A NOTE FROM HISTORY

Thoughts about the Cause of Cancer

Steven I. Hajdu, M.D.

Westlake Village, California.

History teaches that the discovery of cure for a disease rarely precedes the knowledge of its cause. Therefore, it is perhaps important to review attempts, in a timeline presentation, that were made to discover the cause of cancer in humans.

Ancient peoples from prehistoric times believed that cancer was caused by evil spirits, natural forces, contact with wicked men, and disharmony of the planets. According to Hebrew, Greek, and Roman teachings, cancer was caused by sin, violation of religious rules, and the wrath of gods. Hippocrates (BC 460-375) and his disciples were opposed to superstitions and hypothesized that excess or deficiency of blood, mucus, and bile could cause cancer, particularly in old age. Galen (AD 131-203) and his followers, in the Roman Empire and beyond, believed that accumulation of black bile in the breast, uterus, lips, and hemorrhoids caused cancer. Galen's theory was accepted as doctrine by medical practitioners and organized religions for sixteen centuries with little modification. In the early Middle Ages, accumulation of noxious substances in blood as cause of disease, including cancer, was added to Galen's humoral theory and led to introduction of blood letting. Although alchemists, astrologers, and contagion theorists pressed their own thoughts, Galen's doctrine withstood all challenges throughout the Middle Ages.[1]

With revolutionary fervor, an outspoken Swiss physician and chemist, Paracelsus (1493-1541), was the first to openly oppose the Galenists, and Paracelsus almost got away with it. But his opponents caught up with him in Salzburg, Austria, and beat him to death. Paracelsus proposed that deposits of salt of sulfur and arsenic in blood cause cancer, particularly in miners, masons, chemists, and metallurgists.[2] He left for us the first description of an association between occupational diseases and cancer. Ambroise Paré (1510-1590), a distinguished French surgeon, felt that the antecedent cause of cancer was an irregular diet that induced accumulation of feculent material in the blood. Overheating changed this material to a corrosive substance that produced ulceration of the cancer.[3]

Discoveries by anatomists in the 1500s, discovery of blood circulation in 1628 by William Harvey (1578-1657), and the description of lymphatics by Thomas Bartholin (1616-1680) in 1656 introduced the concept of coagulation and fermentation of the blood and lymph as the cause of cancer. By observing deterioration (ulceration and necrosis) of various organs harboring cancer, surgeons pointed out that cancer was a destructive growth and was caused by internal structural transformation of glandular and vascular organs.[4] Although surgeons

Address for reprints: Steven I. Hajdu, M.D., 1759 Drumcliff Court, Westlake Village, CA 91361; Fax: (805) 496-0620; E-mail: sih15@aol.com

Received October 31, 2005; accepted November 15, 2005.

DOI 10.1002/cncr.21807
Published online 13 March 2006 in Wiley InterScience (www.interscience.wiley.com).

did not support the humorists' theories, most physicians continued to accept them with some modification. Noted Dutch physician, chemist, teacher, and bibliographer Herman Boerhaave (1668-1738) believed that cancer was an outlet to the accumulated bad humors that contained the cancer virus (some sort of toxic substance). Venous and lymphatic obstructions facilitated accumulation of this material similarly to accumulation of urea in the urine in urinary obstruction. Boerhaave held that the source of the cancer virus (the bad substance) was most likely in the water or in the soil. After the cancer virus was acquired, he wrote,[5] it remained in the body in such a way that it could be transferred to children by heredity and to members of the family by contagion. His thought forwarded earlier Middle Ages beliefs that cancer was contagious, and cancer patients should be isolated in out-of-town hospitals. After all that was written and spoken about cancer by the early 1700s, everybody was convinced that schirrous and scrophulous tumors, all cancers, were the result of coagulation and stagnation of the flow of blood and chyle. Ulceration was a particularly bad thing and was caused by accumulation of corrosive acids, deprivation of nourishment, and changes in the shape of the moon.[6] Surgeons advocated excision of all swellings, polyps, and tumefactions before they became cancerous.[7] Promotion of early and aggressive treatment by excision superheated the conflict between surgeons (pioneer surgical oncologists) and physicians (pioneer medical oncologists) that lasted for centuries.

In 1775, Percivall Pott (1714-1788) reported[8] an occupational cancer, chimney sweeps' cancer of the scrotum, by long-standing accumulation of soot in the perineoscrotal skin. He believed that soot was an irritant due to its contents, such as ammonia, sulfur, and arsenic. Pott also described cancer of the tongue and cheek caused by carious teeth.

The first monograph on cancer was written by Bernard Peyrilhe (1735-1804) and was published in 1776 (Fig. 1). On one hundred thirty-five pages, Peyrilhe presented his thinking and all that was known about cancer prior to his time.[9] He explained that he wrote the book because the extent of ignorance about cancer was embarrassing. He continued to believe, along with others,[5,6] that there was a cancer virus, but nobody in the whole world, he wrote, knew what it was. As to development of cancer, he thought that the process was similar to how chickens develop from eggs under incubation. Once the blood, lymph, and bile are accumulated by stagnation, fermentation begins to take place. Fermentation is facilitated by heat, humidity, obstruction of vessels, alterations in blood by long use of medications, diminution of transpiration, and cessation of menstruation. Ulceration and local putrefaction (necrosis) are aided by application of corrosive chemicals, long duration, decreased circulation, absence of air, and rupture of cellular tissues (fat and parenchyma). And, he added, cancer attacks sick people, particularly ones who are icteric with scirrhous (firm) liver and have hydropic belly. Peyrilhe believed that the cancerous virus is transmitted from parents to children and others through the air, saliva, and other body secretions. Hence, isolation of cancer patients in cancer wards was justified.

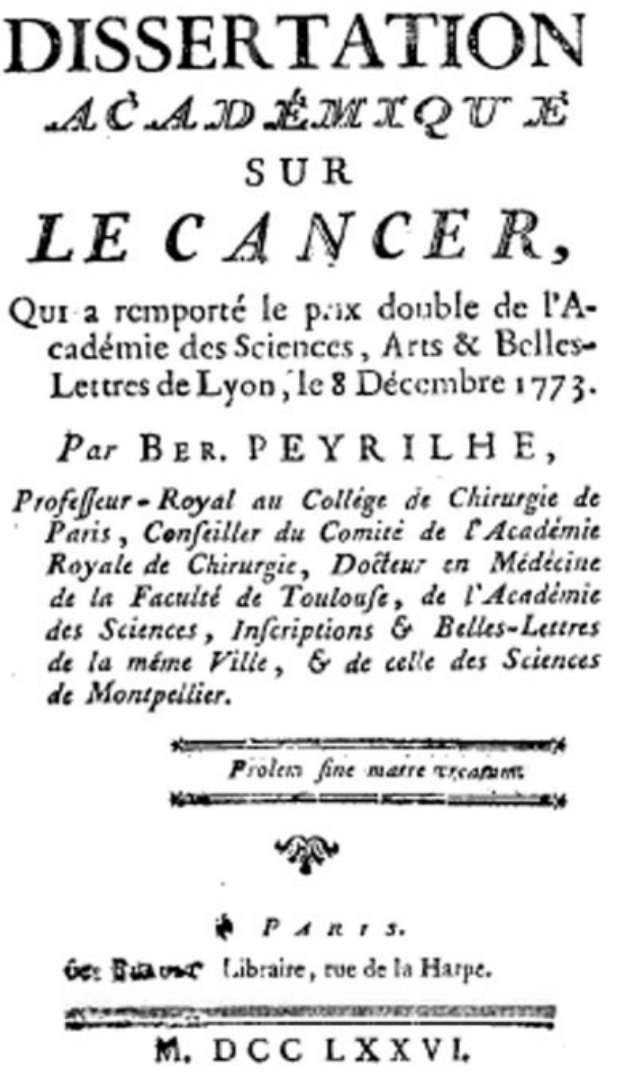

DISSERTATION
ACADÉMIQUE
SUR
LE CANCER,
Qui a remporté le prix double de l'Académie des Sciences, Arts & Belles-Lettres de Lyon, le 8 Décembre 1773.
Par BER. PEYRILHE,
Professeur-Royal au Collège de Chirurgie de Paris, Conseiller du Comité de l'Académie Royale de Chirurgie, Docteur en Médecine de la Faculté de Toulouse, de l'Académie des Sciences, Inscriptions & Belles-Lettres de la même Ville, & de celle des Sciences de Montpellier.
Proles sine matre creatum
PARIS.
Libraire, rue de la Harpe.
M. DCC LXXVI.

FIGURE 1. Title page of Bernard Peyrilhe's Dissertation on Cancer, 1776 (See Reference 9). Reprinted from the author's private collection.

The first illustrated medical dictionary published in 1791 in London[10] listed overheated minute lymphatic vessels as the proximate cause of cancer. Changes induced by celibacy, increased body heat, scanty and irregular menstrual flow, sorrow or other

disturbances of the mind contributed to conversion of the inspissated material into cancer. It was added, as an aside, that earlier suspicion of small worms in ulcerated cancers now can be confirmed with the aid of the microscope.

As examination of corpses of deceased cancer patients became common near the end of the eighteen century, questions arose concerning whether the cause of cancers in different organs was the same. Not having anything to point to as a cause, early researchers concluded that cancer was an idiopathic affection and was linked to cancerous diathesis.[11] With the introduction of this new thought, trauma, irritation, and inflammation were looked upon as sorts of honing devices for cancer, but alone they could not cause cancer without cancer diathesis, a predisposition. This theory received wide acceptance because it explained the frequent origin of cancer without apparent cause. Soon, it was added,[12] that there were two kinds of predisposition, hereditary and acquired. Among hereditary examples, cancer in both breasts and cancer in the uterus and breast were listed. Cancer of the stomach was recorded as an acquired disease and was thought to be caused by chronic inflammation, ulceration, and cicatrization.

The first definitive work[13] listing chronic irritation, chronic inflammation, burns, freezing injuries, and other external conditions as causes of acquired cancer was published in 1826. Accumulation or deposit of albumen (fibrin) in the tissues was named as the point of origin of cancer.

Récamier (1774-1852) in his seminal work on cancer[14] reconfirmed that there are two kinds of cancer, local and constitutional. And he continued that constitutional cancers can be hereditary similar to arthritis and strumatosis but that not all hereditary cancers are constitutional, e.g., breast cancer. As to the cause of local, so-called acquired or spontaneous cancers, he listed changes in eating habits and degeneration of preexisting benign lesions, e.g., pigmented nevi and polyps. Récamier concluded that the fact that no person is exempt from cancer must be because of dispersed embryonic rests in the body. Activation of such congenital rests by changing climate, habitation, lifestyle, or acquiring diseases, such as syphilis and tuberculosis, were further sources of cancer. The local irritation theory was extended to religious communities in cloisters, which claimed that cancer of the uterus was induced by masturbation.[15] Cancer of the uterine cervix was reported as a consequence of trauma by coition and abortion. On the basis of the above statements,[13–15] it was firmly held in French schools for nearly 100 years that without chronic irritation and inflammation, there is no local cancer.

From the early 1800s, emerging new fields in medicine, pathophysiology, microscopic pathology, clinical chemistry, and bacteriology profoundly influenced thinking about the cause of cancer. The year 1838 was a momentous year. In Berlin, this was the year in which Theodore Schwann (1810-1882) introduced the cell theory (the theory that human and animal tissues are composed of cells), and his mentor, Johannes Mûller (1801-1858), came to the conclusion that cancers are formed from blastema.[16] According to Müller, the cancerous blastema was an amorphous granular material that is exuded from blood, the mystical substance, and then by internal burst are formed. Consequently, from the nuclei germ, cells emerged and deposited in a scattered way between normal tissue elements; these served as the primary source of cancer. Within a couple of years, the blastema theory received wide acceptance. Some of the earliest believers in it were Thomas Hodgkin (1798-1866) and James Paget (1814-1899). Paget wrote in his book[17] that cancer was a blood-borne disease. However, he added, because there were so many different cancers in appearance and cellular composition, the morbid material (the blastema) must be deposited from blood into a part of the body that is altered from normal, is receptive to such material, and permits its growth. He pointed out that preexisting benign tumors are good ground for such deposits. Paget admitted that the blastema is not formed from the natural constituents of blood. He speculated that the blastema is formed from some invisible particles that must be separated from blood to become cancerous. Once the particles are in the blood, they cannot be removed and are transferred from parents to children. Hermann Lebert (1813-1878), another believer in the blastema theory, went as far as claiming,[18] with others,[19] that there is no need to have an organ to produce cancer. The only thing needed is a capillary vessel with blood in it. Although Lebert found it surprising that despite high vascularity of the lung, the brain, and the spleen, cancer is far less common in these organs than in many other organs. He reasoned that the cancer diathesis in blood must exist for some time before it appears externally. How was it introduced into the blood he could not tell, but he found that rich people were more liable to cancer than the poor.

One would believe that after announcement that cells come from cells, in 1858, by Rudolph Virchow[20] (1821-1902), a student of Johannes Muller, the blastema theory was given up. No, it did not happen. The blastema theory spread all around the world. Oddly, two eminent physicians in Philadelphia in the United States, Samual D. Gross (1805-1884) and Joseph Woodward (1833-1884), held on to it longer[21,22] than

most others. Woodward, in an award lecture presented[22] at the Smithsonian Institute in Washington, D.C., proposed that cancer cells were formed by metamorphosis from exuded white blood cells.

Despite difficulties in convincing many, the blastema theory was gradually replaced by the embryonic rest theory of Julius Cohnheim (1839-1884). Cohnheim, a student of Virchow, reintroduced[23] in 1877 Récamier's nearly fifty years old[14] embryonic rest theory with some modifications. He named highly vascular sites, e.g., orifices and mucocutaneous junctions, as prevalent sites of unutilized embryonic cell rests. He also considered embryonic vestiges, e.g., the urachus, mesonephros, and the Gartner duct, as well as unused cell rests in the adrenal, thyroid, liver, breast, ovary, and other organs as precursors of cancer.

At just about the time when the cancerous blastema theory was given up and the embryonic rest theory resurfaced, cancer of the tongue and lips were definitively linked to smoking.[24] It was proven that industrial tar, coal tar, and crude paraffin caused skin cancer.[25] Bladder tumors in workers in chemical and rubber factories were linked to exposure to aniline, fuchsin, and related chemicals.[26] Investigations of industrial and occupational exposures showed high prevalence of lung cancer in workers in cobalt, bismuth, and nickel mines, whereas skin cancers in farmers and sailors were linked to chronic exposure to sunlight.[27]

Advances in bacteriology, especially the identification of bacteria and parasites as infection-causing organisms, led to a search for cancer-causing organisms. At the turn of the nineteenth century, an endless number of articles and monographs was published on cancer-causing microbes and parasites.[28–30] Some investigators went as far as claiming that cancer cells were not epithelial cells but that they were parasites, coccidian.[28] Of all these efforts, two parasites, *Schistosoma haematobium*[31] and later on *Clonorchis sinensis* were proven to be related to bladder cancer and cancer of the bile ducts, respectively. The infection theory was also extended to viruses. Although numerous viruses were shown to produce tumors in experimental animals, the first virus, the Epstein–Barr virus linked to human cancer, was not discovered until 1964.

As microscopic examination of cancer cells became routine laboratory procedure, it was inevitable that chromosomal anomalies, including asymmetry, were noticed.[32] Within a decade, hereditary transmission of chromosomal changes was confirmed.[33] In 1914, Theodor Boveri (1862-1915) was the first to propose[34] that a change in the chromosomal constitution of cells is one of the prerequisites for malignant transformation of cells. He wrote that cancer cells almost always contain an abnormal chromosome complex. The abnormality is due to a defect that results in accelerated and abnormal nuclear division that is visible under the microscope as atypical, multipolar, mitosis. It was deducted that if alterations in the chromosomes were prerequisite to cancer, all that caused such changes, including radiation, were carcinogens. Indeed, within a few years after the discovery of the x-ray, the first radiation-induced carcinoma was reported on the hand of a technician.[35] The first report was followed by voluminous literature on the subject. Most of the reported cases occurred in radiologists and were mostly carcinomas with a few leukemias and sarcomas. Similarly, within a decade after radium was isolated from uranium, irradiation-induced cancers began to appear.[36]

In 1911, Moritz Ribbert (1855-1920) of Germany introduced the theory that detachment of cells from each other by increased tissue tension, under external and internal stimuli, caused dislocation and uncontrolled growth of cells.[37] James Ewing (1866-1943) of New York added to the above concept that this uncontrolled growth produced primitive, embryonic cells with unlimited potential.[38] Ewing believed that local irritation can induce such an uncontrolled growth of cells, and he listed several examples, among which were carcinoma of the lower lip due smoking a clay pipe, oral carcinoma due to chewing of betel leaf mixed with tobacco and lime, esophageal carcinoma due to consumption of hot food and spices, skin carcinoma due to burns (from Kangris in natives of Kashmir), and carcinoma of the bladder and other organs due to chronic inflammation, fistulae, ulcers, trauma, stones, and parasites. Among toxic chemicals, he included arsenic and alcohol as carcinogens and pointed out that carcinoma of the lung occurs in workers who inhale tobacco dust in cigar factories and in the chromate industry. As to heredity's role in the etiology of cancer, Ewing felt there was much to be done, but he indicated that it seemed there were two kinds of heredity: direct transmission of the cancer itself with its abnormal antecedents and indirect transmission by transmission of enhanced liability to cancer. He warned that it would be a mistake to believe that the etiology of all cancers is the same. He found puzzling that active growth of cancer is occasionally interrupted by periods of relative or complete quiescence and questioned whether this periodicity in growth is due to changes in the life cycle of an oncogenic virus.[38]

In 1923, the first discussion was published on increased incidence of pulmonary cancer in cigarette smokers.[39]

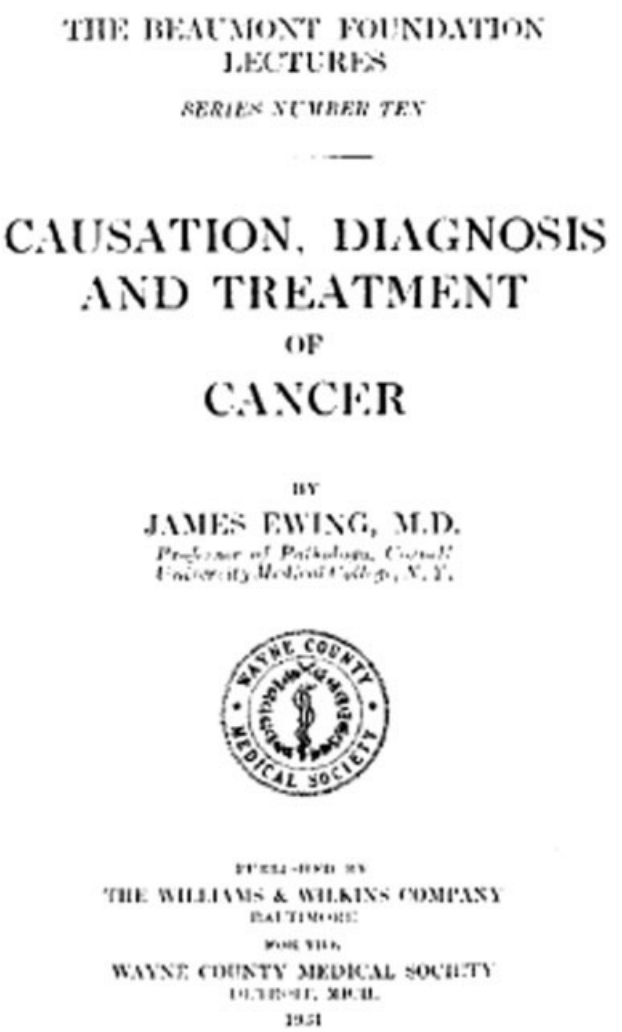
As to brain tumors, theories of tissue tension, displaced heterotopic cells, increased vascularity, and neuroglial repair were entertained, but, ultimately, it was admitted that, when all had been said, the cause of growth of glial neoplasms remained unknown.[40]

Radioactivity in causation of osteosarcoma in luminescent-dial painters brought renewed interest in the danger of radiation.[41]

Before the 1920s ended, the importance of cells and their cytologic alterations in development of cancer were presented in a more concise way than ever before.[42] The author emphasized that the cancer problem is mainly due to chromosomal changes in nuclei of cancer cells and to disruption of the normal connection between the nucleus and the cytoplasm. These phenomena expressed microscopically in many forms, including alteration in the nuclear–cytoplasmic ratio. It was suggested that frequent presence of lymphocytes around cancers may represent an unknown defense mechanism against cancer or that the lymphocytes may be carriers of the carcinogen.

In 1931, James Ewing in his 87-page monograph on cancer[43] devoted 30 pages to causation of cancer (Fig. 2). He wrote that it is a serious misconception to consider cancer a single disease. If there are multiple forms of cancer, he wrote, then there must be multiple causes. Ewing listed scores of known factors that may cause cancer and added a few new ones, injury to chromosomes, viruses, excessive secretion of sex hormones, increased fatty and mineral acids in the diet, foreign bodies and nonhealing wounds, constipation, hyperplasia and hypertrophy, loss of growth restraint in bone, polyps, papillomas, cysts, obesity, alkalosis of blood, and fumes from automobiles. In his concluding remarks, he underlined that experimental production of cancer has thrown much light on the origin of many cancers but has explained none of them completely, particularly not cancers in humans. Ewing was an invited lecturer at the London Cancer Conference in 1928. He presented his thoughts on "The Causal and Formal Genesis of Cancer." Part of his lecture was reproduced in a book dedicated to Ewing.[44] Among the many things Ewing said, he indicated that the observed increase in cancer of the lung during recent years was highly suggestive of its correlation to the immense spread of cigarette-smoking habits. Within a year of the publication of Ewing's monograph,[43] an entire book was published on primary carcinoma of the lung,[45] shortly after cancer of the lung was linked to asbestosis.[46]

Leukemia, from the time the name was coined in 1845 by Rulph Virchow,[20] was not regarded as cancer. This assumption was suddenly changed in 1938 by the publication of a book.[47] The writer stated that although leukemia is widely distributed over the world and no races or groups of people are immune to it, almost nothing is known of the cause of leukemia, a disease that behaves like cancer. As to potential causes, the author listed unidentified infectious agents, excess or deficient formation of some essential substance in blood, or heredity by interaction of primary and associated genes.


THE BEAUMONT FOUNDATION LECTURES

SERIES NUMBER TEN

CAUSATION, DIAGNOSIS AND TREATMENT OF CANCER

BY

JAMES EWING, M.D.

Professor of Pathology, Cornell University Medical College, N. Y.

WAYNE COUNTY MEDICAL SOCIETY

THE WILLIAMS & WILKINS COMPANY

BALTIMORE

WAYNE COUNTY MEDICAL SOCIETY

DETROIT, MICH.

1931

FIGURE 2. Title page of James Ewing's Causation, Diagnosis and Treatment of Cancer, 1931 (See Reference 43). Reprinted from the author's private collection.

The role of heredity in genesis of cancers in general, and in particular in breast cancer, was reviewed[48] in 1946. The author concluded that there are numerous inherited precancerous and cancerous conditions that are unequivocally linked with genetically determined genes. Among neoplasms with genetically transmitted genes, retinoblastoma, breast carcinoma, certain uterine and ovarian can-

TABLE 1
Chronology of Events

Year(s) and Events in Medical History		Year(s) and Events in World History	
129–200	Galen names black bile as carcinogen	160–168	First invasion of the Roman Empire occurs
1567	Paracelsus links cancer to chemicals	1564	Michelangelo dies, Galileo and Shakespeare born
1776	Peyrilhe publishs the first monograph on cancer	1776	U.S. Declaration of Independence signed
1793	The term cancerous diathesis introduced	1793	Louis XVI and Marie Antoinette executed
1811	Heredity of cancer described	1808	Dalton introduces the atomic theory
1829	Embryonic rests origin of cancer proposed	1827	Beethoven dies
1838	Müller's blastema theory published	1838	Schwann provides first description of human cells
1895	Industrial carcinogens referenced	1896	Becquerel discovers radioactivity of uranium
1902	First radiation induced cancer reported	1901	First Nobel Prizes awarded
1923	Cancer of the lung linked to cigarette smoking	1923	Insecticides introduced
1938	Leukemia named as cancer	1939	Second World War begins
1950	Link between cigarette smoking and some lung cancers established	1950	North Korea invades South Korea
1960	Philadelphia chromosome discovered	1959	Hawaii becomes 50th state of the U.S.

cers, neurofibromatosis, and polyposis of the colon were listed.

The aftermath of the Second World War heightened attention to radiation-induced cancer. Reports were documenting local and systemic damages including thorotrast injection-induced angiosarcoma of the liver,[49] radiation-induced leukemia in radiologists,[50] bone sarcomas in irradiated bones,[51] and thyroid cancer in childhood and adolescence after radiation of enlarged thymus.[52]

Following prior leads,[24,39,44] two articles appeared in 1950 that linked lung carcinoma to cigarette smoking.[53,54] The writers pointed out that although they found that cigarette smoking was closely related to carcinoma of the lung, no such association could be found in a group of patients with adenocarcinoma and that 32 percent of female lung cancer patients were nonsmokers[53] (Table 1).

Earlier references to chemical carcinogens followed in the 1950s, placing attention on intracellular, enzymatic changes in cancer cells.[55] Also in the 1950s, advances in chemistry and biochemistry permitted specific identification of carcinogenic compounds in historically known carcinogens.[56]

Specific intranuclear alterations and chromosomal changes were noted in cancer cells during the last several decades before the 1950s,[32–34,42] but the technology to observe minute changes in chromosomes was lacking. In the 1960s, things changed for the better by the discovery of a small chromosome (that was later named the "Philadelphia chromosome") in leukemic cells from patients with chronic myelogenous leukemia.[57] The discovery gave impetus to a relatively new field, cytogenetics. Of course, by everybody's admission, it remained to be resolved whether chromosomal changes were initiators of cancer or were just epiphenomena.

Since 1960, a long list of proven and suspected cancer-causing chemical, physical, and biologic agents has been compiled. But an analysis of thoughts about causation of cancer after 1960 would be beyond the scope of this review, because anything that has occurred during the last five decades cannot be regarded as history.

REFERENCES

1. Hajdu SI. Greco-Roman thought about cancer. *Cancer*. 2004; 100:2048-2051.
2. Paracelsus BHTPA. Von der Bergsucht oder Bergkranckheiten drey Bücher. . .Dilingen: Sebaldum Mayer, 1567.
3. Paré A. Deux livres de chirurgie. Paris: A. Wechel, 1573.
4. Deshais-Gendron C. (Translated from the French by J. Tayler). Enquiries into the nature, knowledge and cures of cancer. London: J. Taylor, 1701.
5. Boerhaave H. Aphorismi de cognoscendis et curandis morbis. Lugduni Batavorum: J. vander Linden, 1709.
6. Etmullerus M. Description of All Diseases Incident to Men, Women and Children with an Account of their Causes, Symptoms and most approved Methods of Cure. London: Andrew Bell, 1712.
7. Le Clerc CG. The Compleat Surgeon. London:Walthos, Wilkin, Bonwicke and Ward, 1727.
8. Pott P. Chirurgical observations relative to the cataract, polypus of the nose, the cancer of the scrotum, the different kinds of rupture and the mortification of the toes and feet. London: Hawes, Clarke and Collins, 1775.
9. Peyrilhe B. Dissertation Académique súr Le Cancer. Paris: Buault, 1776.
10. Motherby G. A new medical dictionary; or general repository of physic, containing an explanation of the terms, and a description of the various particulars. London: J. Johnson, G. and J. Robinson, A. Hamilton, J and J. Murray, 1791.
11. Pearson J. Practical Observations on Cancerous Complaints. London: J. Johnson, 1793.
12. Johson CT. A Practical Essay on Cancer. Philadelphia: E. Parker, 1811.
13. Broussais FJV. Histoire des Phlegmasies ou Inflammations Chroniques. Paris: J.B. Bailliére, 1826

14. Récamier JCA. Recherches sur le Traitment du Cancer. Paris: Gabon, 1829.
15. Lisfranc M. Diseases of the Uterus. (Translated from the French by G. Henry Lodge) Boston: W.D. Ticknor, 1839.
16. Müller J. Ueber den feinern Bau und die Formen der krankhaften Geschwülste. Berlin: G. Reimer, 1838.
17. Paget J. Lectures on Surgical Pathology. London: Longman & Associates, 1853.
18. Lebert H. Traité Pratique des Maladies Cancéreuses. Paris: J.B. Bailliere, 1851.
19. Ollier L. Recherches Anato-Pathologique sur la structure intime des Tumeurs Cancéreuses. Montpellier: Boehm, 1856.
20. Hajdu SI. Rudolph Virchow, pathologist, armed revolutionist, politician and anthropologist. *Ann Clin Lab Sci.* 2005;35: 203-338.
21. Gross SD. System of Surgery. Philadelphia: Henry Lea, 1866.
22. Woodward JJ. On the structure of cancerous tumors and the mode in which adjacent parts are invaded. Washington, DC: Smithsonian Institute, 1873.
23. Cohnheim JF. Vorlesungen über allgemeine Pathologie. Berlin: Hirschwald, 1877.
24. Cooke TW. On Cancer: Its allies and counterfeits. London: Longmans, Green and Co., 1865.
25. Volkmann R. Beiträge zur Chirurgie, anschliessend an einen Bericht über die Thätigkeit der chirurgischen Universitäts-Klinik zu Halle im Jahre 1873. Leipzig: Breitkopf u. Härtel, 1875.
26. Rehn L. Ueber Blasentumorem bei Fuchsinarbeitem. *Arch Klin Chir.* 1895;50:588-600.
27. Unna PG. Die Histopathologie der Hautkrankheiten. Berlin: Hirschwald, 1894.
28. Pfeiffer RFJ. Die Protozoen als Krankheitserreger. Jena: Fischer, 1891.
29. Delepine S. Protozoa and carcinoma. *Brit Med J.* 1892;2:671-676.
30. Andrews E. A study of the locations of 7881 primary carcinomata as illustrating the probability of a cancerous microbe. *JAMA.* 1899;13:738-743.
31. Ferguson AR. Associated bilharziasis and primary malignant disease of the urinary bladder. *J Pathol Bacteriol.* 1911;16: 76-94.
32. Hansemann D. Ueber asymmetrische Zelltheilung in Epithelkrebsen und deren biologische Bedeutung. *Arch Path Anat Physiol.* 1890;119:199-326.
33. Sutton WS. The chromosomes in heredity. *Biol Bull.* 1903; 4:231-251.
34. Boveri T. Zur Frage der Entwicklung maligner Tumoren. Jena: Fischer, 1914.
35. Frieben EAFA. Cancroids des rechten handruckens, das sich nach langdauernder einwirkung von Roentgenstrahlen entwickelt hatte. *Fortsch Geb Roentgenstr.* 1902;6:106.
36. Colwell HA, Russ S. Radium, x-rays and the living cell. London: G. Bell and Sons, 1915.
37. Ribbert MWH. Das Karzinom des Menschen, sein Bau, sein Wachstum, sein Entstehung. Bonn: F. Cohen, 1911.
38. Ewing J. Neoplastic Diseases. Philadelphia: W.B. Saunders Co., 1919.
39. Fahr M. Besprechung. *Verh dt path Ges.* 1923;19:192.
40. Bailey P. Cushing HW. A classification of the tumors of the glioma group on a histogenetic basis with a correlated study of prognosis. Philadelphia: J.B. Lippincott, 1926.
41. Martland HS, Humphries RE. Osteogenic sarcoma in dial painters using luminous paint. *Arch Path.* 1929;7:406-417.
42. Sokoloff B. Recherches Cytologique et Biologique consacrées au Probleme du Cancer. Vienne: Haim & Co., 1926.
43. Ewing J. Causation, Diagnosis and Treatment of Cancer. Baltimore: Williams and Wilkins Co, 1931.
44. Adair FE. Cancer. Philadelphia: J.B. Lippincott Co., 1931.
45. Fried BM. Primary Carcinoma of the Lung. Baltimore: Williams and Wilkins Co., 1932.
46. Lynch KM, Smith WA. Pulmonary asbestosis: Carcinoma of lung in Asbestos-silicosis. *Am J Cancer.* 1935;24:56-59.
47. Forkner CE. Leukemia and Allied Disorders. New York: Macmillan Co., 1938.
48. Jacobsen O. Heredity in Breast Cancer. London: Lewis, 1946.
49. MacMahon HE, Murphy AS, Bates MJ. Endothelial cell sarcoma of liver following thorotrast injections. *Am J Path.* 1947;23:585-611.
50. March HC. Leukemia in radiologists. *Radiology.* 1947;43: 275-278.
51. Cahan WG, Woodward HQ, Higinbotham NL, Stewart FW, Coley BL. Sarcoma arising in irradiated bone. Report of eleven cases. *Cancer.* 1948;1:3-29.
52. Duffy BJ, Fitzgerald PJ. Thyroid Cancer in childhood and adolescence. *Cancer.* 1950;3:1018-1032.
53. Wynder EL, Graham EA. Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma. *JAMA.* 1950; 143:329-336.
54. Doll R, Hill AB. Smoking and carcinoma of the lung. *Brit Med J.* 1950;2:739-748.
55. Greenstein JP. *Biochemistry of Cancer.* New York: Academic Press, 1954.
56. Kennaway E. Identification of carcinogenic compound in coal tar. *Br Med J.* 1955;2:749-752.
57. Novell PC, Hungerford DA. A minute chromosome in human chronic granulocytic leukemia. *Science.* 1960;132:1497.