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RECENT ADVANCES IN CHEMOTHERAPY[1]

By Dr. M. L. CROSSLEY

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TWO paintings, "The Alchemical Making of a Medicine in the 16th Century," by Michael Diemer, and the "Elixer of Life" by John A. Lomax, tell an inspiring story of man's belief that from chemical investigations would result new and potent drugs capable of combating diseases and alleviating human suffering. The discoveries of the past few decades in chemistry are encouraging evidences that the alchemist's dream is being realized. Chemical compounds having no counterparts in nature have been produced and shown to be effective therapeutic agents. A beginning has been made; new and important discoveries will follow. Man may confidently look forward to a time when he will have available the means of destroying the parasitic hosts that find access to his body and conspire to destroy him.

These agents of destruction are many. They are all about man. He is always on the defensive. His life depends upon the state of his preparedness for constant chemical warfare against both plant and animal invaders. He is attacked by worms; roundworms, hookworms, pinworms, other kinds of worms; protozoa, bacteria and viruses. They would convert him into a regular British Museum of infirmities, as Mark Twain once said. They invade his intestines, his muscles and his vital organs, producing diseases which reduce his efficiency and often deprive him of life. These disease-producing organisms are the "reds" of

[1] An address before the Western Connecticut Section of the American Chemical Society, January 22, 1940.

cellular organization and like the reds in human society interpret the privilege of participating in the benefits of organization as a right to destroy what exists. The human system must fight incessantly to maintain its integrity and life.

Disease is one of the most dreaded foes of mankind. To conquer it is one of the chief aims of science. Chemistry and biology, in particular, are jointly charged with the responsibility for seeking knowledge about the diseases which menace man's health and jeopardize his life. While much progress has been made in the study of the agents causing disease, little is yet known about the exact way the causative agent works and the changes brought about in the physical and chemical activities of the cells of the tissues and organs. Also little is yet known about the nature of the chemical defense weapons of the body or of how drugs act on bacteria and other infecting agents. The knowledge of chemotherapy is still highly empirical.

The knowledge of infecting agents and the means by which they reach the human system has led to the establishment of conditions which minimize the chances of infection by them. When diseases such as typhus fever, plague and cholera were shown to be caused by microbes, the guests of vermin, sanitary engineering abolished filth in cities and eradicated vermin. The establishment of bodily cleanliness as a mark of social betterment deprived body lice of their free board and lodging and forced them to give up their human associations. Thus, man, living under such conditions, was spared the ravages of typhus fever, which was transmitted by body lice. Similarly, other insect-borne infections, causing malaria, yellow-fever, cholera and plague, have been eradicated wherever it has been possible to destroy their insect hosts. The war steadily carried on against mosquitoes has greatly improved the conditions and thus reduced the wastage of human life and relieved much suffering from malaria and yellow fever. Plague and cholera have been held in check by incessant war on the rat-flea and the bed-bug, which serve as hosts of the microbes causing the respective diseases.

The results obtained by research in the attempt to make the world safe for humanity inspire greater efforts and justify hope of success. However, to accomplish the desired results there is needed, in addition to the superlative scientific work of many investigators, a better appreciation by the public that the fight against disease is the concern of every one. People must understand the hazards to health and life by infectious agents and accept responsibility for providing conditions which will prevent the transmission of communicable diseases. The individual who sneezes in the air condemns his fellowmen to suffering and losses they should be spared. The public must learn that to treat infecting agents without restraint is to establish disease and invite the possible penalty of an early commitment to the grave for eternity.

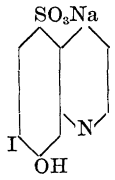
The aim of chemotherapy is to be able to treat diseases with chemical substances capable of selectively destroying disease promoting agents without doing serious injury to any vital part of the human organism. This will be difficult to accomplish. It may never be fully realized. Living organisms, simple and complex, microbe and man, possess certain characteristics shared in common by all living things. They have the capacity to assimilate, to grow and to reproduce. The cycles of events characterizing these processes in microbe and in man may involve similar phenomena. The drug which affects the protoplasm of the parasitic agent may not be wholly without toxic effect on man. If it were it would be in general inffective as a therapeutic agent. It is a matter of degree of toxicity for each. The problem is to find chemical substances which will destroy the agents of infection, *in vivo,* in concentrations so low as to be practically harmless for the human organism.

Some progress has been made in recent years in the chemotherapy of diseases caused by both animal parasites and bacteria. However, until the recent discovery of the sulfanilamide therapy of bacterial diseases, the chief accomplishments had been in the treatment of animal parasitic diseases, particularly in the chemotherapy of amoebiasis, leishmaniasis, malaria and trypanosomiasis. To a lesser degree, progress has been made in the treatment of the diseases caused by various types of worms and flukes that invade the intestine and vital organs of man.

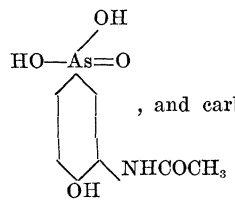
Chemical remedies for worms have been tried for a long time. Santonin and other natural drugs were used with some success. In recent years carbon tetrachloride, tetrachlorethylene and hexylresorcinol have proved to be effective remedies for certain of the intestinal parasitic infections. Thymol seems to give good results in hookworm disease. Carbon tetrachloride is said to be particularly effective against the tapeworm. However, none of these drugs is entirely satisfactory. The ideal drug for such infections is still to be discovered. Besides, there are diseases due to the filarial type of worms which are not benefitted by any of the drugs that have been investigated.

Considerable work has been done to find suitable drugs for the treatment of diseases caused by amoebia-amoebiasis. Emetin, a natural product, a derivative of iso-quinoline, has been used for a long time, but it is not satisfactory because it is a cytoplasmic poison and its effects are cumulative. Extensive investigations of quinoline and iso-quinoline derivatives have

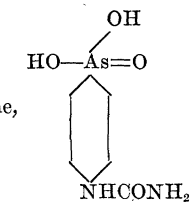
finally led to the dscovery of an iodohydroxyquinoline sulfonate, chiniofon,



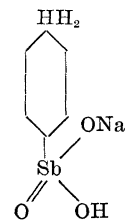
and an iodochlorohydroxyquinoline, Vioform, which have proved to be effective in amoebic dysentery. Chiniofon clears up the diarrhoea and in most cases frees the intestines from amoebae but does not appear to be effective in curing the abscesses of the intestine and liver. Vioform is claimed to be more effective but is also more toxic. Nothing definite is known of the mode of action of these drugs. Besides the quinoline derivatives some success has been had with certain organic arsenicals of the type of acetarsol,



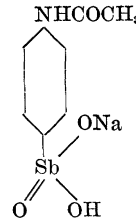
, and carbarsone,



One of the most important contributions to the chemotherapy of protozoal diseases has been the discovery of the effectiveness of quinquevalent antimony organic compounds in the treatment of visceral leishmaniasis. This type of infection causes much suffering and takes a great toll of life in India, Africa and South America. The death rate from such diseases has been greatly lowered in the past few years as a result of treatment with antimony compounds. At first antimonyl tartrates were used, but these proved to be much too toxic for use in the dosage required for satisfactory therapeutic results. The derivatives of phenylstibonic acid, prepared after a satisfactory synthesis had been worked out for the acid, proved superior to the antimonyl tartrates, tartar emetic type, in being less toxic for human and more toxic for the parasite. Important compounds of the quinquevalent type are stibamine, the sodium salt of para-aminophenylstibonic acid,



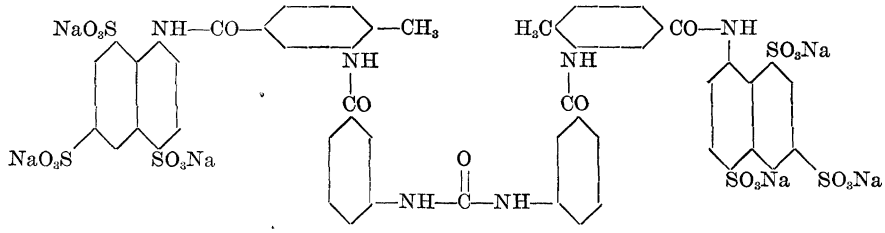
stibacetin or stibenyl,



urea stibamine; neostam; the N-glucoside of stibamine; stibobsan, a stibacetin containing chlorine on the phenyl nucleus; and solustibosan, said to be a combination of hexonic acid with stibosan. Many other similar products have been prepared and tested. Claims are made for some of them which justify a thorough investigation of their clinical possibilities in both visceral and skin infections due to leishmania. The fact that these quinquevalent antimony compounds can be used in comparatively large doses without serious toxic results encourages one to believe that among the group will be found products that will effectively wipe out leishmaniasis, including the oriental sore.

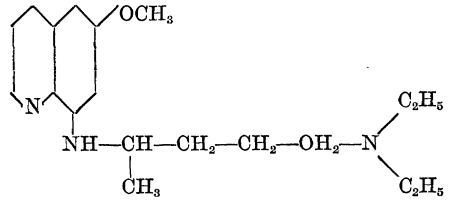
The success with organic arsenicals in the chemotherapy of syphilis has stimulated research to find better and safer drugs for the treatment of this and other diseases caused by similar agents of infection. In the last two decades scores of new organic compounds containing arsenic or bismuth have been made and tested. A few have proved useful. In particular certain bismuth compounds have been shown to be valuable adjuvants to the arsphenamine type of arsenical in the treatment of syphilis. More than two hundred bismuth compounds have been made and studied. The effective bismuth drugs appear to be less toxic than the arsenicals, but they are not good enough therapeutic agents to replace them. Arsphenamine and related arsenicals are still of inestimable value in the treatment of syphilis. It is probable that the bismuth compounds will ultimately replace mercury compounds in the chemotherapy of this disease.

Parasitic organisms of the trypanosoma type cause many diseases which cause great suffering and take a high toll in human lives throughout the infested areas of the world. Sleeping-sickness and fevers of tropical countries have received much attention in recent years. Some of the ablest investigators in the world have enlisted in the army of scientists fighting these diseases and the results obtained in the chemotherapy of trypanosomiasis are promising. The most amazing result is the success in treating sleeping-sickness with complex urea derivatives containing no metal. Numerous arsenic and antimony organic compounds had been studied with discouraging results. Then, it was found that the complex compound,

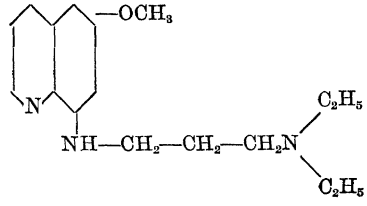


known under the international aliases of Germanin (Bayer 205), in Germany, Moranyl (Fourneau 309) in France and Antropol in Great Britain, was highly effective, particularly in the early stages of the disease before the central nervous system had been attacked. The remarkable thing is that the slightest deviation from the above structure results in a lowering of the trypanocidal activity. Why such a structure is essential no one knows. Many other organic compounds of widely different molecular architecture have been studied, but none of them has been particularly effective.

Of the several parasitic diseases studied intensively during the last decade none has received more attention than malaria. The chemotherapy of malaria has made definite progress. The most promising results have been obtained with quinoline and acridine derivatives. While none of these gives entire satisfaction, those of the type of plasmoquine,



rhodoquine,



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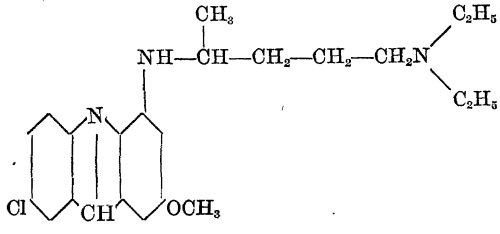
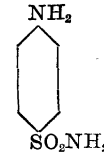
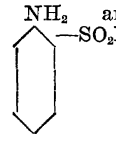
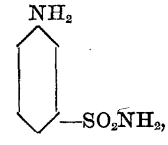


are certainly valuable adjuvants to quinine in the treatment of malaria. The ideal drug to combat the several phases of malarial infection is still to be discovered. The greatest obstacle to progress is the lack of knowledge of the mechanism of the drug action and what properties a compound should have to be effective. In spite of all the work done to date nothing definite can be said about the relation of chemical structure and parasiticidal action. It is possible that certain physical properties are essential and that the structural feature of the molecule is important only in making possible the required geometric arrangement for making these effective. Much more evidence from various sources must be secured and correlated before this problem is solved.

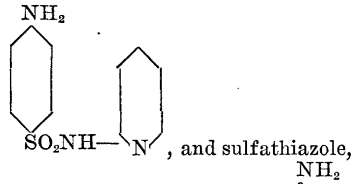
One of the most important, perhaps the most important contribution to the advancement of chemotherapy, is the recent discovery that p-aminobenzenesulfonamide (sulfanilamide) is an effective drug in combating certain diseases due to bacterial infections. With this begins a new era in medicine—the era of chemotherapy of bacterial diseases. This is the direct result of sustained research, in spite of discouraging results. With the exception of a few compounds that proved to be effective in the treatment of infections of the urinary system, no light had broken to dispel the darkness of the wilderness in which scientific investigators groped until the sulfanilamide star rose above the horizon. This shed its rays immediately over the entire world and illuminated the paths of research chemists through the realms of the unknown enabling them to bring forth hosts of sulfanilamide close relatives for study as chemotherapeutic agents. There is no complete record of all the sulfanilamides made but it is safe to estimate that they now exceed two thousand. Of this large number but few are valuable drugs. Why? In spite of all the accumulated evidence this question can not be answered yet.

Sulfanilamide,  , is effective in many infectious diseases, while its twin sisters orthanilamide,  and metanilamide, 

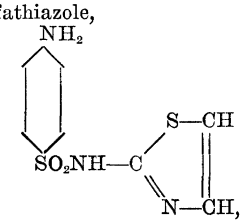
are inactive. This difference in behavior suggests that sulfanilamide must possess some significant property not shared by the other two members of the family. This must be responsible for its activity. Just how it acts and on what it acts are not definitely established. At present it is safe to say that the drug retards the growth of bacteria. Whether this is primarily due to changes brought about in the cycle of events involved in the reproduction of the cells or whether it concerns the food-assimilating functions of the bacteria can not be determined from the available evidence. It is evident that a thorough study of the metabolism and growth of bacteria with active and inactive sulfanilamides should throw some light on the important features of the mode of action of the drugs. The solution of this problem will serve to establish a fundamental basis for the further study of chemotherapy of infectious diseases.

The results obtained with sulfanilamide have been, in many cases, dramatic. In the short time it has been in use it has proved particularly effective in the treatment of infectious diseases, such as erysipelas, scarlet fever, tonsilitis, mastoiditis, meningitis (both streptococcal and meningococcal), peritonitis, puerperal fever, septicemia, osteomyelitis, streptococcal pneumonia and gonorrhea. Infections that proved fatal in practically all cases now clear up with its aid, and recovery follows. Many lives have been snatched from the jaws of death with it.

Of the sulfanilamide derivatives that have proved to be effective in experimental infections, sulfapyridine,



, and sulfathiazole,



appear at present to be particularly important. They are better than sulfanilamide against pneumococcal and staphylococcal infections. Sulfapyridine has been tested clinically and its value as a drug for the treatment of pneumonia established. In experimental pneumococcal infections sulfathiazole appears to be about as good as sulfapyridine, but not sufficient clinical data are yet available to show what place it will take in the chemotherapy of pneumonia. At present the evidence shows the product to be superior to both sulfanilamide and sulfapyridine in the treatment of staphylococcal infections. Further clinical evidence is needed to show its relative importance as a therapeutic agent.

The scope of chemotherapy is wide. Daily, new results appear showing that the sulfanilamides have helped in this and in that disease. There is some evidence that sulfanilamide and certain of its derivatives have a beneficial effect on the course of experimental tuberculosis in guinea pigs, but so far the clinical experiments have not demonstrated that they are valuable therapeutic agents for the treatment of tuberculosis in humans. There is also some evidence that certain of the sulfanilamides are effective for the treatment of gas gangrene, trachoma, undulant fever and lymphopathia venereum.

Enough has been said to indicate that real progress has been made in chemotherapy during the past few years. The results justify the hope that in the not too distant future a definite basis may be established for an understanding of the physical and chemical processes involved in health and disease. Then, the complexity of the human organism with its delicately adjusted mechanism will be better understood and appreciated. It will be seen that man is not necessarily "the animal of the wig, the ear-trumpet, the glass eye, the porcelain teeth, the wooden leg, the silver windpipe"—"a creature that is all mended from top to bottom"—"a basketful of pestilent corruption, provided for the support and entertainment of microbes"; but instead he is "a shop of rules, a well-trussed pack, whose every parcel underwrites a Law." He is a part of a great experiment. His life is like a string of many different colored beads whose beauty and usefulness depend upon the cord that binds them together in unity of pattern and purpose.

LO, THE POOR WHALE!

By Dr. ROBERT CUSHMAN MURPHY

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INFORMATION submitted to the International Whaling Conferences of the past three years discloses the long-expected decline of the fishery in its last and richest field, the Far South. The true measure of the decline lies not in the absolute number of whales killed, which may have been greater than ever before, but rather in the number taken per catching unit. On this basis the 1938–39 season is to be reckoned the