THE CHEMOTHERAPY OF TUBERCULOSIS[1]

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INTRODUCTION

This is not the story of chemistry's triumph over tuberculosis, because that triumph has not yet been achieved. Rather, this is a progress report concerned with investigations which have at least led us to the point of optimism regarding the chemotherapy of tuberculosis.

HISTORICAL

In 1909 it was shown by Paul Ehrlich and his collaborators that syphilis could be successfully treated with arsphenamine. For the first time, a chemical compound had been devised for the destruction of a specific pathogen without serious danger to the patient. In other words, Ehrlich proved his thesis that the human body can tolerate quantities of a drug sufficient to kill an infecting organism, and thus was born modern chemotherapy. In the following years, chemists all over the world suffered continual defeat in their efforts to discover chemical compounds capable of combating other diseases, and it was apparent that Ehrlich's hope of an easy conquest of the microbial world would not be realized.

During this period bacteriologists were also seeking new agents to combat disease. In 1924, Calmette reported the famous B.C.G. vaccine, composed of living, attenuated, bovine tubercle bacilli. Although B.C.G. confers some immunity against tuberculosis upon laboratory animals, results with human patients have not been clear-cut. This work is still progressing.

In 1932, Wells and Long reviewed the progress to date and concluded, "A specific chemotherapy of tuberculosis has not been found and it may be a long time in coming because of the inherent difficulties of the problem."

Sulfanilamide, which had been synthesized in 1908 and ignored while scientists looked everywhere else for a useful drug, was rediscovered in 1935 by an indirect procedure. The potentialities of sulfanilamide were immediately appreciated. There resulted an impetus to experimentation in academic and industrial laboratories that yielded drugs for combating numerous parasitic diseases. Research on chemical compounds related to the sulfonamides led to the discovery by Rist, in 1938, that diaminodiphenylsulfone (DDS) has considerable antitubercular activity. In the last twelve years much progress has been made against tuberculosis, but before discussing these advances we would do well to look for a moment at the disease itself and at the methods used to test new drugs.

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The Nature of the Disease

Importance. It is universally recognized that tuberculosis presents an important problem to all of mankind. In the United States it kills more people between the ages of fifteen and forty-five years than any other disease, being responsible for 160 deaths every day and for the continual confinement of many thousands. Though tuberculosis is truly a preventable disease it is obvious that present public health measures must be supplemented by considerable medical care.

Behavior in the Body. Tubercle bacilli in the human body resist degradation by ordinary defense mechanisms and are treated by the host in an unusual way. Rather than being carried by leucocytes to the lymph nodes for digestion and elimination they are ingested *in situ* by monocytes which swell in size and become epitheliod cells. These apparently multiply in number spontaneously and the resultant agglomeration is known as a tubercle. Formation of the tubercle may be regarded as a protective device of the host, but this has not been proved. The expanding tubercles push aside normal tissue cells, which die from nutritional deficiencies caused by the pressure, and thus considerable damage is done directly. Generally, however, the widespread tissue destruction which characterizes the disease results from a hypersensitivity of the host's normal cells, induced by a protein elaborated in the metabolism of the tubercle bacilli. Probably identical with tuberculin, the protein is harmless to cells which have not become sensitive to it. The clinical disease in all its manifestations follows from this phenomenon of hypersensitivity.

Clinical Manifestations. In human beings tuberculosis appears in such manifold variations that it seems like many diseases rather than one. It may be a localized or a general infection, and it may affect any portion of the body. It may occur as a long-term, chronic affliction or it may strike in several deadly forms which can bring death within a few weeks. Thus tuberculosis poses many problems in therapy.

Evaluation of Drugs

Test Tubes or Animals?

The idea of evaluating bactericides by determining the highest dilution in which they will inhibit the growth of bacteria grown on Petri dishes or in test tubes is always attractive because of its simplicity, ease of interpretation, economy of materials, and low cost. On the other hand, there is usually poor correlation between *in vitro* tests and subsequent clinical trial. Such valuable agents as arsphenamine, the sulfonamides, and penicillin would have been discarded on the basis of *in vitro* tests in favor of substances which are of little value clinically. In tuberculosis the *in vitro* test gives unusually poor returns because the tubercle bacillus is rather easily killed by organic compounds in test tubes, but is phenomenally resistant when entrenched in its host's tubercles.

Animal of Choice

Various animals are currently in use for determining the value of antituberculous agents: mouse, hamster, guinea pig, rabbit, chick embryo, and hatched chick. All of these methods have advantages and disadvantages, but the use of guinea pigs is most popular because the course of tuberculosis in that animal is usually uncomplicated and is well understood. It is true that results obtained with different animals are usually not comparable, and most unfortunately they are often not very significant with respect to human tuberculosis.

Clinical Studies

Final evaluation of antitubercular drugs can only be made upon human subjects and there are now many thousands of volunteers in numerous hospitals throughout the country who are helping in this gigantic task. Pulmonary tuberculosis, especially in the chronic stages, is the most important therapeutic problem among infectious diseases today, and it is always necessary to determine how well a new drug controls that form of the disease. However, there are no good criteria for following the clinical changes in pulmonary tuberculosis. It is very difficult to determine whether treatment has had any influence on the unpredictable condition of the patient. Some of the drugs promote a feeling of well-being with diminution of coughing, etc., which misleads the hopeful patient.

Survey of Tuberculostatic Drugs

Miscellaneous Agents of Uncertain Value

Some of the drugs which may develop into valuable agents or which may suggest valuable agents are listed below. In most cases the compound listed is only one of a series which has been evaluated. Probably most of them will be discarded upon further examination, particularly those which have been examined *in vitro* only.

Synthetic types:

4-Cyanobenzeneazolutidine
1,1,1-Trichloro-2,2-bis(4-aminophenyl)ethane
Safranine
2-Butoxy-5-aminopyridine
Phenothiazine
2,7-Bis(piperidinoacetyl)diphenylenedioxide
Dialkylacetic Acids
2,5-Bis(4-sulfonamidoanilino)benzoquinone

Natural Products:

Acetylcholine
Lupulon
Cepharanthine
Antibiotics

Neomycin
Terramycin
Nisin
Diploicin
Usnic Acid
Licheniformin

The Sulfones

The sulfones, which were discovered shortly after the successful introduction of sulfanilamide, were soon found to possess considerable toxicity and much effort has been expended in attempts to reduce the toxicity without reducing the antitubercular activity. The parent compound, 4,4′-Diaminodiphenyl sulfone (DDS), could not be used clinically. Promin, diasone, and promizole have behaved well in animal tests, but there is reason to believe that each such derivative acts by conversion to DDS and displays an activity and toxicity proportional to the equivalent of DDS contained in it. The British drug, sulphetrone, is claimed to be comparatively free from toxicity. It is currently believed that the activity of the sulfones at the clinical level is of a rather low order and that their use is not justified in view of their toxicity. They have, however, found application in the treatment of leprosy, the causative organisms of which are closely related to *Mycobacterium tuberculosis.*

Promin
Diasone
Sulphetrone
Promizole

Thiosemicarbazones

Although a huge number of thiosemicarbazones have been synthesized for tuberculostatic evaluation, the original German drug, TB-1 (4-Acetylaminobenzaldehyde Thiosemicarbazone), has not been improved upon markedly and has received the most attention. Clinical evaluation in numerous hospitals of this country indicate that TB-1 is not very promising. Its use has been largely discontinued since it has a deleterious action upon certain organs of the body and has produced fatal injury.

p-Aminosalicylic Acid

In 1946 Lehmann discovered that *p*-aminosalicylic acid (PAS) inhibited tubercle bacilli very strongly. Extension of this discovery to animals and finally to human patients resulted in the present opinion that PAS does have a limited beneficial action upon clinical forms of tuberculosis. Actually, the dosage required is large, ranging from eight to thirty grams per day, and since such large doses cause severe gastro-intestinal disturbances, the drug may never have found acceptance had it not been observed that PAS not only kills streptomycin-resistant bacilli, but also greatly retards development of

organisms resistant to streptomycin. PAS is given with meals to minimize the alimentary irritation. Numerous chemical modifications of the PAS structure have failed to yield a more promising drug.

Streptomycin

Streptomycin, an antibiotic derived from *Streptomyces griseus,* was found to be exceedingly effective in curing tuberculosis in various experimental animals. It also holds the most important place among chemotherapeutic agents used for treating clinical tuberculosis. Streptomycin and its reduction product, dihydrostreptomycin, are virtually the only means of treatment for the deadly miliary tuberculosis and tubercular meningitis. The treatment is not always successful, however, largely due to the frequent relapses after treatment. Streptomycin lacks the power to remove a tuberculous infection in many cases and consequently gives temporary relief which becomes less significant when viewed over a period of a year or more. It has not been considered advisable to administer streptomycin over a period of more than 120 days because the tubercle bacilli become resistant to the drug upon continued use, and then it has no further beneficial action. It is now customary to give large daily doses of PAS during streptomycin therapy with a consequent decrease in the rate of formation of streptomycin-resistant strains. In spite of this advance, clinicians believe that streptomycin should be used only in emergency cases and in conjunction with other standard forms of therapy. Thus, the average case of pulmonary tuberculosis (the most common type) would not be subject to streptomycin treatment for fear that resistant strains would be encouraged which would make streptomycin therapy worthless in a possible future emergency. The drug is now being used indiscriminately by some physicians with the result that more and more patients are arriving at the hospitals with infections by streptomycin-resistant bacilli.

Two drawbacks to the use of streptomycin have been pointed out: (a) it is not sufficiently powerful, and (b) tubercle bacilli readily develop resistance to it. A further disadvantage is the toxicity of streptomycin. Dermatitis may develop in hospital personnel handling the drug. Even more important is the neurotoxicity which may result in patients when the drug is used over a long period. Such symptoms as dizziness, numbness about the face, and partial deafness have been encountered. They usually disappear when the drug is withdrawn, and permanent damage to the eighth nerve is rare.

Streptomycin is administered in doses of 1 grm. per day or 2 grms. every third day, with daily oral intake of 10-20 grms. of PAS (as a solution of the sodium salt). Dihydrostreptomycin is generally considered to be equivalent to streptomycin.

Conclusions

Chemotherapy of tuberculosis is still in the elementary stages of development. The combined use of streptomycin and PAS is generally beneficial when considered as an adjunct to normal medical care and surgery. Such chemotherapy must be used with care, as it entails serious disadvantages and should probably be reserved for emergency cases.

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PROBLEMS OF SCIENCE TEACHING IN SMALL HIGH SCHOOLS

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It seems to me as I meet science teachers from the larger towns or city school systems that we in the small rural high schools live in almost another world. The conditions under which we work are so very different. Perhaps if you understood our problems better, you could help us to solve some of them. I am not writing with any intent to complain. Most of us are where we are by preference for rural life, or love of our wonderful mountains, but we do work at a disadvantage.

We might class our difficulties under three general headings: administrative problems, poor equipment, and the very inadequate background and preparation of our pupils. The administrative set-up of the small high school is such that teacher load is heavy anyway so we may be teaching six periods a day, and that leaves no time for science clubs or even for properly setting up our classroom demonstrations. Practically all pupils come by bus so cannot remain for a club activity after school. Then the class personnel is too fluid—partly because the Tennessee truancy law is not enforced. We have some pupils in class two days a week and absent three. Or a boy or girl may "decide to quit" at age fourteen, stay out several weeks, and then return. How can we keep a class going on to new things with members continually coming in who have missed part of the work? Perhaps the real problem began much earlier, and is then, how can

we keep the pupils so interested that they will not want to stay out? Their truancy may be caused by their sense of failure. Can we prevent this feeling of failure without lowering our academic standard?

Next September the State Department of Education will deal a deathblow to our teaching the advanced science and mathematics courses when they begin to enforce the law about minimum classes. Even if we alternate physics and chemistry, plane geometry and advanced algebra, it will probably not be possible to get fifteen in a class in a high school numbering only a hundred pupils. I feel very strongly that physics should be taught often enough so that boys who plan to go into engineering, or into industry, as opportunities at Alcoa or Oak Ridge may open, could study this subject. Many mountain children wish to attend Berea College. They have to have math and science more than the elementary courses to be even considered for entrance. Must we deny these pupils the privilege of taking advanced courses? By so doing we will be discouraging the brighter ones in our schools. Many of us have labored to make our elementary courses interesting enough so pupils will want to study farther in these subjects. But we will find not more than ten ready to enroll. This seems to be a problem that concerns the Tennessee Academy of Science.

When we consider the equipment for science teaching in our small schools, either county or private, we find practically nothing for giving individual laboratory work. Sometimes there is nothing for class demonstrations. A teacher buys his own. We do not need elaborate pieces of equipment. But we should have a room with running water and an electrical outlet, and a lecture table of sorts. It is remarkable what can be done with almost nothing. The reward is in seeing some boy's eyes shine with enthusiasm as he comes up nearer so he may not miss a thing that is going on.

Most textbooks are geared to city life. How can we make meaningful the reading about things a child has never seen like trains and electrical gadgets? Few mountain cabins have electricity or running water or labor-saving devices. On the other hand, of course, a mountain boy knows more about using a lever to get a car out of the mud than does a city lad.

Pupils coming to us from one-room schools may have had no science teaching at all. There may have been a little nature study. There have been no reference books. We must be careful to present our ninth grade science work in a way that can be understood. We have to incorporate into that course all sorts of guidance like learning to study, learning how to use the library and magazines and the dictionary. We have to patiently supervise projects so as to make them meaningful. Some pupils have never done anything like a project before. We must teach habits of thought, and neatness, even reading habits in some cases.