

Some Aspects of Modern Chemotherapy

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The word *chemotherapy* literally means "healing by chemicals". The word was coined by Ehrlich, who thought of the term in connection with his work on the use of chemicals to kill germs. Technically, the term is often defined as "the use of drugs to kill harmful organisms within a host without affecting the host". However, in this discussion we wish to expand the term, not only to include the true chemotherapeutic agents, as the antimalarials, like quinine and atabrine, or the antibiotics, like penicillin and streptomycin, or the anthelmintics, or worm removers, or the sulfa drugs used on bacteria, but also the functional drugs, such as the anaesthetics, both general, like ether, and local, like novocaine. It shall also include the analgesics, such as morphine and the antipyretics like aspirin, used to reduce fever and relieve pain, the hypnotics or sleep producing drugs such as the barbiturates and even the new arrivals, the antihistamines, used in combatting allergies. All of these, too, play an important part in modern medicine.

HISTORY

The field of chemotherapy, although of very present importance, is by no means a new area. It is as old as man himself. In fact, the story of the creation, Genesis 2-21, describes the first case of anaesthesia in these words "and the Lord God caused a deep sleep to fall upon Adam".

The story of chemotherapy may be conveniently divided into four eras. The first era began with early man who, in his earliest wanderings and search for food, found that certain plants or parts of plants strangely affected his body. In some cases they caused pain, in other cases they relieved pain. Some caused thirst, others quenched thirst. Some, like hemlock, caused death. Gradually man, through exchange of information, learned which plants and parts of plants were useful. For example, important findings of the Spaniards not only included silver and gold, but the magic cocoa leaves which dulled pain and permitted long hours without tiredness (they contained cocaine), and the ground bark of a tree which relieved the fever caused by a mosquito bite (the bark contained quinine).

The second era began in an Austrian pharmacy in 1806 when Serturner isolated the active principle of opium which caused sleep and relieved pain, and which he named after the god of sleep, Morpheus (morphine). There followed in quick succession the isolation of many other active principles from plants like quinine, nicotine, caffeine, brucine, and codeine.

About this same time, although the connection was not readily seen, the third era began when Frederick Wohler in 1828 formed urea, the first synthetic organic chemical. This began the great era of synthetic organic chemistry, which was to result in so much fundamental organic chemistry and in the preparation of many compounds of therapeutic interest. This was the age of Pasteur, Koch, and their contemporaries in the bacteriological world who were beginning to understand something of the fundamental nature of disease. This was likewise the age of the great synthetic masters, Perkin, Hoffman, and Emil Fischer, from whose laboratories rolled many synthetic organic compounds. Some of these, although not at all similar to plant products, also affected the body. Some, like ether, had no counterpart in the plant products. Others caused reactions similar to those caused by plants, but often with greater ease, and the reaction could be more easily controlled. This was also the beginning of the analytical era, when dosage could be measured. One of the more interesting stories of early medicine tells how the early doctors, not knowing what drugs would cure what ailment, fed the newly made products to most of their patients, and noted which ones got better, and which ones died.

It was in the 1890's in the laboratory of a young German doctor experimenting with dyes in staining bacteria that the fourth era began.

Here Paul Ehrlich, peering through his microscope, found that certain bacteria were selectively stained by certain dyes. There was then conceived the idea that there might be specific drugs for specific diseases. In the historic words of Paul Ehrlich, "a substance can act on the brain if it is neurotropic, and only on the parasite if it has the appropriate affinity, i.e., if it is parasitropic". This then was the beginning of the modern era, the age of planned and systematic chemotherapy. It is this era around which most of this presentation will be centered.

Following this idea, Ehrlich did his brilliant work on the arsenicals, the story of which has been told as "the magic bullet", the story of 605. However, after the early enthusiasm fired by Ehrlich's successes subsided, for the most part chemotherapy lay dormant. This is not to belittle the work of Jacobs and Heidelberger of the Rockefeller Institute, or of Forneau of the Pasteur Institute, or other important contributions, but there was no general chemotherapeutic activity.

The next real impetus came with Domagk's discovery of the dramatic antibacterial activity of Prontosil which opened up the era of the sulfa drugs. These drugs with their dramatic cures caused intensified and renewed activity. Then came World War II with the successful search for antimalarials and the dramatic story of penicillin which opened up the third stage of this modern age, the antibiotics—streptomycin, for tuberculosis, and auromycin, terramycin, and chloromycetin, the man—I mean woman—made antibiotic. This was followed by cortisone and the interest in hormones. Thus, today all over the scientific world we find increased activity in the search for chemotherapeutics. Over 40 percent of our chemical literature is concerned with this search. The almost magic cures affected plus the need in unsolved problems like cancer, polio, and certain types of heart ailments—these, and many others make this a most pressing problem. Where do we go from here? Admittedly, this is too big a problem for discussion here. I shall merely try to point out some of the landmarks or approaches to chemotherapeutic research, some of the problems of testing faced in this search, some of the more promising tools now available, and finally a brief discussion of problems of interest to the speaker.

APPROACHES

The job is not simple. There are no sure fire steps to success. The complexities of the human body, plus many other problems make this search still very empirical. It is still a matter of "prepare and test". However, there are two basic approaches to the design of biologically active molecules. It should be emphasized that these methods overlap and it is often necessary and desirable to combine both approaches.

The first method has its origin in the known biological activity of a particular compound or type of compound. It may start with some naturally occurring compound and result in attempts to synthesize substances which will reproduce or improve the activity of the natural compound and be easy to make.

Substitutions and variations in structure are made and the effect noted.

This research may also be started by an unexpected laboratory observation, like penicillin or prontosil, which led to sulfanilamide and the sulfa drugs.

The second method starts with a study of the chemical mechanisms essential to the functioning of the organism. Compounds are then made which interfere or accentuate this functioning. The approach was emphasized from studies on the mode of activity of sulfanilamide when it was discovered that the bacteria affected by sulfanilamide used *p*-aminobenzoic acid as an essential metabolite.

We may also cause interference with normal functioning by the modification of certain physico-chemical factors. Thus the long chained quaternary ammonium salts are bacterostatic because they affect the surface tension of molecules. Another physico-chemical factor is concerned

with molecular shape. This concept, although of recent application, really harks back to Pasteur and Ehrlich with their ideas of lock and key.

TESTING

Since, as has been mentioned, the discovery of new chemotherapeutics is still very empirical, testing is very important. Physiological activity may be found where least expected. This means that large numbers of potential therapeutics must be tested or screened. And here the problem begins. First, the compound should exhibit some of the desired activity. But one cannot, as in the story of the early doctors, use humans. Therefore, animals must be used. But animals are expensive. This then means that where practical, as in the case of antibacterial activity, test tube or *in vitro* studies are carried out. But the tests are not always consistent. Compounds good *in vitro* may be worthless, in the living organism, or *in vivo*, or vice-versa. But some organisms, like the malaria parasite, are not conducive to test tube studies. This means means that a suitable host animal must be found. Specifically, antimalarial testing received a great boost when the use of the canary as a test animal was found. After the desired activity is found, then the toxicity must be determined. Not only must it not be toxic, but it must not be toxic in the dose needed to cure. Thus, an important index to the potential value of a drug is the chemotherapeutic index, the ratio of the maximum tolerated dose to the minimum curative dose. Here arises the need for standardized tests, so that values by different investigators may be compared. Here the chemist leaves the problem to the clinician, who after suitable toxicity tests takes the big venture—humans. Now I must leave this aspect. I wish to say only that in so far as *in vitro* and animal tests approximate human activity can they guide the chemist in his search. Many, as yet unsolved problems like cancer, will be greatly benefited as suitable tests are discovered.

NEWER TOOLS

The chemist in his search for better drugs has many new tools to aid him. There are first the better methods of testing. There are then the newer and better physical tools such as the electron microscope and infrared and ultraviolet spectroscopy. Advances in related sciences like biology, bacteriology, and physics, and the newer fields of biophysics, and biometrics, all lead to greater knowledge of the functioning of organisms and ways of better utilizing the chemotherapeutic agents. Likewise newer techniques in chemistry, such as chromatography and low pressure distillations make possible the analysis and synthesis of complex and specific drugs. Another factor which cannot be ignored is the increased public interest in chemotherapeutic research which provides needed morale and cash.

PHENOTHIAZINE RESEARCH

Finally, I should like to briefly present some problems of current interest in my personal research. My recent research has been centered around phenothiazine, sometimes called thiodiphenylamine, and I feel it significant that methylene blue, one of Ehrlich's first dyes and the first synthetic antimalarial, is a phenothiazine derivative.

Phenothiazine, itself, is a good insecticide, anthelmintic, urinary anti-septic, and tuberculostatic compound. Certain phenothiazine derivatives have shown interesting activity. 10-(β -diethylaminoethyl)-phenothiazine, called Diparcol is a good antihistamine and is useful in Parkinson's disease, whereas 3-chloro-10(γ -dimethylaminopropyl)-phenothiazine has been shown to be an useful antiemetic.

My research has centered around phenothiazine ketones, chiefly 2-acetylphenothiazine which is being converted to structures with analgesic, antihistaminic, or nerve activity.

In these pages have been given some concepts of modern chemotherapy. It is an interesting, if challenging field, and we may all expect longer and more enjoyable years through chemotherapy.