

## Historical Landmarks of Chemotherapy

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The earliest history of medicine is that of ancient Egypt and reveals the fact that these primitive people searched the vegetable, animal and mineral kingdoms for substances which would be efficacious against disease.

During the 3000 year Pharaonic Dynasties, ending in 340 B. C., and the Chou Dynasty, 1130-250 B. C., chemicals were employed to combat disease. In the latter period mercurial ointments were used in the treatment of syphilis.

In the early middle ages Paracelsus (1493-1541) used lead, copper, mercury, and even derivatives of gold. Chemotherapy probably had its beginning with the work of Paracelsus in 1526. All of these substances were employed wholly in an empirical manner. These hit and miss methods undoubtedly met with success in some instances. Mercury was used by the Arabians for syphilis and they introduced it into Europe in the 16th century.

The Peruvian Indians of the 17th century used cinchona bark, a source of quinine, against remittent fever, malaria. Also, the Brazilians, according to the writings of Willem Piso (1611-1678), a Dutch physician, who visited South America in 1636-44, recognized the value of ipecacuanha root, ipecac, the active ingredient being emetin, for tropical amebic dysentery. Everything under the sun was tried sooner or later with the idea of changing the reaction of the blood in order to make it unfit for the parasite to develop in.

Discovery of antisera for tetanus and diphtheria in 1894 side-tracked this work. This was renewed in a different spirit in 1900 when protozoal parasites became important. Since that time the laboratory has accomplished wonders.

Real experimental chemotherapy began in 1904 with the significant experiments of Dr. Paul Ehrlich and his collaborators Ulenhuth and Shiga. Reported cures of mice suffering from the otherwise fatal trypanosomal disease of human sleeping sickness by a single injection of trypan red were announced. This dye and trypan blue were used in Leishmaniasis. Ehrlich visited this country in 1904. Ehrlich's aim was "Therapie Sterilisans Magna," to kill everything at once. He hoped to destroy the invading organism in one or two days by a single dose of the drug. The action was compared to a bullet going through the body and destroying the parasite but leaving the cells of the host unharmed. The goal was to find a chemical which had greater affinity for the parasite, that is, parasitotropic, than for the tissues of the host or organotropic.

Arsenic was used early in an empirical way. In 1850 David Livingstone, a missionary to South Africa, administered arsenic to animals

sick with tick-fever. There was a temporary improvement followed by decline, reappearance of the parasite and finally death ensued. In India, Lingard used arsenic in surra, a trypanosomal disease (*Trypanosoma evansi*) of horses, cattle, camels and elephants. Again there was usually death after temporary improvement. In 1903 Laveran, discoverer of the protozoan causing malaria in 1880, injected Fowler's solution (potassium arsenate) and noted the same results.

The parasites that survive the treatment become accustomed to the chemical and are no longer affected by it. Such organisms are known as "fast," "chemofast," "arsenic fast." Consequently, one must guard against such fastness in the treatment of disease. A rotation of different kinds of chemicals is used such as compounds containing arsenic, others bismuth and still others containing antimony.

Some of these synthesized preparations were effective in some diseases but gave no results with others. "Trypan blue" proved to be valuable in the treatment of parasites that cause the general disease known as piroplasmiasis affecting mainly cattle but it is very disappointing in the treatment of trypanosomiasis.

Shortly after Laveran's report, Thomas (1905), an Englishman, showed that a proprietary organic arsenic preparation known as "atoxyl" was effective against trypanosomal infections. This announcement led to an expedition headed by Robert Koch to tropical East Africa for the purpose of trying "atoxyl" on natives suffering from sleeping sickness (*trypanosoma gambiense*). "Atoxyl" had marked effect upon the parasite but it was also very toxic to the host and consequently could not be used.

In 1905 Schandinn and Hoffmann announced the discovery of the causative organism of human syphilis (*Treponema pallidum*). All attempts to produce curative antisera failed. Ehrlich's trial experiments of the effect of arsenic compounds upon this treponema and relapsing fever spirochetes seemed promising. Through long tedious processes of elimination more and more effective arsenicals were synthesized. The 606th preparation seemed to have the properties of an effective agent. Experiments with syphilis infected rabbits gave startling results, the treponema was apparently destroyed, lesions healed and cure resulted.

Tests on syphilitic humans (luectics) were confirmed by animals. In 1909, "arsphenamine," its official name, was given to the medical profession. This was an epoch making discovery against a disease which for centuries was a curse to mankind. Metchinkoff and Roux in 1903 showed that calomel ointment when applied one or two hours after cutaneous inoculation with this treponema prevented infection. Arsenicals of this nature are also most effective for yaws, bejel, pinta and relapsing fevers.

Other developments such as the syntheses of trypanocides followed and in 1921 the Rockefeller Institute for Medical Research produced "tryparsamide." Its effectiveness against human sleeping sickness was established during an expedition to the Belgian Congo. The Germans synthesized "Bayer 205" or "germanin" in 1920. Three years later the

French prepared two very effective trypanocides, "Fournau 270" or "arsanine" and "Fournau 309" or "moranyl." The former is comparable to "tryparsamide" while the latter is similar to "Bayer 205."

Another important advance in chemotherapy was the discovery in 1921 of the value of bismuth compounds. These synthesized preparations greatly surpassed mercury as an effective antisyphilitic remedy. Such preparations are also used in combination with "arsphenamine."

Still another group of chemicals containing antimony have been synthesized. These antimonials are especially effective against the various types of Leishmaniasis. As early as 1913 Vienna employed antimony tartrate in these infections.

There was much interest manifested in the development of new antimalarials and in 1926 "plasmochin" was synthesized. It is claimed that "plasmochin" is effective against all the different types of malaria including the pernicious form which does not respond to quinine.

Another effective antimalarial is "atabrin" which is less toxic than either quinine or "plasmochin." This complex chemical was first synthesized by Mauss and Mietsch in 1933. This yellow, bitter tasting, fluorescing powder destroys the schizonts while "plasmochin" is a gametocide.

The exact synthesis of the alkaloid quinine was accomplished by Robert B. Woodard, Harvard, and William E. Doering, Columbia, in 1944.

### Bacterial Chemotherapy

The greatest triumphs in chemotherapy were against protozoal and spirochetal infections. Since most of the infectious diseases of man are caused by bacteria, it was of prime importance to discover specific chemicals for bacterial diseases.

It was at first thought that bacteria were too simple in structure to lend themselves to treatment by chemicals which in turn would not be toxic to the host. Koch in 1881 failed at bacterial chemotherapy in anthrax of guinea-pigs. Many attempts were made on various laboratory animals with practically no success until 1911 when Morganroth and Levy reported a cure of mice suffering from pneumonia following injections of ethylhydrocuprein. However, it possessed no clinical value because the curative dose was too near the lethal one. The discovery of the group of "sulfonamide" chemicals as therapeutics completely altered the situation.

The historical landmarks of bacterial chemotherapy briefly are as follows: In 1908 P. Gelmo, a student at the University of Vienna, synthesized "sulfanilamide" from coal tar for his Ph. D. degree. His work was forgotten for over twenty years but was again brought to light in 1930 when Fritz Mietzsch and Joseph Klarer, who had just completed the synthesis of "atabrin," began their experiments on bacterial chemotherapy. For some reason or other they decided to use "sulfanilamide," Gelmo's synthesis, as a starting point. In 1933 Dr. Forrester saved the life of a ten-months-old boy who was dying from staphylococcus septicemia following injections of "streptozon" which was

thought to be effective against streptococci. Its name was then changed to "prontosil." This was the first evidence that Mietzsch and Klarer had succeeded. They patented this azo dye in 1932. Domagk in 1935 cured mice and rabbits suffering from streptococcal infections with "prontosil." His published results awoke the world to the fact that a new chemical against bacterial diseases was at hand. Domagk's work was shortly, thereafter, confirmed by Levaditi and Vaisman in France and Colebrook and Kenny in England. Next in 1936 Jacques, Trefouels, Nitti, Dovet of the Pasteur Institute in France and Buttle, Gray and Stephenson in England showed that the simple "sulfanilamide" fraction, which it will be called was prepared by Gelmo in 1908, of the complex "prontosil" was alone the effective agent against bacterial infections, and also, was much less toxic. Thus, the patents on the azo dye "protosil" were valueless.

Ehrlich's purpose of chemotherapy was to destroy all the invading organisms by a single injection of the chemical. However, satisfactory results in the use of these chemicals depends upon two things: Effective blood concentration and a sufficient duration of this concentration. That is, the dose is not the amount of the chemical given but rather should be in terms of blood concentration and duration of time.

Many thousands of chemicals of the sulfonamide type have been tested in mice but only a relatively few, sulfanilamide, sulfadiazine, sulfapyridine, sulfathiazole, sulfaguanidine, and succinylsulfathiazole are employed against diseases of man.

### Antibiotics as Therapeutic Agents

Pasteur in 1877 observed that, when animals, susceptible to anthrax, were injected with the bacillus contaminated with certain organisms, infection often failed. Later in 1889 it was shown that sterilized cultures of the bacillus of green pus, *Pseudomonas pyocyaneus*, and culture filtrates, pyocyanase, were effective when injected into rabbits suffering from anthrax. The action of pyocyanase, however, was not substantiated.

In 1929 Professor Alexander Fleming at St. Mary's Hospital, London, discovered "penicillin" a most effective antibiotic against bacterial infections. Penicillin was obtained from a specific kind of a common green mold, *Penicillium notatum*.

In 1936 Professor H. W. Florey and associates at Oxford University, England, began to investigate the action of "penicillin" and in 1940 isolated it in the form of a brown powder.

Dubos of the Rockefeller Institute in 1939 discovered the antibiotic "gramicidin." Waksman in 1944 gave us "streptomycin" and Meloney in 1947 "bacitracin." Antibiotic substances are produced by actinomycetes, algae, bacteria, fungi and green plants. Millions of experiments are being conducted in order to discover more effective antibiotics. One of the latest to be announced is "circulin" by Drs. Murray and Tetrault of Purdue University. Its effectiveness is especially against so-called Gram negative microorganisms.

And so, as the use of chemicals against disease goes on, this quotation from Sophocles, made about 500 years B. C. in his drama, "Antigone," becomes more and more realistic, "Only against death shall he call for aid in vain, but from the baffling maladies he hath devised escape."