# DIGITAL AGE

## Special Topics: Cancer

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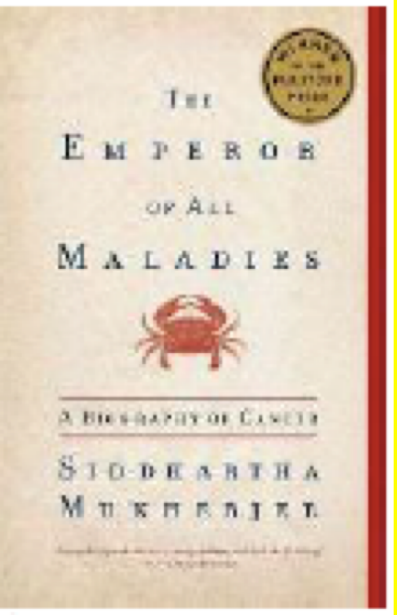



# HISTORICAL LANDMARKS

Following mainly the book:
The Emperor of all Maladies / Siddhartha Mukherjee

# Cancer documented in antiquity

**1862 Edwin Smith papyrus** documented scripts, probably of **Imhotep from 2500 BC** describing cancer as a stiff and cold lymph.

**440 BC Herodotus** described breast cancer to the queen of Persia, Darius' wife, who was operated by Demosdes the Greek (who probably convinced Darius to invade Greece).

**400 BC Hipocrates** coined the name "CANCER" from the structure of blood vessels around it.

**Galen 129-210 AC** linked Cancer to black humor, and claimed there is no cure. The surgical procedures without anesthesia (e.g. cutting with dull knifes, burning with red-hot iron, or treatment with sulfuric acid), it may have been better not to treat cancers… Since probability of cancer increase with age, it was not very common in antiquity.

**1533 Andreas Versallius** Studied corpses of the death sentenced, and skeletons of the black plague piled in the catacombs. He published a book in anatomy, and found many errors in Galen books, e.g. no black humor. .

**1793 Matthew Baillie** published in London a book on anatomy. Described lung and gut cancers. Also failed to locate black humor channels.

**1760 John Hunter** a Scottish physician, classified cancer stages of development.

**1846 William Morton** Applied anesthesia in surgery, demonstrated in Boston.

**1865 Joseph Lister** a Scottish physician who understood that open wounds cause pus, fever and infection. He cleans (disinfects) wounds with Carbolic acid (used to disinfect sewage)
**1869** Performed surgeries with disinfection and under anesthesia,

**1856 Louis Pasteur** discovered that meat rots in air, but preserved in close containers – connects to bacteria in the air.

**Marie Curie** died from cancer, after long exposure to radioactive materials in her research.

**1890 William Halsted** radical surgery to extrude cancer and remove metastases – Mastectomy, yet cancer retured.

Famose European surgeons that Halsted studied with:
**Theodor Billroth, 1880** Vieneese that initiated the radical surgery to remove cancer.
**Richard von Volkmann** from Haley, Germany. Expert in breast cancer surgery.
**Hans Chiari** Liver cancer surgeries.
**Anton Wolfer** Surgeries of thyroid cancers
With time Halsted taught anatomy with specialty in cancer removal by surgery of various organs: brain, lungs, liver etc.
But surgeries involved heavy blood shedding, and without blood transfusion technology they often caused death.

**Charles Moore** identified the margins of the solid cancer as the source of cancer reoccurrence, and supported radical surgery in breast cancers, including removal of lymphs, despite the resulted inflated hand from accumulation of liquids.

Cancer grading (local or metastatic) is related to chance of recovery.

**1838 Matthias Schleiden & Theodor Schwann** "Cell theory" – all life is built from a basic unit.

**1840-58 Rudolf Virchow** "Omnis cellula e cellula" cells comes from cell (do credit to Lamarc…).
Another step in Schleiden & Schwann's cell theory. No spontaneous life.
Leukemia – blood cancer – is uncontrolled proliferation of white cells. Neoplasia – uncontrolled cell growth – a characteristic of all cancers.

**1937 President Rosevelt** established the National Cancer Institue. The president, who was hit by Polio, drove the "MARCH OF DIMES" to raise funding for the children's hospital in Boston.
**1940 Jonah Salk & Albert Sabin** developed polio vaccines.
**1939-** – antibiotics (penicillin, chloramphenicol, tetracyclin, streptomycin) and vaccines (Polio, tuberculosis and more). The resulting death prevention brings forth heart failures and cancers and the main causes of death.

**1926 George Minot** lack of vitamin B12 causes anemia. Nobel 1934.

**1928 Lucy Wills** Folic acid is necessary for DNA synthesis, and its deficiency causes anemia.
**Sidney Farber** and the chemist **Yellapragada Subbarao** try to cure anemia by "antagonists" to folic acid

**1856 William Perkin** – London chemist, purple Aniline from coal tar.
**1928 Fredrich Wöhler** Following his synthesis of Urea, organic chemistry developed.
**Adolf von Bayer** the German industralist followed with synthesis of anillin, alizarin and crimson dyes, with impact on textile, cosmetics and pharmaceuticals.

**1878 Paul Ehrlich** "Magic bullet" strategy to apply dyes derivatized from Aniline to stain tissues from biopsies.

**1882 Robert Koch** stained bacteria, and confirmed their role in tuberculosis.
Ehrlich discovered that injection of some poisons to the body induce synthesis of "anti-poisons" in the blood: antibodies fitting the poisons like "key to keyhole" and specifically bind and precipitate the poison. Start of chemotherapy. He found chemicals that suppressed bacteria causing sleeping sickness (Trypan red) and sifilis (Salvarsan). Ehrlich received Nobel 1908 for discovering the specific affinity, but the similarity of cancer to normal cells makes specific binding unavailable to locate cancers.

**1900 Henri Becquerel, Pierre & Marie Curie: Uranium, Radium , William Röntgen: X-rays**
**Emil Frubbe** After the discoveries of the effect of radiations on killing cells, built a x-ray source in Chicago that he used to focused irradiation of cancers, Later for similar application radioactive sources were used. Although it was clear that radiations also cause cancers, (specially leukemia), the technology was used as a surgical knife with low risk, and effective solid cancer killing results. It failed to suppress metastases.

**1919 Edward & Helen Krumbhaar** , following WWI use of mustard gas, found tat survivers of gas attacks suffered low blood counts and bone marrow injuries. Already **Percelsus**, at the 16th century, noted that every poison may be a useful drug at low doses.

**1942 Louis Goodman & Alfred Gilman** therefore applied mustard gas to attack white blood cancer cells. They succeeded to obtain remission in leukemia, proving that chemicals can specifically target cancers.

**1838  George Hitchings & Gertrude Elion** searched for synthetic chemicals as drugs. Trudi Elion was a chemist working in color preservation of pickles and mayonese, and joined Hitchings lab in the medical studies. She received Nobel for the chemistry of Purines. 6-mercapto-purine was found effective for ALL - Acute Lymphoblastic Leukemia.

By 1955 tens of thousands chemicals from fermentation of yeast, plant extracts, marine life and more were tested as chemotherapy agents.
Selman Waksman isolated Actinomycin-D from purple bacteria, and found synergistic to radiation treatments.
**1940 Streptomycin** found effective treatment for tuberculosis
Discovery of bacterial resistence to drugs developed antibiotic cocktails.
Markers, typically hormones, that indicate cancer speard and retraction, facilitate feedback of treatment efficiency. Continued chemotherapy even after cancer retracted was found effective in preventing reoccurrence.
**1958 Vincristin** – a plant alkaloid, was found to arrest cell proliferation, and included in VAMP cocktail.
To treat brain cancers, and cross the brain-blood barrier, chemotherapy is directly injected into the brain.
Morphological identification of blood cancers by microscopy
**1950 Caplan** in San Francisco used accelerators as focused beams to treat cancer
**1909 Peyton Rous sarcoma virus** was found to cause cancer due to somatic mutations.
Nobel 1966
**Papiloma virus** was found to cause ovary cancer

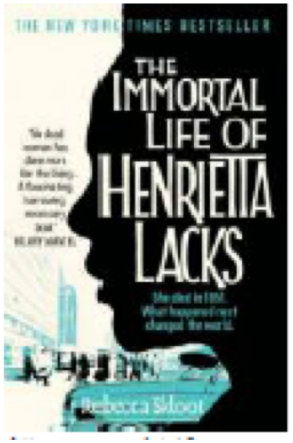
**1947 Sydney Farber** was first to apply chemotherapy: he injected to sick children Aminopterin that arrest white blood cell division.

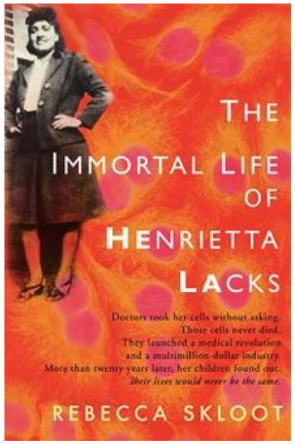
Following the "march of dimes" and "Gimmy fund" (Gimmy was a sick child who drove the funding campeign) he built the childred hospital. **Marry Lasker** volunteered to head raising funds, founded "The American Cancer Society" and recruited Farber to raise governmental support. **Gordon Zubrod** was the first director (after he organized the war agains Maleria during the world war, and established the first controlled drug experiments). He was responsible for Nixon's extensive cancer funds.

**Jay Freireich & Tom Fri** joined the search for natural and synthetic chemicals as anticancer drugs. They developed driug cocktails (first two, then three and four) hoping to see synergism. WAMP was their first successful cocktail.

**David Nathan** spead the combinatorial treatments..

**1951 George Otto Gey** used cells he took from Henrietta Lacks , a ovary cancer patient (probably without her permission), and showed they continue to proliferate in culture without losing their vitality (as typically cell cultures do). They established HeLa “cell line” very commonly used today in cell biology. They followed by generating other cell lines from different organs and tissues, cancerous and normal, with varying levels of vitality. Such lines are usually not stable genetically for many generations, therefore the “age” is indicated for such cultures (by number of “transfers” from a confluent dish into a diluted reseeded plate) . The NIH holds a large bank of cell lines, frozed and preserve in capsules, and supply them to researchers all over the world.




Ribecca Sloot’s
Best seller
“The immortal life
Of Henrietta Lacks”

**Establishment of controlled procedures for medical research**

**1928 Noiman & Pearson** Statistics**,** p-value

Placebo and tested drug in the same study

**1976 Barnet Rosenberg** Studied electric effects on cells –ith platinum electrodes. Arrested cell division.

**Cisplatin** - a known chemical reapplied for chemotherapy (affects DNA)

**Taxol –** extracted from tree bark, arrest cell proliferation. A main component in chemotherapy. The high doze applied cause vomiting and hair loss.

**1929 Edward Doisy** discovered estrogen & testosterone and treated bladder and breast cancers with male and female hormones.

**1890 George Beaston** found that uterus dissectomy for caws reduced the amount of milk

**1968 Elwood Jensen** discovered the receptor for estrogen – found only in part of breast cancers. Treated with tamoxifene as an antagonist to estrogen.

Combined surgery and chemotherapy inprove recovery probabilities

Early diagnosis methods – pap smear, mammography: prevention is the best therapy

Problem with over-treatment of benign cancers - false positives versus negative diagnostics.

Already **Rober Koch, 1884**, showed correlation between bacteria and diseases, but understood correlation is not a proof of cause.

**Carcinogens** – chimney cleaners, smokers, asbestos.

# Cancer as a genetic mutation

Cancer cells have defects in cell control mechanisms

**1989 Bishop & Vermus** discovered Src phosphorylation (Nobel 1989)

**Weinberg** – cancer is a defect in cellular control mechanisms – oncogens: Mek, Erc, Her2, myc, neu, ras : signaling pathways molecules. Their mutations cause cancer.

**BRCA, Rb-retino blastoma** – cancer as an hereditary disease.

**P53** cancer suppressors.

**1988 Bet Vogelstein** – a minimal number of mutations are needed for cancer to develop:

- Angiogenesis – attract blood vessels to the cancer
- Apoptosis – cause programed cell death if detected malfunctions.
- Kinase suppressors – to stop uncontrol activation of cell growth and division.
- Cell migration – evasion of individual cell from the cancer main body into surrounding normal tissues, or to the blood and settling in far tissues – Metastasis.

Cancer starts locally – surgery for removal is then effective.

Cancer cells divide fast – chemotherapy including suppression of cell proliferation cause cancer recession: for breast cancer- Tamoxifen, Herceptin (recombinant DNA technology for its production – Genentech).

For leukemia (CML chronic myeloid leukemia) - c-kvt, Gleevec

For stopping blood vessel extension – Avastin

To suppress the waste-removal mechanisms, very active in cancer cells - Velcade

The human genome project facilitated identification of various mutations found in different cancers, in a systematic research to treat the results of mutation.
Personal gene sequencing is expected to serve for prevention and prediction,
And single cell sequencing will identify the mutations occurred in a specific cancer and develop “directed medicine” or “personalized medicine” to overcome cancer diversity and the need to treat each type differently.