environmental factors in carcinogenesis has led to the development of preventive measures, the application of which is still beneficial.

Until the twentieth century, in the wild and windy moorlands of Devonshire, fields of bracken were set ablaze aiming to encourage rainfall (Grieve, 1971). Perhaps not even a drop was generated, but due to this popular belief, a potential carcinogen-promoting agent for urinary bladder carcinoma was inadvertently incinerated. Indeed, many important carcinogens of bladder cancer aetiology occur in nature and may have been present on this planet as long as man (Bryan, 1983). Bracken (*Pteridium aquilinum*) was used by several Pacific Northwestern Indians tribes as a dietary staple as long ago as 14,000 BC, and in more modern times as food for both humans and animals in many parts of the world (Domico, 1979). This fern is now recognised as a potent experimental plant to induce urinary bladder carcinoma (Bryan, 1983). Chemical carcinogenic compounds (e.g. ptaquilosides or ptaquilosides analogues) have been isolated in several kinds of ferns, including bracken fern (Potter, 2000).

Infectious agents are believed to cause over 20% of malignancies worldwide (Bouvard, 2009). *Schistosoma haematobium* is a trematode parasite endemic in Africa and the Middle East, which invades the system venules and capillaries of the human urinary bladder and other pelvic organs (Khaled, 2013). It was Theodor Bilharz (1825-1862) who first identified this blood fluke during an autopsy at the Kasr El Ainy Hospital (Cairo) in 1851 (Bilharz, 1853) (Figure 1). The existence of an association between schistosomiasis and urinary bladder cancer was first theorised by the German surgeon Carl Goebel in 1905 (Berry, 2017). Some years later after investigating 40 autopsy cases, Alexander Robert Ferguson (1870-1920), Professor of Pathology and Microbiology at the Faculty of Medicine in Cairo, reported that urinary bladder carcinoma could be linked to granulomas caused by *Schistosoma*
haematobium (Nash, 1982; Berry, 2017). But it was not until 1994 that this hypothesis was validated by the International Agency for Research on Cancer (IARC) (WHO, 1994). Several paleoparasitological studies have shown that Schistosoma haematobium was already endemic even in Ancient Egypt (Barakat, 2013). Sir Marc Armand Ruffer (1859-1917) started this intriguing journey through time in 1910, when he discovered calcified schistosome eggs in two Egyptian mummies of the 20th dynasty (Ruffer, 1910). Conventional radiology on two other mummies revealed calcified urinary bladders likely to result from Schistosoma haematobium infection (David, 1997). An Egyptian adolescent who lived 5,000 years ago would never have imagined being the earliest documented case of human schistosomiasis, a diagnosis carried out using the enzyme-linked immunosorbent assay (ELISA) (Deelder, 1990). This technique allowed the diagnosis of Schistosoma haematobium infection in two other mummies aged 3,000 and 4,000 years, respectively (Contis, 1996). The first contact of Europeans with Schistosoma occurred in 1779 during the 3-year French invasion of Egypt. Many soldiers are believed to have been infected as well as Napoleon himself (Ayer, 1966). Increased travel for business, education and tourism between countries has led to unusual schistosomiasis cases in non-endemic countries.

Throughout the centuries, human exposure to natural agents posing urinary bladder carcinogenic hazards is deliberate, with varying degrees of awareness of potential risks. Following the expeditions by Christopher Columbus (1451-1506) at the turn of the XV to XVI century, shipments of gold, silver and precious stones arrived in Europe from the "New World". Just as important from the economic point of view, plants of the Solanaceae family, i.e. potatoes, tomatoes, eggplants and peppers, also reached Europe. Besides these widely used food plants, other species of the Solanaceae family, i.e. Mandragora, Datura, Atropa and Belladonna, were well known for their psychotrophic effects, or for being poisonous. Last but not least, another plant of the same family was introduced: tobacco (Bryan, 1983). Tobacco was used for many centuries in tribal ceremonies by North American Indians. The tobacco smoking culture was introduced into Europe in 1519 by Spanish explorers, and its use spread rapidly to Asia and Africa (Lower, 1982) (Figure 2). John Hill (1716-1775), the English physician and botanist, reported a link between tobacco use and cancer in 1761 (Lower, 1982).

However, evidence that cigarette smoking was etiological for human urinary bladder cancer only came to light in the 1950s (Lower, 1982). It is now widely acknowledged that cigarette smoke contains a huge number of carcinogens, some of which are reported to induce urinary bladder cancer (Chung, 2015). Smoking is the main contributor to this disease in most populations and estimated to cause as many as half of such cases (Freedman, 2011).
In his famous "De morbis artificium" (1700), Bernardino Ramazzini (1633-1714) recommended physicians to add the question “et quam artem exerceat” to the Hippocratic anamnestic interview to accurately evaluate their patients (Ramazzini, 1700). Several neoplastic diseases may occur because of professional or occupational activities. Indeed, urinary bladder cancer was one of the first diseases for which specific industrial chemicals were identified as causative agents of human cancer (Bryan, 1983). In 1895, the German surgeon Ludwig Rehn (1849-1930) described three cases of occupational-related bladder cancer in approximately 45 labourers working with fuchsine dye in Frankfurt, Germany (Dietrich, 2012). The following 50 years saw many other reports regarding workers in several countries. All shared the same characteristics of clusters of industrial exposure to aromatic amines and development of urinary bladder cancer (Bryan, 1983). Benzidine and 2-naphthylamine were classified as potent human urinary bladder carcinogens (Case, 1954). The second major advance in urinary bladder cancer causation studies came in 1938 when the pathologist Wilhelm Carl Hueper (1894-1978) demonstrated that the application of 2-naphthylamine to dogs could trigger the growth of urinary bladder cancers (Hueper, 1938). This major achievement led to the development of laboratory methods to investigate known or suspected chemical carcinogens under controlled conditions. It also provided opportunities to examine the cellular and molecular mechanisms in the pathogenesis of urinary bladder cancer to elucidate these phenomena and create a rational approach for their inhibition or reversal. These epidemiological and experimental studies proved that arylamines caused urinary bladder carcinomas, and several industrialized countries have taken steps to limit or abolish the manufacture of these chemicals (Bryan, 1983).

REFERENCES

FIGURES

*Figure 1.* An Egyptian stamp issued in 1962 to commemorate the centenary of the death of Theodor Bilharz (1825-1862).

*Figure 2.* “Gentlemen Smoking and Playing Backgammon in an Interior” by Dirck Hals, 1627.
Figure 3. In 1856 William Henry Perkin (1838-1907), a chemistry student, produced fortuitously the first aniline dye, subsequently called “mauvine”. In the picture a silk skirt and a blouse dyed with Sir Perkin’s purple colour.
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Environ Health Perspect 1983;49:201-207
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Infectious agents are believed to cause over 20% of malignancies worldwide. Schistosomiasis, a water-borne parasite endemic in Africa and the Middle East, invades small vessels in the human urinary bladder and other pelvic organs. Increased travel for business, educational, and tourist purposes between countries has led to unusual schistosomiasis cases in non-endemic countries.

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