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Edited by

Henry Welch, Ph.D., and Felix Marti-Ibañez, M.D.

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PROCEEDINGS OF THE

SECOND ANNUAL SYMPOSIUM ON ANTIBIOTICS

Edited by

HENRY WELCH, Ph.D., and FELIX MARTI-IBAÑEZ, M.D.

SECOND ANNUAL SYMPOSIUM ON ANTIBIOTICS

Chairman: Henry Welch, Ph.D.

Director, Division of Antibiotics, Food and Drug Administration

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Dear Dr. Welch:

I send my warm good wishes to all participating in the Second Annual Symposium on Antibiotics.

This is truly an occasion for honoring all those who, through their work in antibiotics, have made profound changes in the practice of medicine. It is also a time to be thankful that dedicated men and women of many lands have joined together to share the results of their scientific research. In extending special greetings to the Ministers of Health and distinguished scientists who have come to this symposium from thirty-five other nations of the world, I express for the American people the earnest hope that such international cooperation in the years ahead may bring ever closer a world of peace and happiness for all mankind.

Sincerely,

Dr. Henry Welch
Chairman of the International Symposium
on Antibiotics
Food and Drug Administration
Department of Health, Education and Welfare
Washington, D. C.

Antibiotics Annual 1954-1955

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Opening Remarks

HENRY WELCH, Ph.D.

Director, Division of Antibiotics, United States Food and Drug Administration

It is a pleasure for me to open the Second Annual Symposium on Antibiotics and to greet you who are to make it a success through your contributions to the knowledge of antibiotic drugs and their uses. No one anticipated that there would be so much new and important material available one short year after our first Symposium. As a matter of fact, it was with some hesitancy that the plans for the second meeting were put into operation. However, the enthusiasm with which the announcement of the Second Symposium was received has fully justified our decision to proceed with it. I need not tell you the program is an extremely heavy one, you have noted that some 172 speakers are to be heard this week. We will learn more about the activities of the "old" antibiotics—if one can call any antibiotic old—and several new ones will be described. Carefully controlled studies in the use of antibiotics in human nutrition will stimulate a great deal of interest and perhaps open a new field of usefulness for these drugs. Although we have yet to find a new antibiotic for the small viruses and cancer, we will hear this week of one or two substances found in nature with antitumor and anticarcinogenic effects. These findings will certainly stimulate greater activity among our academic and industrial investigators.

It would take too much time to list the infectious diseases now either under partial or complete control through use of chemotherapy, but certainly in this audience there are few of us indeed who do not have among our friends or relatives one or more made well, or whose life has been saved, through the use of antibiotic drugs.

Much credit for bringing the antibiotics to their present state of usefulness should go to two groups of people. The first are those who have been most responsible for the isolation, development, and critical clinical evaluation of these drugs. Many of these investigators are on this program. The second group are those men who organized and established the antibiotic industry and were responsible for a production of over 2,000,000 pounds of these drugs in 1953, and who are spending great sums of money currently in the quest for new, broader, and more efficient drugs.

It is a pleasure for me at this time to introduce to you our new Commissioner of Food and Drugs, Mr. George P. Larrick. Mr. Larrick has been with the Food and Drug Administration for 31 years and has had the unique advantage of working closely with three former commissioners, Walter G. Campbell, Paul B. Dunbar, and Charles W. Crawford, all of whom had their part in establishing the present Food and Drug Administration. We in the Administration are delighted that the Secretary of the Department of Health, Education, and Welfare saw fit to appoint a career man in this position, and we feel sure that those of you who have dealings with us will find Mr. Larrick an excellent replacement for our previous commissioners and eager to be of assistance to you in solving any problems you may have.

A Message of Welcome

GEORGE P. LARRICK

Commissioner, United States Food and Drug Administration

It is with great pleasure that the Department of Health, Education, and Welfare and the Food and Drug Administration welcome you to the Second Annual Symposium on Antibiotics. Last year, when the first Symposium was held, we were all impressed with the enthusiastic response it received; but it was with some skepticism that we planned the second one, believing that current investigational studies in the field might have been well covered.

Judging from the present program, we have been quite justified in again calling together the outstanding investigators in the antibiotics field to present the results of their most recent researches. We are always glad to participate in meetings of this kind since the information that we obtain can be used to better serve the public.

Having followed the development of the antibiotics industry since its inception in 1942 it has been a source of great wonderment to us to see the tremendous strides made in antibiotic therapy. It is hard to believe that an industry that did not exist in 1942 could develop, in the short space of a decade, to a point where the antibiotics produced weekly are measured in tons and their value measured in millions of dollars.

When Mr. Campbell, the commissioner in 1942, was asked to set up specifications and test for the Army all of the penicillin produced, he recognized the importance that penicillin would have to the medical profession, although I must say he has since remarked that he had no idea that 10 years later production would reach the point that it has today.

For a period of three years, from 1942 to 1945, the Food and Drug Administration tested all penicillin manufactured in this country for the Armed Forces. It may be of interest in passing that in the first year approximately 29 pounds of penicillin were produced, while in 1953 over 372 tons were produced. In the latter year Dr. Welch and his group, under the certification procedure, were still testing the great bulk of penicillin produced.

New advances are made almost monthly in the antibiotics field, and I have noted on your program that there are a number of new antibiotics that will be discussed in the following few days. No one could have prophesied a decade ago the scientific rise of the antibiotics to their present state of value to the public health. Today they constitute approximately 40 per cent of all physicians' prescriptions.

In view of the brief but important history of the antibiotics, one should not hesitate to predict that the future still holds many important advancements in this field. This Symposium, in our opinion, will set the pace.

I sincerely hope that you will enjoy the scientific sessions that have been organized for the next few days, and may I repeat our cordial welcome to you.

Historical Background of Antibiotics

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Antibiotics have recently come to occupy a prominent place in many of the biologic and chemical sciences, in agriculture, and especially in the fields of medicine and veterinary practice. The scientific progress has been so rapid and the practical results so remarkable that many physicians cannot speak of an infectious disease without bringing up the subject of antibiotics. These tremendous developments in a new field of science, barely 15 years old, have even been responsible for certain derogatory comments frequently heard to the effect that "antibiotics enjoy at present a *succès de scandale*." On the other hand, the important contributions of antibiotics to human welfare are often so highly glorified that these substances are sometimes designated in the popular mind as the true "miracle drugs," of which mankind has dreamt for so many centuries. Some persons even advocate calling the present age, medically speaking, the "antibiotic era," or the "antibiotic age." Whatever attitude one may assume, the fact must be recognized that antibiotics have revolutionized the practice of medicine and promise to contribute greatly to animal nutrition and to various fields of human endeavor.

Our present knowledge of antibiotics has a complex origin. It has been accumulated through the effort not only of those who studied microbial populations, mixed infections, and microbial antagonisms, but also those who were concerned primarily with problems of chemotherapy. Students of soil microorganisms, microbiology of waters and sanitation, and plant diseases have also contributed to our knowledge of the effects of one microbe upon another and the production and utilization of antibiotics.

The advances in chemotherapy, notably the introduction of salvarsan and later the sulfa drugs, established the fact that there are chemical substances that have the property of selective activity upon microbial cells causing infection of higher forms of life and upon the host cells. Such substances could be used to treat infectious diseases, resulting in the eradication of the parasite without affecting the host. Methods for the study of the activity of these substances, both in the test tube and in experimental animals, were introduced.

The recent progress made in the chemistry of natural products has also contributed to the development of this subject by the methods now in use for the isolation of antibiotics. Further, the progress made in the production of organic acids, alcohols, and other fermentation products by microorganisms served as a basis on which surface and submerged cultures for the growth of antibiotic-producing organisms were developed.

In attempting to evaluate the contributions of the numerous investigators in this field, it must be emphatically stated here that no one man can be called "the father of antibiotics," as Paul Ehrlich is frequently spoken of as "the father of chemotherapy." The subject of antibiotics progressed slowly through various channels and through many approaches, the most rapid advance being made only after the discovery of tyrothricin in 1939 and the subsequent practical success of penicillin and of streptomycin.

EARLY OBSERVATIONS

Our earliest knowledge of the antagonistic properties of microorganisms can be traced to folklore. Stories abound among both primitive and civilized peoples to the effect that cheese, moldy bread, and moldy meat, as well as other spoiled food products, urine, and animal excreta, manures, and composts, and various other natural materials, including such odd formations as spider webs, can be used in control of human and animal infections. I have personally received numerous letters from all parts of the world listing these and other materials as highly effective in the treatment of wounds and infections.

It is only with the beginning of the fourth quarter of the last century that we find specific references to the antimicrobial properties of certain specific groups of microorganisms. Among these, fungi and bacteria have received particular consideration.

In 1874, Roberts, in a paper entitled "Studies on Biogenesis," stated: "The avoidance of air contamination is important for another reason. The air is admitted, by most observers, to be highly charged with fungoid germs, and the growth of fungi has appeared to me to be antagonistic to that of bacteria, and vice versa. I have repeatedly observed that liquids in which the *Penicillium glaucum* was growing luxuriantly could with difficulty be artificially infected with bacteria; it seemed, in fact, as if this fungus played the part of the plants in an aquarium, and held in check the growth of bacteria, with their attendant putrefactive changes. On the other hand, the *P. glaucum* seldom grows vigorously, if it grows at all, in liquids which are full of bacteria. It has further seemed to me that there was an antagonism between the growth of certain races of bacteria and certain other races of bacteria."

Soon afterward, in 1876, Tyndall made some striking observations on the growth of wild cultures of bacteria and fungi in organic media. This suggested to him the concept of "the struggle for existence" between these two groups of microorganisms. In some of the tubes the bacteria were triumphant, whereas in others the fungi predominated. It is of particular significance to refer to Tyndall's observation that "the bacteria which manufacture a green pigment appear to be uniformly victorious in their fight with the penicillium." This is probably one of the earliest references to the antagonistic properties of the pseudomonas group of bacteria.

The following year, in 1877, Pasteur and Joubert noted that the production of anthrax in susceptible animals could be repressed by the simultaneous inoculation with various nonpathogenic bacteria. This led Pasteur to make the following significant suggestion: "One can infect abundantly an animal with anthrax without the animal becoming diseased; it is sufficient that the fluid contain in suspension simultaneously the anthrax organism and a common or harmless bacterium." He added prophetically: "These facts perhaps justify the highest hopes for therapeutics."

THE FORMATIVE PERIOD (1885–1939)

The period of 1885–1939 may be considered as one in which the real foundation was laid for the development of our knowledge of antibiotics. At first, the antagonistic activities of microorganisms were emphasized without reference to their production of specific substances. Numerous theories were proposed to explain these effects: they ranged from ideas of exhaustion of nutrients to space antagonisms and reaction changes. Gradually, the production of chemical agents came to be recognized as responsible for the inhibitory effect. These agents were at first designated as "lethal principles" and "toxic substances." Their designation as "antibiotics" is only of recent origin.

The development of our knowledge concerning the antimicrobial effects of microorganisms and the production of specific antibiotics proceeded, during this period of more than half a century, along several distinct lines, that often overlapped. Principally, they comprised studies of: (1) mixed cultures and mixed infections; and (2) formation and isolation of specific antimicrobial agents or antibiotics.

ANTAGONISTIC EFFECTS IN MIXED CULTURES AND MIXED INFECTIONS

In the study of the antagonistic effects of microorganisms growing in mixed cultures, observations were usually made upon two or more organisms, comprising bacteria, fungi, or both, and growing naturally together, or found in contaminated cultures, or in specific mixtures of organisms inoculated for the specific purpose of observation and study. There was only a very vague appreciation of the effects of these organisms *in vivo,* as compared to their interaction *in vitro,* as can be well recognized from the "classical" book of Papacostas and Gaté.

Effects of bacteria upon bacteria. Cantani attempted in 1885 to explore the fact that certain bacteria have the capacity to destroy cultures of other bacteria if they come into contact with them, as in the treatment of infectious diseases with saprophytic organisms. He believed that patients suffering from tuberculosis benefited from treatment with a saprophyte, *Bacterium termo*. The latter was believed to be a mixture of nonpathogenic bacteria. It was used in the form of an aerosol.

Other observations of a similar nature soon followed. Babès demonstrated in that same year that a certain microbe could produce, both on solid and in liquid media, chemical substances which had the capacity to inhibit the growth of other organisms. He emphasized the fact that the reciprocal action produced by bacteria upon one another was much more obvious when one bacterium was sown in the medium after the other. Babès added significantly: "If the study of the mutual antagonisms of bacteria were sufficiently far advanced a disease caused by one bacterium could probably be treated by another."

Garré, in 1887, made a detailed study of methods for demonstrating the antagonistic action of bacteria. His results led him to an enthusiastic conclusion that: "Bacteriotherapy, which we already recognize as a prophylactic procedure in different infections, now no longer appears to be in the realm of dreams as a means of fighting already developed diseases."

Doelhe, in 1888, used the gelatin plate method for measuring the action of nonpathogenic cocci upon the anthrax organism. He isolated an antagonistic culture that he designated as *Micrococcus anthracotoxicus*. Its inhibitory action was believed to be due to the production of a metabolic product that diffused into the medium and rendered it incapable of supporting growth of the pathogen.

The most important investigations of this period, however, centered around the action of the pyocyaneus organism upon other bacteria. Garré and Freudenreich observed that *Pseudomonas pyocyanea,* or *Pseudomonas aeruginosa,* as it is now known, inhibited the growth of various bacteria *in vitro*. In 1889, Bouchard demonstrated that inoculation with *Ps. pyocyanea* of rabbits infected with *Bacillus anthracis* conferred a considerable degree of protection to these animals; in guinea pigs, the results were not so favorable. Klein, however, reported good results in the treatment of experimental tuberculosis in guinea pigs with the pyocyaneus organism.

Charrin and Guignard demonstrated that *Ps. pyocyanea* produced a "soluble product" that destroyed the anthrax bacillus but did not cause hemolysis of the red blood cells. They came to the conclusion that chemical substances produced by the antagonistic organism are more injurious to the pathogenic bacterium than to some types of animal cells. This was a highly significant assumption that should have opened the way to the use of microbial products, rather than living microorganisms, as chemotherapeutic agents. However, the sciences of microbiology, chemistry, and medicine were not ready to take advantage of this important observation.

Another milestone in these investigations was reached in 1899 by Emmerich and Löw when they obtained an antibiotic preparation designated as pyocyanase from old pyocyaneus cultures. This preparation had a marked inhibiting effect upon the growth of numerous bacteria, causing the lysis of some of them. It had no injurious action upon animals when injected intravenously in proper concentration. Without appreciating the fact that they were dealing with a new type of antibacterial agent, they considered the substance to be an enzyme of the nature of a nuclease. This selective action of pyocyanase, which acted upon bacteria but not on animal cells, proved to be highly significant. Unfortunately, chemotherapy was confused with immunotherapy, a fact largely responsible for the insufficient appreciation of the action of pyocyanase in animals and its possible use in the control of disease.

The interest in pyocyanase grew rapidly, however, and an extensive literature soon accumulated. Gradually hopes began to rise that here was an agent of great therapeutic value. This was well expressed in 1913 by Sonnenberger, who said that the use of pyocyanase as a therapeutic agent was based on clear-cut experiments both *in vitro* and *in vivo*. It was found to be harmless within certain limits and was capable of healing a large number of diseases; it could thus be considered as an important addition to therapeutics. Unfortunately, the practical results obtained from the use of pyocyanase did not justify these high hopes. This was due primarily to the instability of the preparations obtained, their relatively high toxicity, and a lack of sufficient understanding concerning their specific effect in the test tube and in the animal body.

In the meantime, considerable information continued to accumulate concerning the ability of another group of bacteria, namely the aerobic spore-formers, to produce antimicrobial agents. Although this recognition came somewhat later than that of pyocyanase, it carried much further. It gradually came to occupy an important, even