Newsletter

February 2018

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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.

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 anesthesia; 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

1. Morgan J. A discourse upon the Institution of Medical Schools in America. Philadelphia: William Bradford 1765
2. Thiene G. More Basic Research on Atherosclerosis to find targeted therapy and improve prevention. Circulation 2013;128:f54
3. [No authors listed]. Editorial – Looking back on the Millennium Medicine. N Engl J Med 2000;342:42-49
4. Lenfant C. Clinical research to clinical practice – lost in translation? N Engl J Med 2003;349:868-74
5. Schroeder SA. Shattuck lecture – We can do better improving the health of the American people. N Engl J Med 2007;357:1221-8
6. Ford ES, Ajani UA, Croft JB, Critchley JA, Labathe DR, Kotke TE, et al. Explaining the decrease in US deaths from coronary disease, 1980-2000. N Engl J Med 2007:356:2388-98
7. Ford ES, Capewell S. Coronary heart disease mortality among young adults in the US from 1980 to 2002: concealed leveling of mortality rates. J Am Coll Cardiol 2007;50:2128-32
8. Braunwald E. The Simon Dack Lecture – Cardiology: the past, the present, and the future. J Am Coll Cardiol 203;42:2031-41

FIGURES

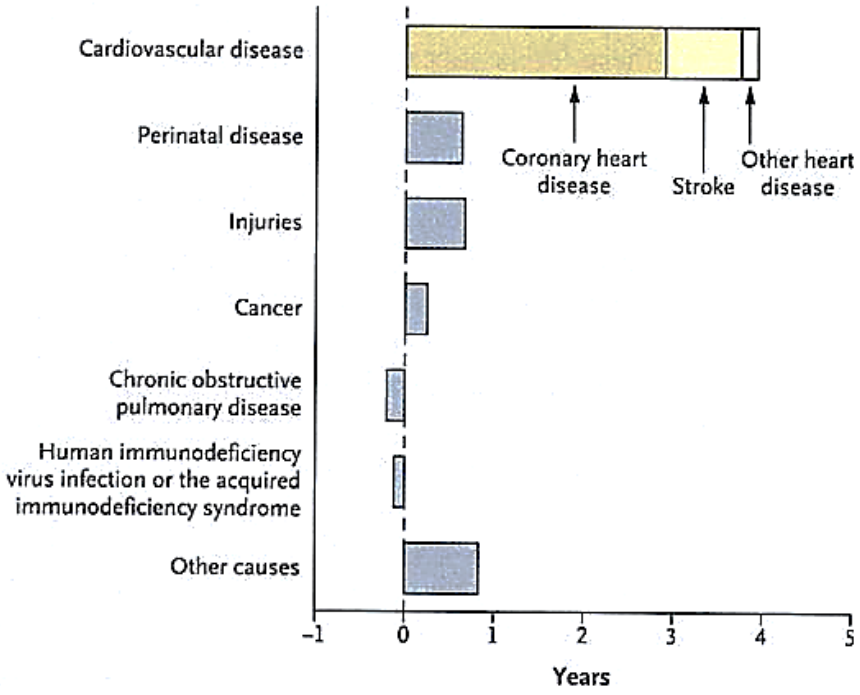

Figure 1. The fight against cardiovascular disease accounted for 3.8 years gain of life expectations in the last 30 years (4).

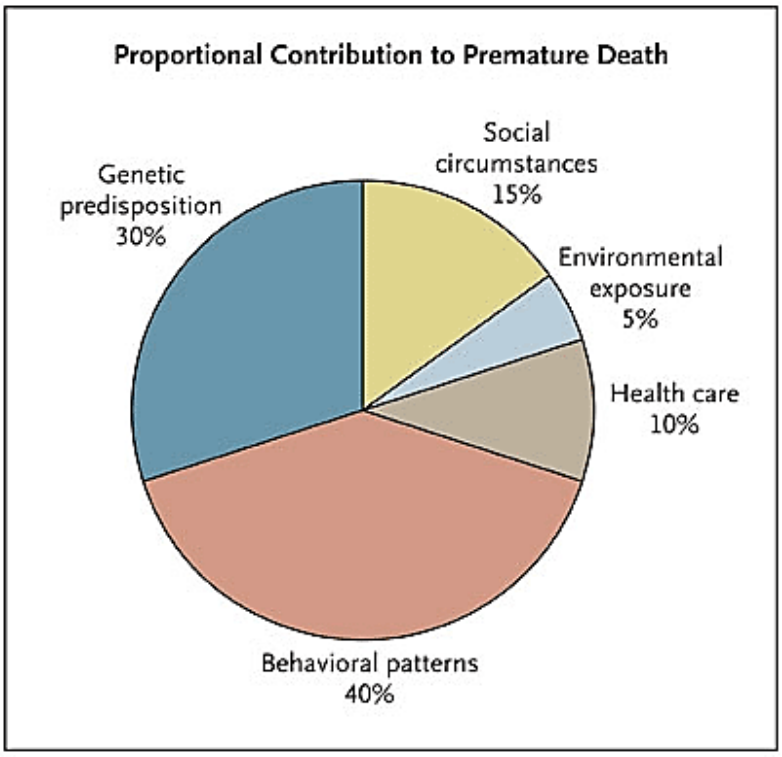

Figure 2. Factors accounting for premature death. Behavior plays the major role (5).

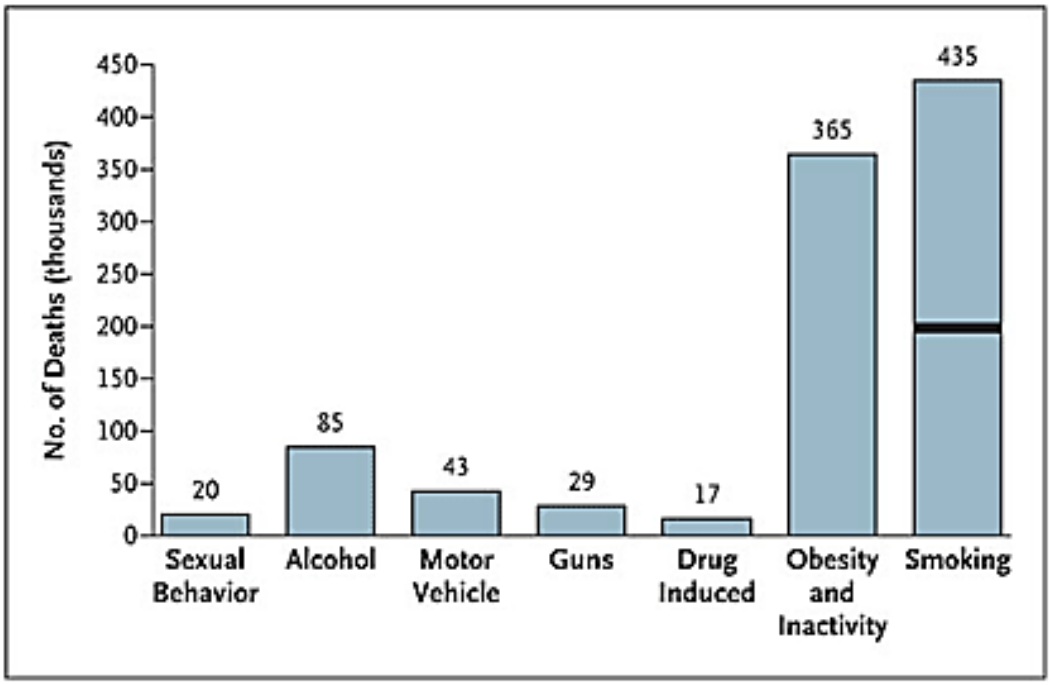

Figure 3. Behavioural risk factors for death: smoking and obesity rank first (5).

Causes	Number	%
Smoking	39,925	12%
Systolic blood pressure	68,800	20%
Cholesterol	82,830	24%
Physical inactivity	17,445	5%
Body mass index	- 25,905	-8%
Diabetes	- 33,465	-10%
Total	**149,635**	**44%**

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).

	Number	%
Acute myocardial infarction – Unstable angina	35,145	10%
Secondary prevention after myocardial infarction	28,565	8%
Chronic angina	17,730	5%
Secondary prevention after CABG or PTCA	7,435	3%
Heart failure	30,235	9%
Hypertension	23,845	7%
Statin for lipid reduction, primary prevention	16,580	5%
TOTAL	**159,330**	**47%**

Figure 5. The success of medical/surgical treatment accounted for a decrease of cardiovascular death by 47%: less mortality of acute myocardial infiltration (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).

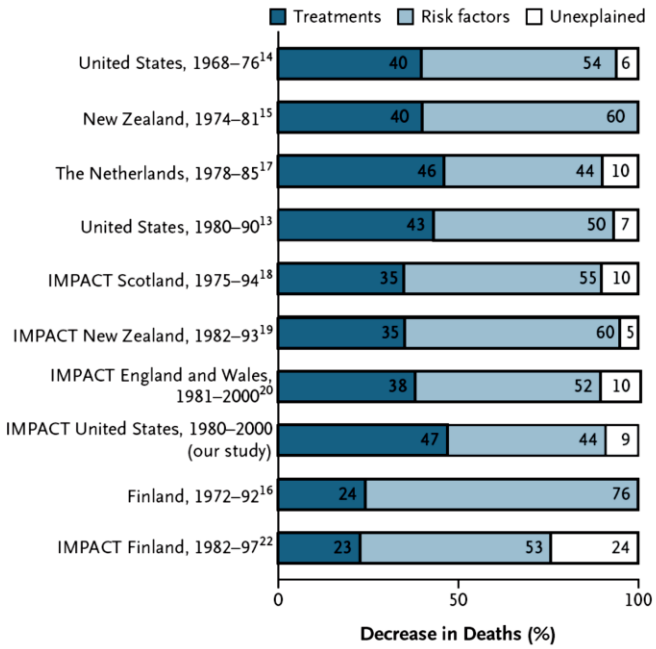

Figure 6. Overall decrease in death (prevented or postponed) in USA was due almost equally by medical/surgical treatment (40%) and control of risk factor (54%) whereas in Finland the intervention on risk factors (76%) prevailed vs treatment (24%) (6).

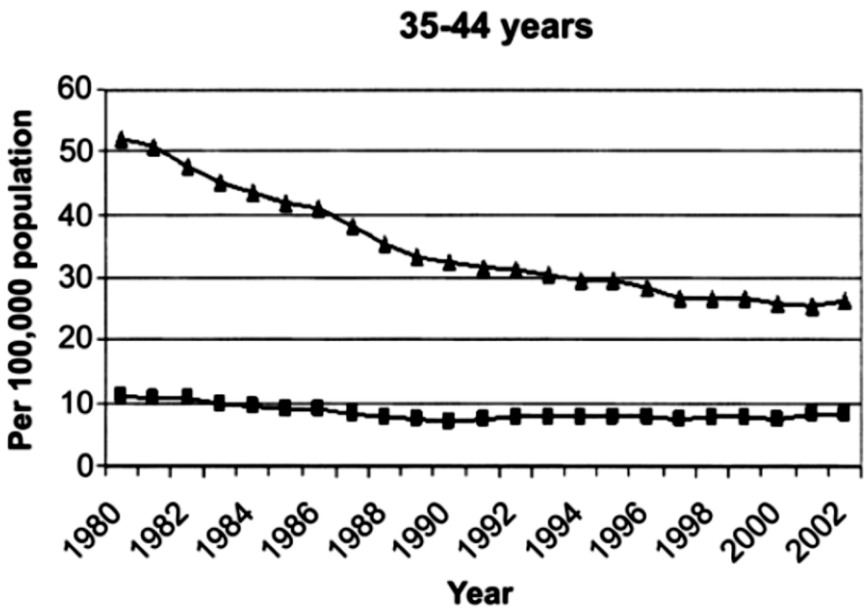

Figure 7. After 2000, there is a trend of increase in coronary artery disease interval, both in male and female (7).

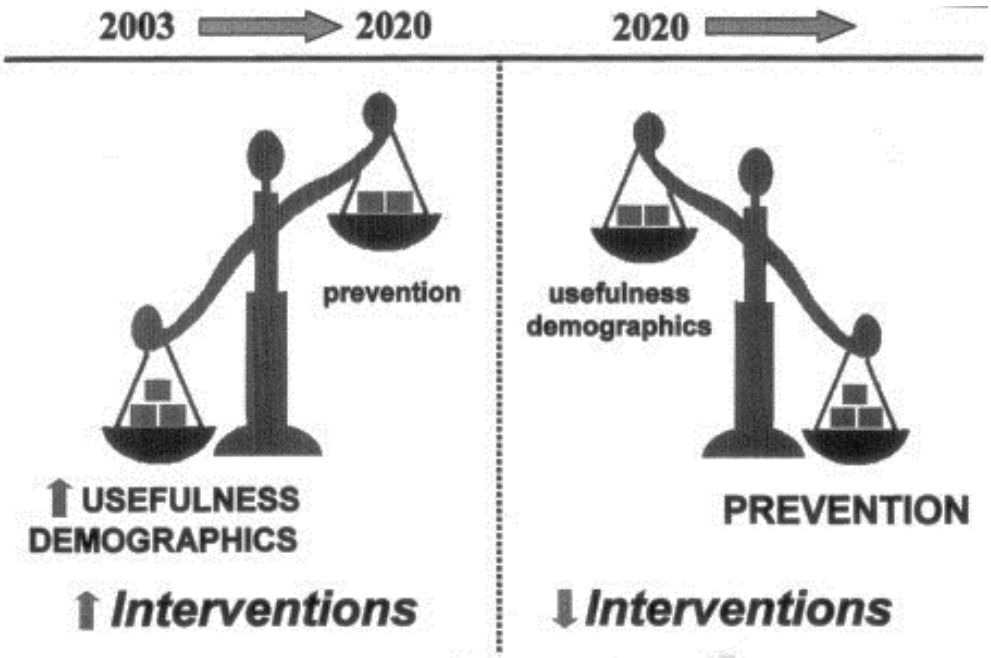

Figure 8. Prediction of the impact of intervention vs prevention in the next decades (from Braunwald E, J Am Coll Cardiol, 2003) (8).

AN ALL-PERVADING ENEMY: ENVIRONMENTAL CAUSES OF DISEASE THROUGH THE AGES

Gaetano Thiene
University of Padua, Italy

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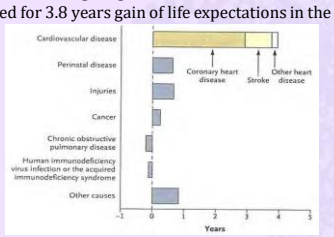
Disclosure of Relevant Financial Relationships

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 individual or spouse/partner that have occurred within the last 12 months with any commercial interest(s) whose products or services are related to the CME 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

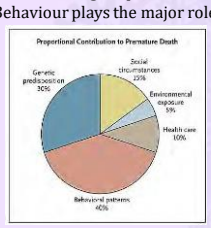
USCAP staff associated with the development of content for this activity reported no relevant financial relationships.

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



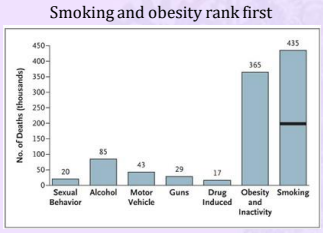
(from Lenfant C, N Engl J Med 2003:349:868-74)

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



(from Schroeder SA, N Engl J Med 2007:357:1221-8)

Behavioural risk factors for death: Smoking and obesity rank first



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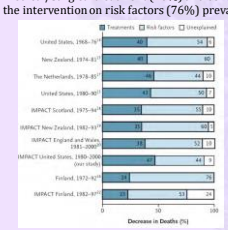

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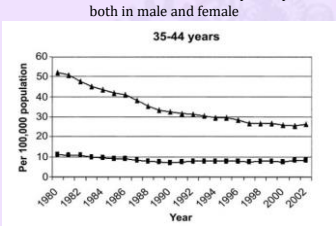
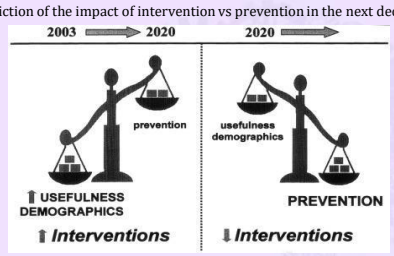


(from Ford ES and Capwell S, J Am Coll Cardiol 2007;50:2128-32)

Prediction of the impact of intervention vs prevention in the next decades



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REFERENCES

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THANK YOU

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

1. Archer VE, Saccomanno G, Jones JH. Frequency of different histologic types of bronchogenic carcinoma as related to radiation exposure. Cancer.1974;34(6):2056-60.
2. Dobrzynski L, Fornalski KW, Reszczynska J. Meta-analysis of thirty-two case-control and two ecological radon studies of lung cancer. J Radiat Res.2017 Nov 23:1-15. doi: 10.1093/jrr/rrx061.[Epub ahead of print].PMID: 29186473.
3. Enterline PE. Changing attitudes and opinions regarding asbestos and cancer 1934-1965. Am J Ind Med.1991;20(5):685-700.
4. Field RW, Withers BL .Occupational and environmental causes of lung cancer. Clin Chest Med.2012;33(4):681-703.
5. Greenbert M, Selikoff IJ. Lung cancer in the Schneeberg mines: a reappraisal of the data reported by Harting and Hess in 1879. Ann Occup Hyg.1993;37(1):5-14.
6. Greenberg M. A study of lung cancer mortality in asbestos workers: Doll, 1955. Am J Ind Med.1999;36(3):331-47.
7. Grupe G. Metastasizing carcinoma in a medieval skeleton: differential diagnosis and etiology. Am J Phys Anthropol.1988;75(3):369-74.
8. Land CE, Shimosato Y, Saccomanno G, Tokuoka S, Auerbach O, Tateishi R, Greenberg SD, Nambu S, Carter D, Akiba S, et al. Radiation-associated lung cancer: a comparison of the histology of lung cancers in uranium miners and survivors of the atomic bombings of Hiroshima and Nagasaki. Radiat Res.1993 May;134(2):234-43.

9. Saccomanno G, Archer VE, Saunders RP, Auerbach O, Klein MG. Early indices of cancer risk among uranium miners with reference to modifying factors. Ann N Y Acad Sci.1976;271:377-83.
10. Saccomanno G, Yale C, Dixon W, Auerbach O, Huth GC. An epidemiological analysis of the relationship between exposure to Rn progeny, smoking and bronchogenic carcinoma in the U-mining population of the Colorado Plateau – 1960-1980. Health Phys.1986 May;50(5):605-18.
11. Saccomanno G, Huth GC, Auerbach O, Kuschner M. Relationship of radioactive radon daughters and cigarette smoking in the genesis of lung cancer in uranium miners. Cancer.1988 Oct;62(7):1402-8.
12. Schttmann W. Schneeberg lung disease and uranium mining in the Saxon ore mountains (Erzgebirge). Am J Ind Med.1993;23(2):355-68.
13. Tsinsk E. Epidemiological studies of lung carcinoma incidence in uranium miners (accumulation and retrospective use of diagnostic data). Prague Med Rep.2009;110(2):165-72.
14. Witschi H. A short history of lung cancer. Toxicol Sci.2001;64(1):4-6.

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

Cover-ups and Camouflage

Introduction

- Lung cancer in never smokers is the 7th leading case 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

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

RM 42

- Gross exam
- Radiographs
- Microscopy
- Trace element analysis and comparison to others
- Hypotheses

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

RM 42- Occupational Theory #1

- 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

RM 42- Trace Elements mg/gm

Element	All Adult Skeletons	Aged Adult Males	RM 42
Co	0.528	0.486	0.289
Cs	0.035	0.011	1.584
Mg^2	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

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

RM42- Occupational Theory #2

- Could he have been a metal worker?

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

Vulcan Forging the Thunderbolts of Jupiter Peter Paul Rubens, 1638 In the public domain

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)

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

In the public domain

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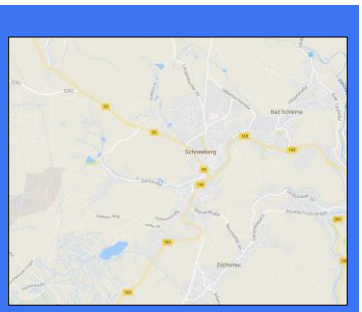


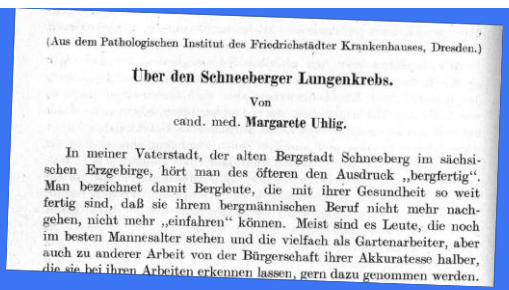
In the public domain

Schneeburg Lung Disease

- 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



(Aus dem Pathologischen Institut des Friedrichstädter Krankenhauses, Dresden.)

Über den Schneeberger Lungenkrebs.

Von

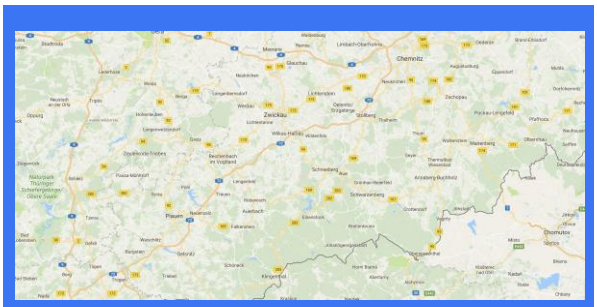
cand. med. **Margarete Uhlig.**

In meiner Vaterstadt, der alten Bergstadt Schneeberg im sächsischen Erzgebirge, hört man des öfteren den Ausdruck „bergfertig". Man bezeichnet damit Bergleute, die mit ihrer Gesundheit so weit fertig sind, daß sie ihrem bergmännischen Beruf nicht mehr nachgehen, nicht mehr „einfahren" können. Meist sind es Leute, die noch im besten Mannesalter stehen und die vielfach als Gartenarbeiter, aber auch zu anderer Arbeit von der Bürgerschaft ihrer Akkuratesse halber, die sie bei ihren Arbeiten erkennen lassen, gern dazu genommen werden.

Uhlig M. Virchows Archiv 1921; 230: 76-98 (in the public domain)

Schneeburg Lung Disease

- Uranium emits Radon-222 (α particles)
- "A single bronchial epithelial cell that has sustained genetic damage can initiate lung cancer" (Field RW, Withers BL. Clin Chest Med 2012;33:681-703)
- Silicosis necessary?
- Led to some improvements in mine ventilation
  - 1925: "First Ordinance on Occupational Diseases of the German Reich"

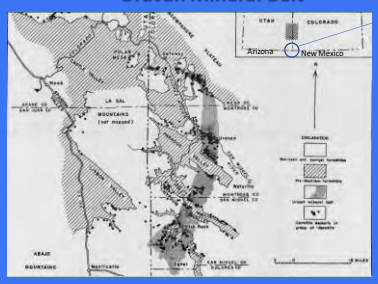


In the public domain

Camouflage

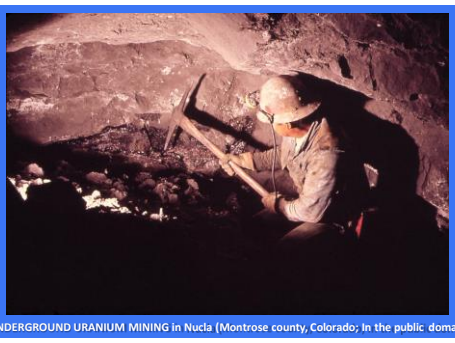
- USSR
  - Wismut (Bismuth) Corporation 1946-1990
  - 100,000 workers, 400 shafts, 15 mills
  - > 9000 deaths

Uravan Mineral Belt



Four Corners Region of Southwest USA

(in the public domain)



UNDERGROUND URANIUM MINING in Nucla (Montrose county, Colorado; In the public domain)

The Manhattan Project

"Ventilating the mines is unnecessary and too expensive."
Witschi H.
Toxicol Sci 2001;64:4-6.

Holding ponds at Uranium processing mill in Uravan, Montrose county, Colorado (in the public domain)

Development of Carcinoma of the Lung as Reflected in Exfoliated cells. Saccomanno G et al. Cancer 1974; 33:256-270.

An Epidemiological Analysis of the Relationship between Exposure to Rn Progeny, Smoking and Bronchogenic Carcinoma in the U-Mining Population of the Colorado Plateau--1960-1980. Saccomanno G et al. Health Physics 1986;50:605-18.

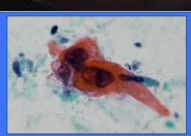


Photo of Dr. Saccomanno courtesy of Saccomanno Research Inst. Grand Junction, Co.

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

Pukkala E et al. Acta Oncol 2009: 48:636-790

In the public domain

Silica and Lung Cancer

- Sandblasters
- Glass manufacture
- Construction
- Denim
- Oil and gas extraction
- Agriculture

Courtesy of Dr. Andrew Churg

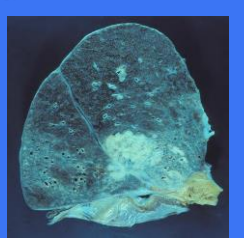
Relationship of Silica Exposure to Carcinoma of the Lung

- 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 (ex, cristobalite) and industry specific associations

Courtesy of Dr. Andrew Churg

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



Courtesy of Dr. Andrew Churg

Other Environmental/Occupational Causes of Lung Cancer

Toxin	Environment/Occupation
Diesel exhaust	Drivers, loader
PAH	Coal gasification, coke production, foundry workers
Benzene, lead, phthalates, chromates, Ni	Painters
Nitrosamines, asbestos contaminated talc, PAH, phthalates	Rubber workers
Arsenic	Glass and ceramic workers, fireworks manufacturing, textile production
Beryllium	Aircraft, space vehicles and defense industries

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

THANK YOU

Environment and Liver Cancer: A Historical Perspective

Stephen A. Geller
Weill Cornell Medical College, New York

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). The

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

1. Castiglione A. *A History of Medicine* (tr by EB Krumhaar), New York, Alfred A. Knopf, 1941.
2. Chen TS, Chen PS. *Understanding the Liver - A History*. Westport CT, Greenwood Press, 1984.
3. Craig JR, Peters RI, Edmondson HA. *Tumors of the Liver and Extrahepatic Duct*s. Atlas of Tumors Pathology, 2nd ed, Fascicle 26, Washington, D.C., Armed Forces Institute of Pathology, 1989.
4. Edmondson HA, Steiner PE. Primary carcinoma of the liver. A study of 100 cases among 48,900 necropsies. Cancer 1954:7:462-503.
5. Eggel H. Über des primäre Carcinoma der Leber. BEitr z path Anat z Allg Path 1910;30:506-604.
6. El-Seraj HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. New Engl J Med 1999;340:745-750.
7. Fitzgerald PJ. *From Demons and Evil Spirits to Cancer Genes*. Washington, American Registry of Pathology, 2000.
8. Geller SA. The Liver, in van den Tweel JG, Gu J, Taylor CR (eds): *From Magic to Molecules - An Illustrated History of Disease*. Beijing, Peking University Medical Press, 2016.
9. Goldzicher M, Bokay Z. Der primäre Leber Krebs. Virchows Arch (A) 1911;203:75-131.
10. Groopman JD. Environmental carcinogens and risk for liver cancer, in Carr BI (ed): *Hepatocellular Carcinoma, Current Clinical Oncology*, Springer Publishing, 2016.
11. Hanot V, Gilbert A. Études sure les maladies du foie. Paris, Asselin et Houzeau, 1888.

12. Popper H, Thomas LB, Telles NC, et al. Development of hepatic angiosarcoma in man induced by vinyl chloride, thorotrast and arsenic. Am J Pathol 1978:92:349-378.
13. Popper H, Thomas L. Alterations of liver and spleen among workers exposed to vinyl chloride. Ann NY Acad Med 1975;346:172-194.
14. Yamagiwa K. Primary parenchymatous carcinoma of the liver (hepatoma). Gann 1911;5:225-282.

History of Pathology Society
March 18, 2018

Disease and Environment: Liver Cancer

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

Environmental agents incriminated in liver injury

Amanita phalloides	DDT	Hexachlorobenzene	Polychlorinated biphenyls
Anabolic steroids	4,4'diaminodiphenylmethane	Hypoglycin	Ponceau-MX
Arsenicals	Dieldrin	Lead	Safrol
Benzene	Diethyl nitrosamine	Methylene chloride	Senecio
Beryllium	Dimethyl nitrosamine	Methylenedianiline	Styrene
Bush tea	Dinitrophenol	Mycotoxins (aflatoxin)	Tetrachlorethylene
Carbon tetrachloride	Dioxin	Organochlorine pesticides	Tetrachlorodibenzo-p-dioxin
Chlorinated naphthalene	Epichlorhydrin	Pethachlorophenol	Tetrachlorethane
Chromium	Ethionine	Perchlorethylene	Thorotrast
Copper	Ethylene dibromide	Phenobarbital	Toluene diisocyanate
Crotolaria	Galatosamine	Phenytoin	Trichlorethylene
Cyanide	Heliotropium	Phosphorus	Trinitrotoluene
Cycasin	Herbal remedies	Polybrominated biphenyls	Vinyl chloride

Understanding of cancer

Hippocrates (46-377 BCE) - introduces the word "cancer" or "carcinoma"

Galen (138-201) - "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 animal called the crab."

Virchow (1821-1902) - cancer arises as metaplasia of connective tissue; *omnis cellula e cellula*

Remak (1815-1865) - 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 embolism lymph and blood channels

Ewing (1866-1943) - "Neoplastic Diseases"

Liver tumors and etiologic associations

Tumor	Etiology	Author(s), year
Hepatocellular carcinoma	Cirrhosis	Sabourin, 1881
	Hemochromatosis	Letulle, 1897
		Achard, 1911
	Hepatitis B	Prince, 1970
		Sherlock, 1970
	α-1-antitrypsin	Berg, Eriksson, 1972
	Androgens	Bernstein, 1971
Cholangiocarcinoma	*Clonorchis sinensis*	Katsurada, 1900
		Hou, 1956
Angiocarcinoma	Thorotrast	MacMahon, 1947
	Arsenic	Roth, 1956
	Vinyl chloride	Creech, Johnson, 1974
Liver cell adenoma	Oral contraceptives	Buam, 1973

Malignant epithelial liver tumors

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

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.

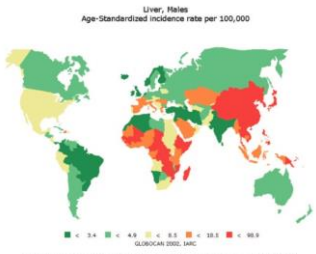


Fig. 1. Age-standardized incidence of liver cancer in men worldwide (8).

Don't forget the *internal* environment:

Worldwide, liver cancer is more common in men (~555,000/year) than women (~228,000) year.

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

Primary carcinoma of the liver - historical background

- **Rigveda** (~4000 BCE) **- oldest Indo-European book - Hindu Sanskrit - alludes to malignant tumors**
- **Ramayana** (~2000 BCE) **- Indian epic poem alludes to malignant tumors**
- **Ebers-Smith papyrus** (~1500 BCE)
- **Hippocrates** (46-377 BCE) **- introduces the word "cancer" or "carcinoma" as a descriptive term for all new tissue formations which could not be cured - distinguished "scirrhus," a hard type of tumor, from open "carcinoma" - classic descriptions of breast and skin cancers**
- **Aretaeus** (1st or 2nd C) **- regarded liver cancer as result of hepatitis**
- **Galen** (129-210) **- early description of liver cancer**
- **Morgagni** (1682-1711) **- founder of pathologic anatomy - described "steatomata" or "hard" tumors of the liver - first autopsy descriptions of cancers of the liver, almost certainly metastatic**

Primary carcinoma of the liver - Morgagni forward

- **Matthew Baillie** (1761-1823) **- extended Morgagni's work - described "large white tubercles" in the liver, comparing them with "scirrhus" in other organs - could not distinguish neoplasia from tuberculosis, syphilis and other diseases**
- **Gaspard Bayle** (1774-1816) **- first clear description of cancer of liver - showed that "steatomata" of Morgagni and "white tubercles" of Baillie were true cancers, similar to cancer of breast - thought that metastasis represented a consitutional cancerous diathesis**
- **Thomas Hodgkin** (1798-1865) **- understood nature of cancer, including metastasis**



Primary carcinoma of the liver - histopathology

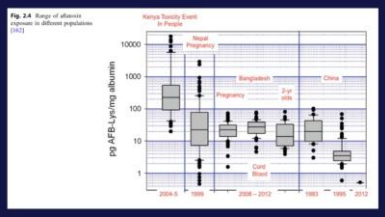
- **Rudolf Virchow** (1821-1902) **- defined primary and metastatic**
- **Kelsch and Kiener** (1876) **- two cases of primary liver cancer**
- **Sabourin** (1881) **- benign primary liver tumors from malignant**
- **Hanot and Gilbert** (1888) **- classification of primary liver cancer** (gross: "massive," "nodular," "cancer with cirrhosis" - microscopic: "trabecular epithelioma" "alveolar epithelioma")
- **von Hansemann** (1890) **- incidence of primary liver cancer low**
- **von Heukolom** (1894) **- introduced term "adenocarcinoma" for primary liver cancer**
- **Eggel** (1901) **- modified Hanot/Gilbert to add "diffuse" - separated into two histologic types** ("carcinoma solidum," "carcinoma adenomatosum")
- **Katsusaburo Yamigawa** (1911) **- "hepatoma" and "cholangioma"** (benign and malignant)
- **Goldzieher and von Bokay** (1911) **- "hepatocellular carcinoma and "cholangiocarcinoma"**
- **Edmondson and Steiner** (1954) **- grading of hepatocellular carcinoma**
- **Hugh Edmondson** (1958) **- first AFIP fascicle on liver tumors**


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.

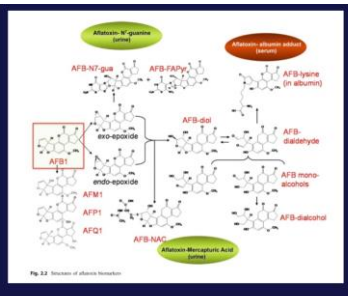


Biomarkers

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.**

Groopman JD. Environmental carcinogens and risk for human liver cancer, in Carr BI (ed) Hepatocellular Carcinoma, Current Clinical Oncology, Springer Publishing, 2016.



Groopman JD. Environmental carcinogens and risk for human liver cancer, *in* Carr BI (ed) Hepatocellular Carcinoma, Current Clinical Oncology, Springer Publishing, 2016.

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**

Modified from El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Eng J Med 1999;340:745-750.

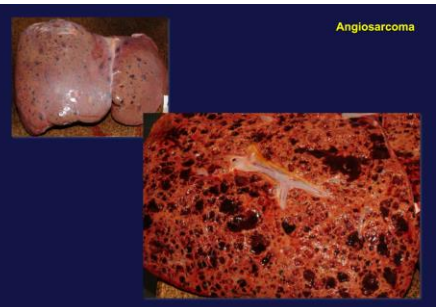
Hepatic angiosarcoma

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

Etiology of hepatic angiosarcoma

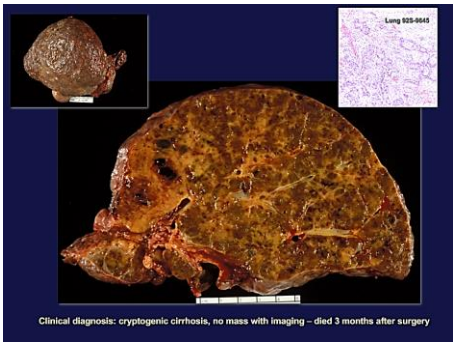
Physical/chemical injury	*Circumstances of exposure*	*Latency (years)*
Thorotrast (thorium dioxide)	Contrast medium for angiography	15-40
Radium	Needle implant for breast cancer therapy (1 case)	3
External radiation	Atomic bomb, Hiroshima (1 case), radiotherapy	35
Vinyl chloride	Manufacturing; in sprays using vinyl chloride as propellant	12-28
Inorganic arsenic	Insecticides; Fowler's solution; drinking water contaminant	6-33
Copper	Copper sulfate in sprays for vineyards (1 case)	35
Iron	Idiopathic hemochromatosis cirrhosis	?
Androgenic/anabolic steroids	Treatment of Fanconi anemia and other disorders	2-35
Contraceptive steroids	Birth control (1 case)	10
Diethylstilbesterol	Treatment of prostate carcinoma (1 case)	13
Phenelzine	Antidepressive – (1 case)	6

	Cavernous hemangioma	Infantile hemangioendothelioma – type 1	Infantile hemangioendothelioma – type 2	Kaposi sarcoma	Epithelioid hemangioendothelioma	Angiosarcoma
Gross involvement	Single or multiple	Single or multiple	Single or multiple	Multiple	Single or multiple	Usually multiple
Microscopic involvement	Replaces acini	Replaces acini	Replaces acini	Grows in portal tracts	Infiltrates, destroys acini	Infiltrates, destroys acini
Hepatic acini remnants	no	no	no	no	yes	no
Sinusoid infiltration	no	no	yes (rare)	no	yes	yes
Vein invasion	no	no	yes (rare)	no	yes	yes
Capsule invasion	no	no	no	no	yes	yes
"Dendritic" cells	no	no	no	no	yes	no
F VIII, CD31, etc	yes	yes	yes	variable	yes	yes
Bile ducts in tumor	no	yes	yes	no	no	no
Collagenous stroma	yes	yes	yes	yes	yes	no
Extramedullary hematopoiesis	no	yes	yes	no	no	yes
Nodular hyperplasia	no	no	no	no	yes	yes
Metastases	no	no	yes	yes	yes	yes

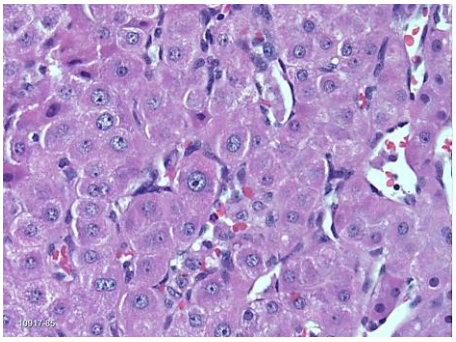


Macroscopic features:

- 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%)



How in the world did I miss that?



Microscopic features - 1:

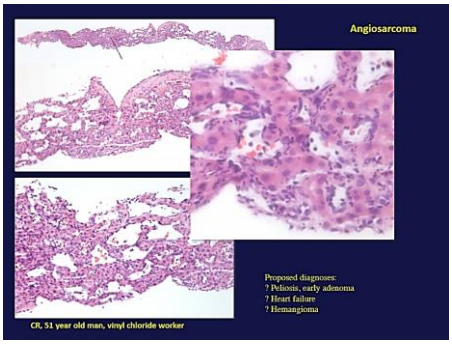
- Malignant spindle-shaped or irregular endothelial cells with irregular borders
- Lightly eosinophilic cytoplasm
- Hyperchromatic elongated and/or irregular nuclei
- CD31, CD34, F VIII, ulex, etc

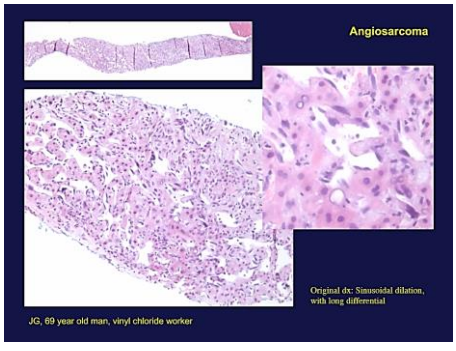
Microscopic features - 2:

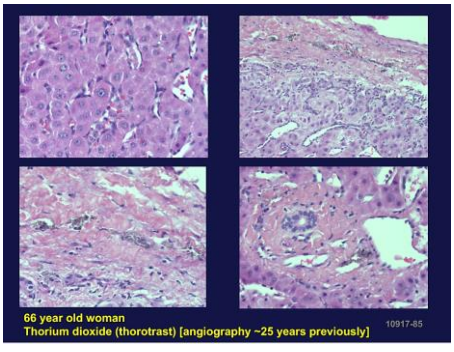
- Tumor cells grow along preformed vascular channels
- Sinusoidal growth leads to liver plate atrophy and disruption
- Liver cell hyperplasia
- Larger vascular channels ("peliotic") and cavitary spaces develop
- Spaces lined by tumor cells – may have papillary/polypoid projections

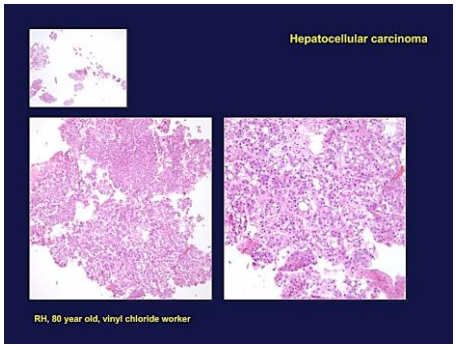
Microscopic features - 3:

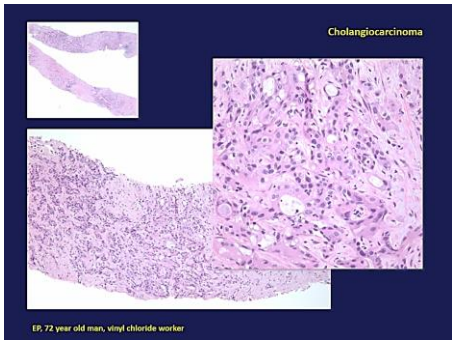
- Vein (THV, portal) invasion ⟶ obstruction
  - hemorrhage, infarction, necrosis
- Solid pattern resembes fibrosarcoma
- Hematopoiesis (especially Thorotrast related)
- May have simultaneous hepatocellular carcinoma or cholangiocarcinoma

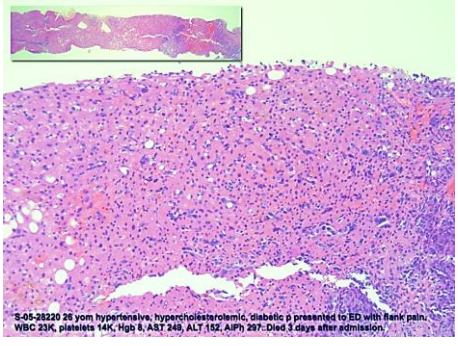


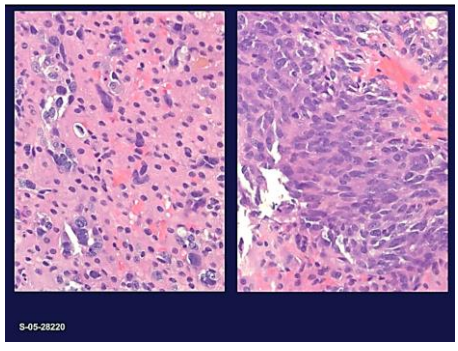





Hepatocellular carcinoma
RH, 80 year old, vinyl chloride worker


Cholangiocarcinoma
EP, 72 year old man, vinyl chloride worker


S-05-28220 26 yom hypertensive, hypercholesterolemic, diabetic p presented to ED with flank pain.
WBC 23K, platelets 14K, Hgb 8, AST 249, ALT 152, AlPh 297. Died 3 days after admission.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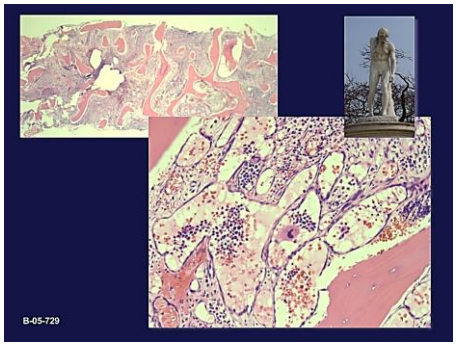

B-05-729


Cleo, 11 year old – (not a vinyl chloride worker)
Cleo
Angiosarcoma

Special Communication

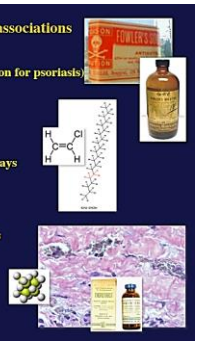
Angiosarcoma of Liver in the Manufacture of Polyvinyl Chloride

L. L. Creech, Jr., M.D., and H. N. Johnson, M.D.

JAMA, 1974

Hepatic angiosarcoma - etiologic associations

- Arsenic (vintners, Fowler's solution for psoriasis)
- Thorotrast (Thorium dioxide)
- Vinyl chloride (monomeric)
- Radiation – external, implanted
- ? Dioxin
- ? Copper-containing vineyard sprays
- ? Iron
- ? Steroids
  - ? contraceptive pills
  - ? androgenic/anabolic steroids
  - ? diethylstilbesterol
- ? Phenelzine (MAO inhibitor)
- ? Urethane
- Idiopathic

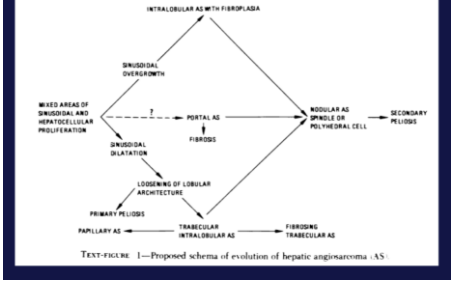


Development of Hepatic Angiosarcoma in Man Induced by Vinyl Chloride, Thorotrast, and Arsenic

Comparison With Cases of Unknown Etiology

Hans Popper, MD, PhD, Louis B. Thomas, MD, Norman C. Telles, MD, Henry Fitts, MD, and Irving J. Selikoff, MD

Popper H et al. Am J Pathol 1978;92:340-378.



TEXT-FIGURE 1—Proposed schema of evolution of hepatic angiosarcoma (AS).

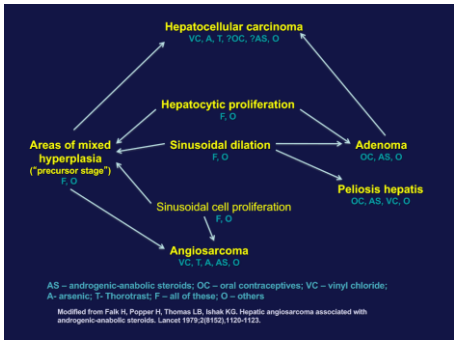
- Fibrosis
  - Portal
    - Portal vein wall
  - Intralobular
  - Capsular (most characteristic)
- Cholestasis, with bile plugs
- Hepatocyte proliferation
  - Nodules
- Endothelial cell atypia
- Sinusoidal dilation

Popper H, Thomas L. Alterations of liver and spleen among workers exposed to vinyl chloride. Ann N Y Acad Med 1975;246:172-194.

TABLE 1. HAS Cases, CDC Survey, 1964–1974. Distribution by Etiologic Status and Year of Death

Etiology	1964	1965	1966	1967	1968	1969	1970	1971	1972	1973	1974	Total
Idiopathic	4	10	9	13	12	13	11	12	13	11	18	126
Vinyl chloride	1	–	–	–	3	2	1	1	–	3	1	12
Arsenic	1	–	1	2	1	–	–	–	–	1	–	6
Thorotrast	–	–	–	1	2	2	3	2	4	1	5	20
Androgenic-anabolic steroids	–	–	–	1	–	–	–	1	–	1	1	4
Total	6	10	10	17	18	17	15	16	17	17	25	168

Falk H, Caldwell GG, Ishak KG, Thomas LB, Popper H. Arsenic-related hepatic angiosarcoma. Am J Ind Med 1981;2:43-50.



Constitutional genetic diseases leading to liver tumors*

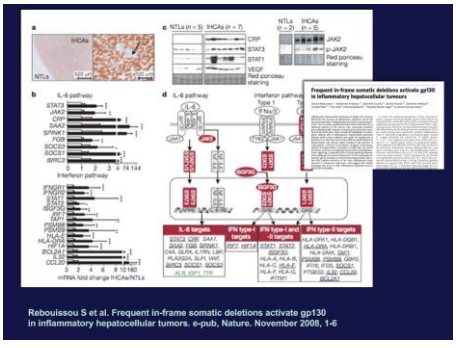
Disease	Tumor type	Chromosome location	Gene
Trisomy 18	Hepatoblastoma	18	
Beckwith-Wiedemann	Hepatoblastoma, hemangioendothelioma	11p15.5	P57KIP2, others
Familial polyposis	Hepatoblastoma, adenoma, biliary adenoma, hepatocellular carcinoma	5q21,22	APC
Li-Fraumeni	Hepatoblastoma, undifferentiated sarcoma	17p13	P53, others
Glycogen storage I	Adenoma, hepatocellular carcinoma, hepatoblastoma	17	Glucose-6-phosphatase
Alagille	Hepatocellular carcinoma	20p12	Jagged-1
Hereditary tyrosinemia	Hepatocellular carcinoma	15q23-25	Fumarylaceto-acetate hydrolase
Familial cholestatic syndromes	Hepatocellular carcinoma, cholangiocarcinoma	18q21-22, 2q24	Fic-1, BSEP, [ABCB11]
Neurofibromatosis	Hepatocellular carcinoma, angiosarcoma, malignant Schwannoma	17q11.2	
Ataxia-telangiectasia	Hepatocellular carcinoma	11q22-23	ATM
Fanconi anemia	Hepatocellular carcinoma, fibrolammelar hepatocellular carcinoma	1q42, 3p, 20q13.2-13.3	FAA, FAC, BRCA 2
Tuberous sclerosis	Angiomyolipoma	9q34, 16p13	TSC 1, TSC 2

*Modified from Finegold MJ: Hepatic tumors in childhood, in Russo P, Ruchelli E, Piccoli DA (eds). *Pathology of Pediatric Gastrointestinal and Liver Disease*, New York, Springer-Verlag, 2004.

Hepatocellular carcinoma chromosomal abnormalities*

Region	% of tumors affected	Abnormality	Method
1p36	30	Loss of heterozygosity	Microsatellite markers
1q	70	9 copies	Comparative genomic hybridization
1q (12.13)	33	Loss of heterozygosity	Microsatellite polymorphism
1q (34-qter)	70	Loss of heterozygosity	Restriction fragment length polymorphism
4p	33	8 copies	Comparative genomic hybridization
	37	9 copies	Comparative genomic hybridization
8p	41	8 copies	Polymorphic markers
	64	Loss of heterozygosity	Polymorphic markers
8p 21.3-p22	42	Loss of heterozygosity	Restriction fragment length polymorphism
8q	60	8 copies	Comparative genomic hybridization
	77	Loss of heterozygosity	Polymorphic markers
11p	42	Loss of heterozygosity	Restriction fragment length polymorphism
13q	20	Loss of heterozygosity	Restriction fragment length polymorphism
	33	Loss of heterozygosity	Comparative genomic hybridization
	37	9 copies	Comparative genomic hybridization
16p	22	Loss of heterozygosity	Restriction fragment length polymorphism
16q	34	9 copies	Comparative genomic hybridization
16q 22-23	70	Loss of heterozygosity	Microsatellite polymorphism
17p	41	Decreased copies	Comparative genomic hybridization
17q	33	Increased copies	Comparative genomic hybridization
20q	37	Increased copies	Comparative genomic hybridization

*Selected examples from more than 35 documented chromosomal abnormalities
Modified from Finegold MJ: Hepatic tumors in childhood, in Russo P, Ruchelli E, Piccoli DA (eds). Pathology of Pediatric Gastrointestinal and Liver Disease, New York, Springer-Verlag, 2004.



Rebouissou S et al. Frequent in-frame somatic deletions activate gp130 in inflammatory hepatocellular tumors. e-pub, Nature. November 2008, 1-6

Future directions

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

James Watson
Francis Crick

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 psychotropic 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

1. Ayer WD. Napoleon Buonaparte and schistomiasis or bilharziasis. *NY State J Med* 1966;66:2295-2301.
2. Barakat RM. Epidemiology of Schistosomiasis in Egypt: Travel through Time: Review. *J Adv Res* 2013;4:425-432.
3. Berry A, Iriart X, Fillaux J and Magnaval JF. Urinary schistosomiasis and cancer. *Bull Soc Pathol Exot* 2017;110:68-75.
4. Bilharz T. Further observations concerning Distomum haematobium in the portal vein of man and its relationship to certain pathological formations with brief notes by Seibald. *Z Wiss Zool* 1853;4:72.
5. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens--Part B: biological agents. *Lancet Oncol* 2009;10:321-322.
6. Bryan GT. Pathogenesis of human urinary bladder cancer. *Environ Health Perspect* 1983;49:201-207.

7. Case RA, Hosker ME, McDonald DB and Pearson JT. Tumours of the urinary bladder in workmen engaged in the manufacture and use of certain dyestuff intermediates in the British chemical industry. I. The role of aniline, benzidine, alpha-naphthylamine, and beta-naphthylamine. *Br J Ind Med* 1954;11:75-104.
8. Chung KT. Occurrence, uses, and carcinogenicity of arylamines. *Front Biosci (Elite Ed)* 2015;7:322-345.
9. Contis G and David A. The epidemiology of Bilharzia in ancient Egypt: 5000 years of schistosomiasis*. Parasitol Today* 1996;12:253–255.
10. David A. Disease in Egyptian mummies: the contribution of new technologies. *Lancet* 1997;349:1760–1763.
11. Deelder A, Miller N, De Longe M and Krijker F. Detection of schistosome antigen in mummies. *Lancet* 1990;335:724–725.
12. Dietrich HG and Golka K. Bladder tumors and aromatic amines – historical milestones from Ludwig Rehn to Wilhelm Hueper. *Front Biosci (Elite Ed)* 2012;4:279-288.
13. Domico T. Wild Harvest Edible Plants of the Pacific Northwest. Hancock Home Publishers Inc. Seattle, 1979. p.86.
14. Faguet G. Environmental Carcinogens. In: The Conquest of Cancer. Springer, Dordrecht, 2015.
15. Freedman ND, Silverman DT, Hollenbeck AR, et al. Association between smoking and risk of bladder cancer among men and women. *JAMA* 2011;306:737-745.
16. Grieve, M. A Modern Herbal; Volume I: A-H: The Medicinal, Culinary, Cosmetic and Economic Properties, Cultivation and Folk-Lore of Herbs, Grasses, Fungi, Shrubs & Trees with All Their Modern Scientific Uses. Dover Publications, Inc. New York, 1971. pp. 305-306.
17. Hueper WC, Wiley FH and Wolfe HD. Experimental production of bladder tumors in dogs by administration of ß-naphthylamine. *J Ind Hyg Tox* 1938;20:46-84.
18. Khaled H. Schistosomiasis and cancer in Egypt: review. *J Adv Res* 2013;4:461-466.
19. Lower GM Jr. Concepts in causality: chemically induced human urinary bladder cancer. *Cancer* 1982;49:1056-1066.
20. Nash TE, Cheever AW, Ottesen EA, Cook JA. Schistosome infections in humans: perspectives and recent findings. NIH conference. *Ann Intern Med* 1982;97:740–754.
21. Potter DM, Baird MS. Carcinogenic effects of ptaquiloside in bracken fern and related compounds. *Br J Cancer* 2000;83:914–920.
22. Ramazzini B. De Morbis Artificum Diatriba [Diseases of Workers]. Carnevale F (curator) 1982, Carocci Editore, Rome.
23. Ruffer M. Note on the presence of ‘‘Bilharzia haematobia’’ in Egyptian mummies of the twentieth dynasty. *Br Med J* 1910;1:16.
24. World Health Organization. Evaluation of carcinogenic risk to humans. Schistosomes, liver flukes and Helicobacter pylori. *IARC Monogr* 1994;61:45–119.

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.

Environment and Urinary Bladder Cancer: a Historical Perspective

Gabriella Nesi
University of Florence, Florence, Italy

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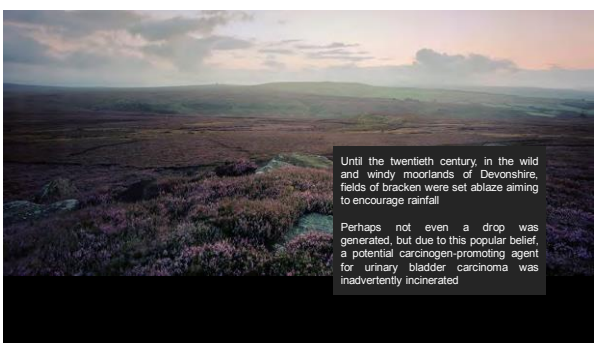

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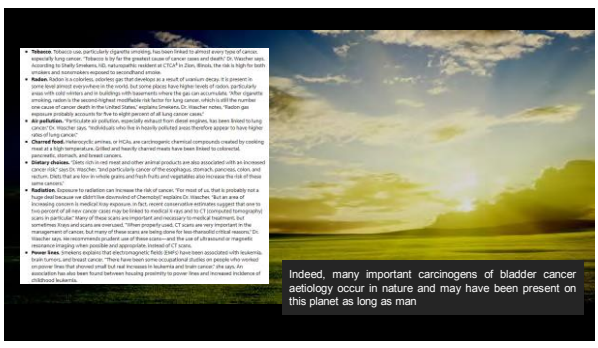


- **Tobacco.** Tobacco use, particularly cigarette smoking, has been linked to almost every type of cancer, especially lung cancer. "Tobacco is by far the greatest cause of cancer cases and death," Dr. Visscher says. According to Shelly Smokens, HS, naturopathic resident at CTCA® in Zion, Illinois, the risk is high for both smokers and nonsmokers exposed to secondhand smoke.
- **Radon.** Radon is a colorless, odorless gas that develops as a result of uranium decay. It is present in some level almost everywhere in the world, but some places have higher levels of radon, particularly areas with cold winters and in buildings with basements where the gas can accumulate. "After cigarette smoking, radon is the second-highest modifiable risk factor for lung cancer, which is still the number one cause of cancer death in the United States," explains Smokens. Dr. Visscher notes, "Radon gas exposure probably accounts for five to eight percent of all lung cancer cases."
- **Air pollution.** Particulate air pollution, especially exhaust from diesel engines, has been linked to lung cancer," Dr. Visscher says. "Individuals who live in heavily polluted areas therefore appear to have higher rates of lung cancer."
- **Charred food.** Heterocyclic amines, or HCAs, are carcinogenic chemical compounds created by cooking meat at a high temperature. Grilled and heavily charred meats have been linked to colorectal, pancreatic, stomach, and breast cancers.
- **Dietary choices.** "Diets rich in red meat and other animal products are also associated with an increased cancer risk," says Dr. Visscher. "And particularly cancer of the esophagus, stomach, pancreas, colon, and rectum. Diets that are low in whole grains and fresh fruits and vegetables also increase the risk of these same cancers."
- **Radiation.** Exposure to radiation can increase the risk of cancer. "For most of us, that is probably not a huge deal because we didn't live downwind of Chernobyl," explains Dr. Visscher. "But an area of increasing concern is medical xray exposure. In fact, recent conservative estimates suggest that one to two percent of all new cancer cases may be linked to medical x-rays and to CT (computed tomography) scans in particular." Many of these scans are important and necessary to medical treatment, but sometimes X-rays and scans are overused. "When properly used, CT scans are very important in the management of cancer, but many of these scans are being done for less-threshold critical reasons," Dr. Visscher says. He recommends prudent use of these scans—and the use of ultrasound or magnetic resonance imaging when possible and appropriate, instead of CT scans.
- **Power lines.** Smokens explains that electromagnetic fields (EMFs) have been associated with leukemia, brain tumors, and breast cancer. "There have been some occupational studies on people who worked on power lines that showed small but real increases in leukemia and brain cancer," she says. An association has also been found between housing proximity to power lines and increased incidence of childhood leukemia.

Indeed, many important carcinogens of bladder cancer aetiology occur in nature and may have been present on this planet as long as man

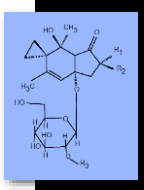
Bracken (*Pteridium aquilinum*) was used by several Pacific Northwestern Indians tribes as a dietary staple as long ago as 14,000 BC, and in more modern times as food for both humans and animals in many parts of the world

Environ Health Perspect 1983;49:201-207

Table 1 Distribution of the ptaquilosides in ferns (Saito et al, 1989; Niwa et al, 1983)

Species	Ptaquiloside or ptaquiloside analogue
Cheilanthes myriophylla	+
Cibotium hainmeiz	+
Conogramme gracilis	–
C. intermedia	–
C. japonica	–
Dennstaedtia dissecta	–
D. hirsta	+
D. scabra	+
Histiopteris incisa	+
Hypolepis barklamana	+
H. tenuifolia	+
H. punctata	+
Microlepia marginata var hancockii	–
M. strigosa	+
Monachosorum arakii	–
Monachosorum flagellare	–
Onychium japonicum	–
Pityrogramma calomelanos	+
P. sulphurea	+
Pteridium aquilinum	+
Pteris cretica	+
P. dispar	+
P. excelsa	+
P. faurei	+
P. nipponica	+
P. oshimensis	+
P. purpurascentes	+
P. tsukiyamensis	–
P. semipinnata	+
P. tremula	+
P. wallichiana	+
Sphenomeris chusana	–

(+ corresponds to present, – to not detected)



This fern is now recognised as a potent experimental plant to induce urinary bladder cancer

Chemical carcinogenic compounds (e.g. ptaquilosides or ptaquilosides analogues) have been isolated in several kinds of ferns, including bracken fern

Br J Cancer 2000;83:914-920

Infectious agents are believed to cause over 20% of malignancies worldwide

Schistosoma haematobium, a trematode parasite endemic in Africa and the Middle East, invades small vessels of the human urinary bladder and other pelvic organs

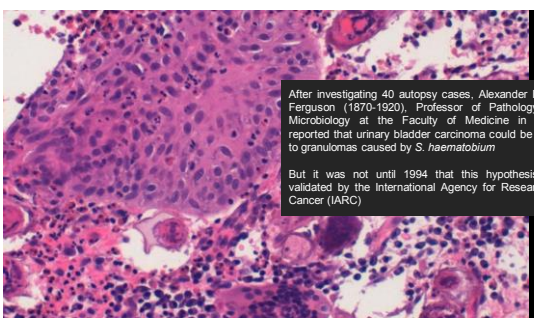
Increased travel for business, education and tourism between countries has led to unusual schistosomiasis cases in non-endemic countries

J Adv Res 2013;4:461-466

It was Theodor Bilharz (1825-1862) who first identified this blood fluke during an autopsy at the Kasr El Ainy Hospital (Cairo) in 1851

The existence of an association between schistosomiasis and urinary bladder cancer was first theorised by the German surgeon Carl Goebel in 1905

J Adv Res 2013;4:425-432



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 *S. haematobium*

But it was not until 1994 that this hypothesis was validated by the International Agency for Research on Cancer (IARC)

J Bull Soc Pathol Expt 2017;110:68-75

Sir Marc Armand Ruffer (1859-1917) discovered calcified schistosome eggs in two Egyptian mummies of the 20th dynasty

BMJ 1992;304:555-6

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

Following the expeditions by Christopher Columbus (1451-1506), 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. Another plant of the same family was introduced: tobacco

The tobacco smoking culture was introduced into Europe in 1519 by Spanish explorers, and its use spread rapidly to Asia and Africa

John Hill (1716-1775), the English physician and botanist, reported a link between tobacco use and cancer in 1761

Cancer 1982;49:1056-1066

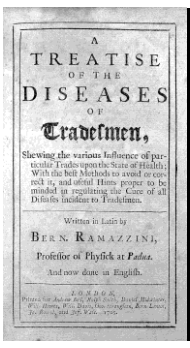
Association between smoking and risk of bladder cancer among men and women

Neal D Freedman, PhD, MPH[1], Debra T Silverman, ScD, ScM[1], Albert R Hollenbeck, PhD[2], Arthur Schatzkin, MD, DrPH[3], and Christian C Abnet, PhD, MPH[1]

Conclusions

Tobacco smoking was a strong risk factor for bladder cancer, with PARs of approximately 50% in both men and women. We found higher risk estimates for current cigarette smoking relative to never smoking in the NIH-AARP cohort, initiated in 1995, than were reported in previous publications from cohorts initiated between 1963 and 1987. These results support the hypothesis that the risk of bladder cancer associated with cigarette smoking has increased with time in the United States, perhaps a reflection of changing cigarette composition. Prevention efforts should continue to focus on reducing the prevalence of cigarette smoking.

Cancer 1982;49:1056-1066



A
TREATISE
OF THE
DISEASES
OF
Tradesmen,
Shewing the various Influence of particular Trades upon the State of Health;
With the best Methods to avoid or correct it, and useful Hints proper to be minded in regulating the Cure of all Diſeaſes incident to Tradeſmen.

Written in Latin by
BERN. RAMAZZINI,
Profeſſor of Phyſick at *Padua*.
And now done in Engliſh.

In his famous "*De morbis artificium*", Bernardino Ramazzini (1633-1714) recommended physicians to ask the question *"et quam artem exerceat"* in order to accurately evaluate their patients

Several neoplastic diseases may occur as a result of professional or occupational activities

Urinary bladder cancer was one of the first diseases for which specific industrial chemicals were identified as causative agents of human cancer

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

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

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

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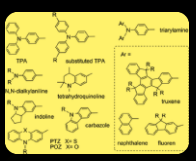
Epidemiological and experimental studies proved that arylamines caused urinary bladder carcinomas, and several industrialised countries have taken steps to limit or abolish the manufacture of these chemicals



THANK YOU