

A NOTE FROM HISTORY

2000 Years of Chemotherapy of Tumors

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From the earliest time there have been remedies for the treatment of cancer, usually in the form of ointments, pastes, plasters, powders, aromatic water, wine, and medicated herbal solutions. The first written prescriptions date back to 2000 BC to the Sumerians, Chinese, Indians, Persians, and Egyptians.

Although plant remedies ("Herbals") were the most common, ingredients derived from minerals (iron, copper, sulfur, arsenic, and mercury) and animals (liver, bones, and urine) were also used.

The Greeks and Romans followed the traditional art of collecting and preparing remedies. The first herbal, a simple *Materia Medica*, was put together by the Romans and remained to be used for 15 centuries.¹ Pliny the Roman (AD 23-79) modified substantially earliest herbalists' simple remedies (for example, cabbage juice) for cancer by preparing concoctions, compound remedies. For the internal therapy of cancer he recommended a boiled mixture of ash of sea crabs, egg white, honey, stinging nettle with salt, and botryon (a powder made from the dried feces of falcons). Pliny's work was one of the first scientific texts to be printed, shortly after the invention of the printing press in 1469.²

Despite the generalized superstition of the Greeks and Romans when it came to the care of diseases, their rational thinking led them to recognize that a remedy can be medicinal as well as poisonous. Celsus (25 BC-AD 50) an influential Roman physician, taught that cancer can be cured by diet, medicaments, and surgery. However, his thinking and reasoning were replaced by the dogmatic teaching of another Roman physician, Galen (130-200). Galen prescribed simple and compound natural herbal remedies for cancer because he believed cancer was caused by an accumulation of bad bile and it must be purged from the body. His authority and his followers prevented any thought of alternative causes of cancer and new remedies for 16 centuries.³

Paulus of Aegina (625-690), the last of the eminent Greek physicians, had an elaborate list of drugs, all unappreciated with the exception of mandrake. Mandrake is a plant with split roots. It resembled to those with vivid imaginations the body and legs of a man; therefore it was believed to possess a cure for all ailments, including cancer (Fig. 1). The juice of mandrake became a popular remedy and remained so throughout the Middle Ages because it supplied physical evidence to the believers in magic and ghosts.¹

In Medieval Europe medicinal remedies were prepared by monks in monasteries according to Galenian formulas. It was an

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FIGURE 1. Mandrake, a plant with roots like a carrot, was used as a remedy for all diseases, including cancer. Reprinted from the author's private collection.

accepted fact that cancer in the body must be diluted with sugar water and cleared out with purgatives and related soothing, Paregoric, remedies. One of the most popular Paregoric preparations was used for internal ailments, wasting, and hidden cancer, and was a formula containing arsenic, camphor, licorice, honey, alcohol, and boiled viper's flesh.⁴ It was optional to add dried toad. Another remedy, *Blatta bizantina*, was particularly well received by nonherbalists and was prepared from dried cockroaches and used as an oily preparation for skin tumors, warts, ulcers, and cancer.¹

Among the mediaeval legacies of Arabian medicine are: the introduction of alchemical techniques (the transmutation of metals with each other), writing of prescriptions, creation of pharmacies, and introduction of the rule of "Quid pro Quo," meaning, if a drug was not available a substitute drug was permitted to be prescribed. This type of permissive approach called for standardization in the preparation of remedies that began with the publication of the Nuremberg Dispensatorium in 1546. A major contributor to the success of standardization was the introducer of iatrochemical (balance of chemicals) hypotheses, Paracelsus (1493–1541).

Paracelsus (Fig. 2), a native of Switzerland, studied metallurgy, alchemy, and chemistry at the University of Basel. He was a capable physician and an original thinker. He did not accept authority, particularly not the Galenian humorists' teachings.⁴ He criss-crossed Europe many times and because of his beliefs he



FIGURE 2. Paracelsus, Theophrastus Philippus Aureolus Bombastus von Hohenheim (1493–1541). Reprinted from the author's private collection.

made many enemies. After he was forced to flee from Basel, he settled in Salzburg. Shortly after he arrived in 1541, he died due to trauma he suffered in a tavern brawl with his foes. Paracelsus believed that diseases, including cancer, were caused by the precipitation of chemicals and that health can be restored only by chemicals. He is credited with the introduction of many chemicals as internal remedies, including mercury, lead, sulphur, iron, zinc, copper, arsenic, iodine, and potassium.⁵ Paracelsus published hundreds of chemical formulas and wrote several monographs on therapeutics. His book *De Grandibus*,⁶ published posthumously in 1562, contains most of his innovations in chemical therapy, chemotherapy. He believed that cancer could be effectively treated with simple or compound chemicals in gradually increasing doses. However, he warned that all chemicals are potentially poisonous and that the dose is what makes them poisonous or not poisonous.¹

During the immediate post-Paracelsus period mercury was used externally as a caustic and internally in solution under the name of "Calomel," and recommended for the destruction of fleshy cancer, for example cancer of the tongue. Arsenic was employed internally and was claimed to prevent firm cancer from ulcerating. It was also the remedy to stop bloody discharge. It was advanced that iodine of iron and

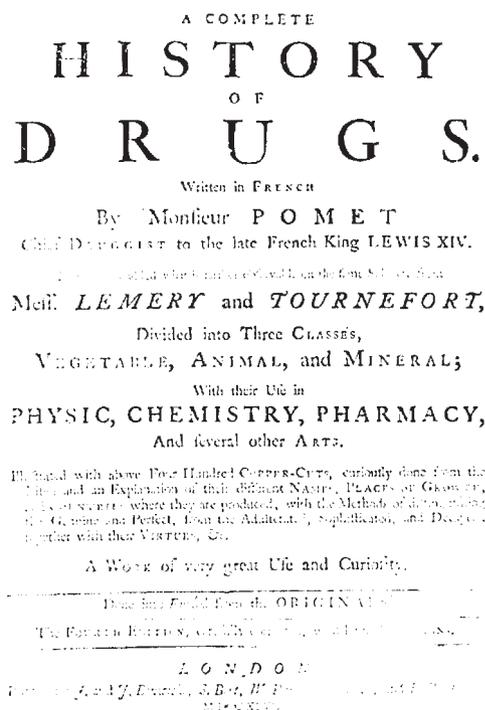


FIGURE 3. Title page of the English translation of Pierre Pomet's *History of Drugs*, 1748. The original was published in France in 1694 (see Reference 9). Reprinted from the author's private collection.

iodine of starch given in solvent twice daily, 2 hours after eating and continued for several months, prevented the spread of breast cancer beyond the breast.^{7,8}

Near the end of the 17th century it was generally accepted that cancer started as a local lesion and grew by destroying surrounding tissues. With this in mind, more and more remedies were introduced to cure cancer before it became destructive. The most complete *Materia Medica* of the time, compiled by the druggist Pomet,⁹ listed all known remedies (Fig. 3). This was followed in 1712 by an English publication of available recipes.¹⁰ Some of the highly recommended prescriptions were *Tinctura vitriolata* (two drops a day) and solution of alkali such as camphor, chalk, gold, silver, and salts of lead to correct the accumulation of malignant acids. One prescription was found to be particularly beneficial. It consisted of crab's eye (1 scruple), red coral (1 scruple), salt of tartar (15 grains), oils of cloves (12 drops), oil of cumin (12 drops), and opium (5 grains). The mixture was fermented to powder and divided for seven doses, and one dose was given per day.¹⁰

Despite all claimed cures, Motherby's *Medical Dictionary*,¹¹ published in 1791, admitted that if a cancer cannot be cured with the knife, the method of treatment with medicinal preparations is only pallia-

tive. As a palliative remedy, it was recommended to use a mixture of vinegar and water for ulcerated cancer. If this failed a plaster made of crow's foot, dog-fennel, and arsenic powder should be prepared. The mixture was dried in the sun and after adding the yolk of an egg it was smeared upon a piece of pig's bladder and then laid over the cancer.¹¹ It was indicated that the plaster drops off of itself in about a week and that repeated applications are often needed because the ingredients only reach as far as into the cellular membrane.

For uterine cancer, particularly at postmenopausal age, Motherby¹¹ recommended a tar-water, hemlock, and ferrum ammoniacale bath. For cancerous ulcers of the womb he suggested vaginal injections of a decoction of hemlock, arsenic, opium, gentian of roses, and carrot. Adding carrot was important, he wrote, to control bleeding and to remove the nauseous smell that often attends cancerous ulcers. As to internal remedies, muriated quicksilver (mercury), ferrum ammoniacale, chloride of bromide, and tablets of arsenic were suggested.¹¹ For children with cancer of the eye, three teaspoonfuls of arsenic solution per day was recommended. Finally, he listed a highly recommended prescription of sulphur of zinc, aqueous opium, and extract of conii for lymphatic glands secondarily affected by cancer.

The introduction of pure chemicals as therapeutic agents was extremely slow, as reflected in Récamier's book on treatment of cancer,¹² published in 1829. In over 1200 pages, in 2 volumes, he listed only a few medical remedies: pate of arsenic, nitrate of mercury, and solution of conium. It seems there was a general agreement in the mid-1800s among therapists that long-term application of belladonna plaster and mercurial soap could achieve the long-term cure of scirrhus breast carcinoma.^{13,14} Of all the preparations used as caustics, according to Walshe¹³ and Dupuytren,⁴ arsenic acid combined with soot and saliva held the most promise. Similar results were obtained by the fumigation of superficial cancers with cinnabar and chloride of zinc. Internally, cod liver, milk, boiled figs, and gray lizard were tried with limited success.¹³ Due to inconsistent results, the Medical Committee and the Board of Governors at the Middlesex Hospital in London approved the first clinical trial in the history of medicine to compare the results of internal (medical) and external (surgical) therapies of cancer. The protocol and results were reported by Fell without a convincing conclusion.¹⁵

Increased interest in chemotherapy of tumors during the second half of the 19th century is a conse-

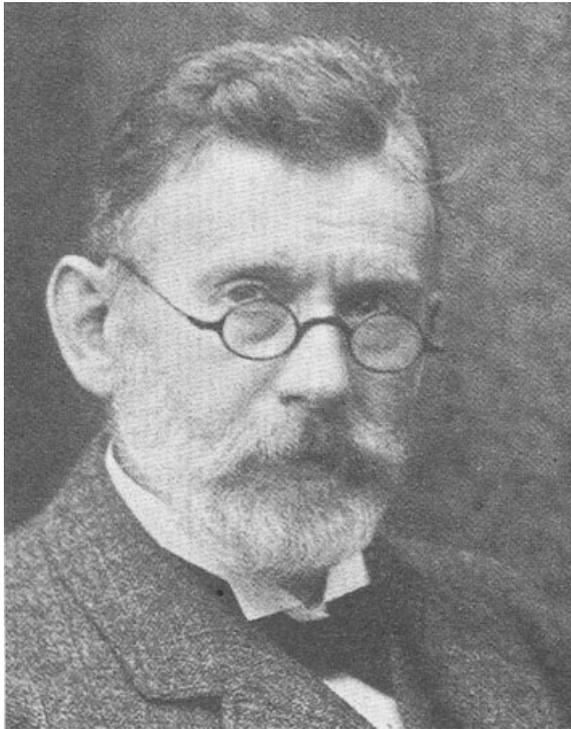


FIGURE 4. Paul Ehrlich (1854–1915). Reprinted from the author's private collection.

quence of the demonstration that microorganisms causing infectious diseases can be killed by chemotherapy. Louis Pasteur (1822–1895), Robert Koch (1843–1910), and Joseph Lister (1827–1912) were pioneers in pathobiology and bacteriology as well as in the chemotherapy of infectious diseases. A contemporary of Lister and a disciple of Koch, Paul Ehrlich (1854–1915), while he was a medical student at the age of 24, discovered by using methylene blue that certain parts of the cells absorbed the stain and other parts did not. In 1891, Ehrlich (Fig. 4) applied his staining methods to the study of blood and bone marrow and was able to distinguish lymphoid and myeloid cells and coined the term of myeloid leukemia.¹⁶ Soon after his work with blood films and intravital stains, Ehrlich discovered the arsenical compound salvarsan to be an effective agent against syphilis and trypanosomiasis. For his work on serum therapy and cellular immunity he shared the Nobel Prize with Metchnikoff in 1908.⁵ Ehrlich's application of the old Paracelsian idea of specific remedies for specific diseases led him to the idea that cancerous cells can be damaged by chemicals without harm to the healthy host tissues.¹⁷ At the time Ehrlich received the Nobel Prize, he was deeply involved in the study of immunology and the chemical effect of paramidobenzol, phenylarsenoxyl, diamidoarsenobenzol, and pyocyanase on carcinomas

Beiträge
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experimentellen Pathologie
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1909

FIGURE 5. The first chemotherapy book in history of medicine (see Reference 18). Reprinted from the author's private collection.

and sarcomas. He summarized his observations in a book¹⁸ of 247 pages that is known to be the first book on chemotherapy (Fig. 5).

After the outbreak of the First World War all scientific works came to halt in Europe. After the war, the seeds of chemotherapy, which were planted in Europe before the war, began to grow in the United States. In 1921 trypsin and amylopsin were introduced as new treatments for cancer, followed by the discovery in 1925 that the injection of urathan in rabbits and rats decreased circulating lymphocytes.¹⁷ The national interest in the United States of conquering cancer was expressed, in 1937, in the National Cancer Act, passed by the Congress.

An observation made during the First World War that mustard gas poisoning caused leukopenia led to the introduction in 1942 of nitrogen mustard as a promising agent to treat lymphomas and leukemias.¹⁹ The conclusion that two naturally occurring substances, inositol and folic acid, inhibited the growth of breast cancer in mice induced thinking regarding whether they were suitable for chemotherapy in humans.²⁰ While these and other chemotherapeutic agents were seriously considered for clinical trials at the conclusion of the Second World War, in 1946, the American Association for Control

TABLE 1
Chronology of Events

| Year(s) | Medical History | Year(s) | World History |
|----------|--|---------|--|
| AD 23–79 | Pliny's remedies for cancer | AD 43 | Roman invasion of Britain |
| 129–200 | Galen and his herbal remedies | 161–180 | Marcus Aurelius Roman emperor |
| 1525 | Hippocratic Corpus printed | 1517 | Martin Luther published his 95 Theses |
| 1541 | Death of Paracelsus | 1532 | Suleiman besieges Vienna |
| 1618 | First <i>Pharmacopoeia</i> issued in England | 1657 | Fountain pen invented |
| 1778 | First <i>Pharmacopoeia</i> published in America | 1775 | War of Independence begins in America |
| 1878 | Ehrlich's differential blood stain | 1863 | Founding of the International Red Cross |
| 1907 | American Association for Cancer Research founded | 1902 | Rockefeller Institute founded |
| 1909 | Ehrlich's book on chemotherapy published | 1910 | Carrel and Burrows first to grow tumor in vitro |
| 1914 | American Society for the Control of Cancer (ASCC) founded | 1915 | Einstein's relativity theory published |
| 1919 | Nitrogen mustard found to cause leukopenia | 1919 | Versailles Treaty signed |
| 1943 | Nitrogen mustard introduced for the treatment of Hodgkin disease | 1943 | Winston Churchill's pneumonia cured with sulfapyridine |
| 1946 | The American Cancer Society formed | 1946 | The United Nations established |
| 1947 | Remission of acute lymphocytic leukemia with aminopterin | 1947 | State of Israel formed |
| 1948 | A new journal, <i>Cancer</i> , is published by the American Cancer Society | 1948 | The first computer programs installed |
| 1952 | Acute lymphoid and chronic myeloid leukemias are treated with 6-mercaptopurine | 1953 | The summit of Mt. Everest reached |
| 1956 | Choriocarcinoma of the uterus cured with methotrexate | 1956 | Soviets crushed the Hungarian Revolution |

of Cancer was reorganized as the American Cancer Society. The publication of the Society's own periodical, *Cancer*, was inaugurated in 1948. In the same year, it was announced that the remission of acute leukemia in children can be achieved with folic acid antagonists.²¹

As a continuation of these efforts, it was realized in the early 1950s that the solution of the cancer problem rested on the discovery of chemical molecules that can reach and destroy the cancer cells in the body. With this realization, the period of a new area in medicine, modern chemotherapy, began. After it was shown in a fast sequence that a pyrimidine antagonist is effective in the treatment of myeloblastic leukemia, vinca alkaloids are useful in the treatment of lymphomas and lymphocytic leukemias, and actinomycin-D possesses carcinolytic properties,^{22,23} it was time to announce in 1956 that a human cancer, choriocarcinoma of the uterus, could be cured with methotrexate.²⁴

Disappointing as it may be, historians are not permitted to dwell into anything that occurred during the last five decades because it cannot yet be regarded as history and therefore cannot come within the scope of this review (Table1).

All in all, the saga of chemotherapy began in prehistoric time with the use of natural remedies and continued in the prebiblical time through the addition of herbal and animal products. In the Middle Ages first minerals and then metals were added to the *Materia Medica*, and by the 1800s chemical compounds were introduced. Finally, in the 1900s, advances in immunology and molecular technology permitted the pro-

duction of a wide spectrum of synthetic drugs to conquer cancer.

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