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Streptomycin and Dihydrostreptomycin

Louis Weinstein and N. Joel Ehrenkranz

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STREPTOMYCIN and DIHYDROSTREPTOMYCIN

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FOREWORD

During the past 20 years, new and powerful weapons have been forged for use in the all out war against bacterial infections. Among the most effective agents, the antibiotics lead the field. These agents have completely revolutionized the treatment of infections, and they have changed the pattern and course of many diseases. While it is impossible to assess the total benefits that have flowed and continue to flow from the discovery, developments, and application of antibiotics, it can be said that the benefits to mankind in preventing premature death, alleviating suffering, and the shortening of illness when it strikes have been sensational.

With the discovery and development of streptomycin and dihydrostreptomycin, there appeared upon the stage of the theater of antibiotics an agent that provided new hope for patients with tuberculosis and many other diseases, which are so well discussed in this monograph by Weinstein and Ehrenkranz.

There is no bacterial disease that has attracted more attention than tuberculosis, and until streptomycin appeared upon the scene, there was no chemotherapeutic agent available for the treatment of the disease. Streptomycin marked the dawn of the new era, and the results to date are summarized in this monograph by the authors.

Aside from tuberculosis, the various diseases that are influenced favorably by streptomycin are discussed in this monograph. We have here in one place a complete and comprehensive summary of what is known about streptomycin, and the story is told clearly and concisely and in a way that is readily available and useful to the physician.

Streptomycin and dihydrostreptomycin are discussed thoroughly and throughout their entire range. There are illustrative case reports, based upon the personal observations of the authors. There is a clear discussion of the use of streptomycin in disease and an excellent bibliography.

Doctors Weinstein and Ehrenkranz deserve to be congratulated upon the production of this monograph. It is a contribution worthy of the effort, and it will serve as an example for the presentation of a complicated and important subject. The book can be read with profit to all, and it will take its place along with other antibiotic monographs as a real contribution to the knowledge and literature upon a most important subject.

Chester S. Keefer, M.D.

Boston, Massachusetts
May 12, 1958

PREFACE

The area of therapeutic application of streptomycin and dihydrostreptomycin has become greatly constricted since the development of antimicrobial agents with broader and more potent antibacterial effects. Since the tetracycline compounds, chloramphenicol, polymyxin, and neomycin have become available for the treatment of many infections due to gram-negative bacteria, the need to use streptomycin for the management of disorders due to such organisms has been sharply reduced. Tuberculosis is the disease in which streptomycin still has its widest application; this infection is not discussed here because it forms the subject of a separate monograph in this series. Although limited in their usefulness, both streptomycin and dihydrostreptomycin, alone and in combination with other antimicrobial agents, nevertheless are still very important therapeutic agents. The areas in which these drugs are of value are discussed in this monograph. Much has been included that is primarily of historical interest; a great deal has been omitted because it is at present *only* of historical interest.

No attempt has been made to include in this monograph a review of every paper that has been published concerning streptomycin and its derivatives. From 1944 through 1952, 5550 reports dealing with one or another phase of the activity of this antibiotic were written. It was obviously impossible to include all of these in a work intended to be a short monograph. The authors have tried to select only some of those papers that were of help in documenting specific points of information, without trying to review every pertinent publication. If they have omitted any important papers, this has been completely inadvertent.

During the period when this monograph was written, the senior author was Associate Professor of Medicine at Boston University School of Medicine and Chief of the Department of Infectious Disease at the Massachusetts Memorial Hospitals in Boston, Massachusetts. The junior author was Instructor in Medicine, Boston University School of Medicine, and a Fellow of the National Foundation for Infantile Paralysis in the Department of Medicine (Infectious Disease) of the Massachusetts Memorial Hospitals.

L.W.
N.J.E.

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Chapter I

History of the Development of Streptomycin and Dihydrostreptomycin

The ineffectiveness of penicillin in the treatment of infections due to gram-negative bacteria stimulated the search for antibiotic substances effective against this group of organisms, which alone or in combination with gram-positive agents are responsible for a considerable segment of human disease. Unlike the serendipitous discovery of penicillin, the development of streptomycin resulted from a well-planned, scientifically carried out search for antimicrobial substances. Among the organisms studied by Dr. Selman Waksman during his investigations in soil microbiology were the actinomycetes. It was natural for him to turn to this group, therefore, in his quest for new antibiotics. Between 1939 and 1943, Waksman and his co-workers demonstrated the production of actinomycin, clavicin, fumigacin, chaetomin, micromonosporin, and streptothricin by actinomycetes;[1] all of these were found, however, to be too toxic for clinical use, or only slightly active in vitro and in vivo. The *Streptomyces* strain from which streptomycin was produced was isolated in the laboratory of the Department of Microbiology of the New Jersey Agricultural Experiment Station, Rutgers University, in September, 1943. The first public announcement of the discovery of the new drug was made by Schatz et al in January, 1944.[2] Before the end of the year, streptomycin was shown to be effective against the tubercle bacillus both in vitro and in vivo.[3, 4] and, although available only in small quantities, was being subjected to clinical trial in infections due to susceptible organisms. In less than two years after its initial production, extensive bacteriological, chemical, pharmacological, and clinical studies had been carried out, and the practical potentialities of streptomycin as a chemotherapeutic agent were established.

The Committee on Chemotherapeutics of the National Research Council, which, under the leadership of Chester S. Keefer, M.D., performed the difficult task of the clinical evaluation of penicillin prior to its release for general

clinical use, assumed the arduous job of determining, under controlled conditions, the value of streptomycin in the treatment of infection. First consideration for use of the new antibiotic agent was given to the Army, Navy, United States Public Health Service, Veterans Administration, and the National Research Council; certain civilian hospitals were also allocated supplies for controlled clinical evaluation. The program of the National Research Council was supported by a contribution of nearly $1,000,000 from 11 pharmaceutical and chemical companies and constituted the first privately financed, nationally coordinated clinical evaluation of a drug in history. It has been estimated that by the fall of 1946, manufacturing laboratories had invested $2,000,000 in production facilities for streptomycin.[1] By early 1947 the work of evaluating streptomycin was considered completed and the agent was released by the National Research Council for general clinical study and use.[5]

The rapidity with which the production of streptomycin increased to high levels is reflected by the fact that, within four years of the time that Waksman and his co-workers announced the isolation of this agent, 3,000,000 Gm. was being produced monthly. At present, eight manufacturers are producing as much as 14,000,000 Gm. of the drug monthly. Production of streptomycin and dihydrostreptomycin combined in 1950 was 95,174.6 Kg.; in 1951, 151,635.8 Kg.; and in 1952, 147,777.3 Kg. In an emergency, there is sufficient plant capacity to produce about 200,000 Kg./year.

The synthesis of dihydrostreptomycin was announced almost simultaneously in 1946 by Peck, Hoffhine, and Folkers[6] and Bartz et al.[7] This agent is produced by catalytic hydrogenation of streptomycin. It has about the same degree of antibacterial effectiveness as the parent substance, although it is thought to be somewhat less effective against some gram-negative organisms. In general, however, dihydrostreptomycin is qualitatively very similar to streptomycin, although it is less toxic to the vestibular portion of the eighth cranial nerve. The manufacture of dihydrostreptomycin increased rapidly because it was at first thought to be less damaging to the ear. The demonstration that it produces serious deafness, which may be delayed in its onset, removes the advantage that this substance was thought to have and has resulted in a decreased utilization of the drug.

Chapter II

Chemical and Biological Properties of Streptomycin and Dihydrostreptomycin

CHEMISTRY OF STREPTOMYCIN

Streptomycin is a basic substance and forms salts with anions. The molecular formula is $C_{21}H_{39}N_7O_{12}\cdot 3HX$ for streptomycin salts.[8] The antibiotic is made up of three compounds: streptidine, streptose, and N-methyl glucosamine;[9-11] the formulas for these are shown in figure 1. A hypothetical reaction of these three substances, which perhaps takes place at least in part biogenetically with the elimination of two molecules of water, yields streptomycin. The formula for streptomycin is also shown in figure 1.

Streptomycin is a relatively stable substance. In the dried state it retains its potency when stored at room temperature for at least one year.[12] In solution it remains active at or below 28 C. at *p*H 3 to 7 for about two months. At a temperature of 85 C., the activity of solutions of the drug is reduced by about 50 per cent in 37 hours when the *p*H is 5.5.[12] Dilute buffered solutions at *p*H 6 to 8 and 10 C. remain stable for at least three months.[13] Heating at 70 C. for one-half hour produces no appreciable loss in activity;[14, 15] at 100 C. half of the antibacterial effectiveness is lost in 10 minutes.[16]

Two cations, magnesium and calcium, decrease the potency of streptomycin.[17] Nitrates, lactates, phosphates, chlorides, tartrates, and citrates are the anions that decrease the effectiveness of the drug.[17] Among other compounds that inhibit streptomycin effect are glucose,[18-20] cysteine,[21] cevitamic acid,[18] beta-mercaptomethylamine,[21] several ketone reagents,[9] the cyanate ion, Soerensen's buffer,[22] and the oxidizing agents, potassium permanganate, nitric acid, potassium metaperiodate, hydrogen dioxide, and chloric acid.[23] Streptomycin forms a complex with albumin, desoxyribonucleic acid, thymonucleoprotein, and calcium chloride.[24] No biological system or enzyme has yet been found that is capable of destroying the antibiotic.[21]

The hydrogen ion concentration of the medium is of great importance in

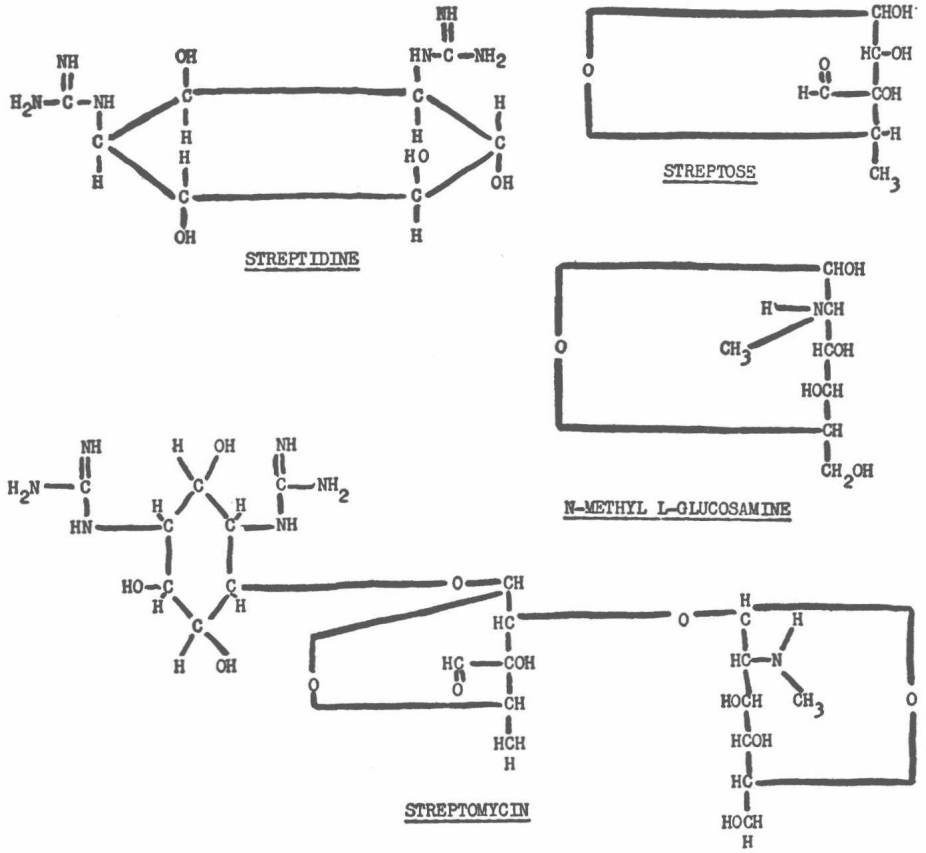

FIG. 1. The structures of streptidine, Streptose, N-Methyl L-Glucosamine, and streptomycin are shown.

determining the effective activity of streptomycin.[14, 25-27] There is a twenty- to eightyfold reduction in potency at *p*H 5.8, as compared with a *p*H of 8. At 25 C. the drug is not affected appreciably between *p*H 2 and 9, but it is decomposed by 1*N* hydrochloric acid or 0.1*N* sodium hydroxide.[18] Streptomycin is only one-half as active in a hydrogen atmosphere as it is in air; it is considerably less antibacterial under nitrogen and is almost completely inactivated in an atmosphere of carbon dioxide.[18]

Streptomycin is soluble in water but not in alcohol, ether, or chloroform; it is optically active.[28] It forms salts with acids; the hydrochloride and calcium chloride complex have been used extensively clinically, but have now been almost completely replaced by the sulfate. The antibiotic reacts with a number of carbonyl reagents because it has a free or potential carbonyl group, as demonstrated by the formation of an oxime and semicarbazone.[9]

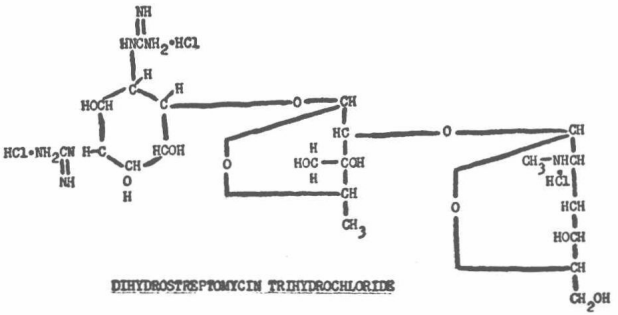

FIG. 2. Dihydrostreptomycin trihydrochloride.

CHEMISTRY OF DIHYDROSTREPTOMYCIN

Reduction of streptomycin in the presence of platinum results in the addition of 1 molecular equivalent of hydrogen per molecular equivalent of the drug, at pressures of from 1 to 4 atmospheres, with the formation of dihydrostreptomycin, the formula for which is shown in figure 2.[6, 7, 29] This agent not only has increased stability, particularly toward alkaline reagents, but its biological activity is qualitatively and quantitatively comparable to that of the parent substance. The dihydro- compound is not inactivated by cysteine or carbonyl reagents and does not form maltol when heated with alkali.[6, 7, 29-31] The empirical formula of the sulfate is $(C_{21}H_{41}O_{12}N_7)_2 \cdot 3H_2SO_4$.

MODE OF ACTION OF STREPTOMYCIN

Streptomycin is both bacteriostatic and bactericidal, the degree of antibacterial effect depending on a number of factors.[16, 32, 36] With a small number of bacteria and high concentrations of antibiotic, a killing effect is produced. The length of time of contact between drug and organism is another important determinant. The total number and type of bacteria, the concentration of antibiotic, and, in vitro, the temperature, *p*H, and age of the culture determine whether a bactericidal or bacteriostatic effect results. Streptomycin is effective, under certain conditions, against stationary or slowly dividing cells as well as against rapidly dividing ones, when a large enough quantity of the agent is used. In subinhibitory concentrations the drug stimulates morphological changes;[37] *Salmonella typhosa*[38] and *Pasteurella tularensis*[38] become large and bizarre in shape, while *Shigella sonnei, Salmonella typhimurium, Aerobacter aerogenes,* and *Proteus* become elongated.[35]

It has been postulated that streptomycin penetrates cell membranes either not at all or only in minute amounts. In the animal, it appears to be distributed as if it were present in extracellular water only. Ultramicroscopic study reveals that the calcium chloride complex of streptomycin forms a colloidal sol in water rather than a true solution, the particle size of the dispersed phase being about 65 μ. The drug passes readily through a cellophane dialysis membrane, however, indicating that its physical dispersion is

such that the particle size per se is not an obstacle to penetration through a cellular membrane. The tendency for streptomycin to collect at cell surfaces rather than penetrate cell walls would appear, therefore, to be dependent on some physicochemical barrier to penetration rather than on particle size.

The exact mechanisms by which streptomycin inhibits bacterial growth have not yet been elucidated. Many theories have been proposed, and although some have appeared to be supported by experimental data, they have had to be discarded on the basis of new evidence. Attention has been focused on the effect of the drug on various enzyme systems of a variety of susceptible and insensitive bacteria, because this is very likely to be the most important mechanism involved in the production of antibacterial activity.[39] Streptomycin interferes with normal cell division without disturbing cell growth. It has been shown that inhibition of "resting" bacteria by the antibiotic is not related to the killing effect but rather to the substrate being metabolized.[40] The drug seems capable of disintegrating the cell wall of *Klebsiella pneumoniae*. Some studies have suggested that it interferes with reaction between pyruvate and oxalacetate (the Krebs condensation), a system that controls terminal respiration in cell metabolism;[41] this has been shown to occur in animal as well as bacterial cells.[42] This hypothesis is supported by the observation that resistant and dependent variants of a streptomycin-sensitive organism *(Escherichia coli)* do not possess the ability to affect the oxalacetate-pyruvate condensation. It has been proposed that a permeability barrier exists at the animal cell wall that prevents streptomycin from penetrating to the site of the Krebs condensation reaction; in the bacterial cell, the reaction system may not be protected and hence metabolic function is interrupted.

In bacteria that are capable of oxidizing acetate, the oxidation of pyruvate or oxalacetate is not affected by streptomycin; in those in which acetate is only minimally or not at all oxidized, pyruvate and oxalacetate oxidation is markedly suppressed. The pathways from pyruvate to citrate or from citrate to cis-aconitate are not sensitive to the antibiotic agent. Streptomycin inhibition is thus most marked on organisms in which the major portion of the pyruvate cannot be diverted through acetate oxidation and can be oxidized to completion only by the streptomycin-sensitive mechanism; in the presence of the drug, this oxidative mechanism is blocked.

Although it has been postulated that streptomycin may react with sulfhydryl groups in the bacterial cell and thus interfere with its metabolism, this remains to be proved. The most recent investigations of this phenomenon have revealed that the antibiotic is not a very powerful sulfhydryl reactant.

A study of the oxidation of long-chain fatty acids by an avian strain of *Mycobacterium tuberculosis* has shown that the reactions do not proceed to completion in the presence of streptomycin.[43] The oxidation of the breakdown products rather than that of the fatty acids themselves is apparently reduced

by the antibiotic. Similar inhibition by streptomycin of stearate oxidation by *E. coli* has also been observed, although the two organisms oxidize this substance somewhat differently.

Studies with *S. sonnei* have shown that, coincident with the inhibition of multiplication by streptomycin, a decrease in carbohydrate substrate utilization and the quantity of oxygen consumed per cell occurs.[44] After bacteriostasis of *Bacillus cereus* by exposure to the antibiotic, the total nitrogen and phosporus content of the organisms decreased, but the quantity of reducing substances increased.[44]

In very high concentration, streptomycin does not affect catalase, carbonic anhydrase, cytochrome, cytochrome-oxidase, succinoxidase, carboxylase, urease, or trypsin.[45] Quantities of the drug that are just bacteriostatic appear to inhibit noncompetitively the metabolism of certain carbohydrate intermediates in susceptible strains of *Staphylococcus aureus, B. cereus,* and *S. sonnei.* It has been postulated, on the basis of these observations, that streptomycin suppresses either the formation or the activity of enzyme systems involved in the metabolism of carbohydrate, resulting in an accumulation of acetate.[45]

Although no conclusions can be drawn concerning the exact mechanisms by which streptomycin produces antibacterial effects from the data just presented, the evidence is highly suggestive that its activity is in some manner associated with an ability to interfere with certain essential metabolic processes by virtue of a damaging or inhibiting effect on specific enzyme systems with which the antibiotic forms irreversible combinations.[39] There is no evidence that the mode of action of streptomycin is different in vivo than it is in vitro.

FACTORS INFLUENCING THE BIOLOGICAL ACTIVITY OF STREPTOMYCIN

A number of factors influence the antibacterial activity of streptomycin.[56] Most of these have been studied in vitro. Some, however, undoubtedly play an important role in determining the effectiveness of the antibiotic agent in eradicating infection in man and animals.

The concentration of streptomycin to which organisms are exposed is of importance in determining the degree of activity of the drug: the larger the quantity of antibiotic with which bacteria come in contact, the more intense the antibacterial effect. The effect of concentration is a function of the innate sensitivity of an organism to streptomycin. Although it may be possible to increase the quantity of antibiotic in vitro to the point where inhibition of even highly sensitive strains is manifest, this is not possible in vivo; in infections in man and animals, the most important factors that limit the usefulness of streptomycin are the susceptibility of the infectious agent and the toxicity of the drug.

The size of the inoculum in vitro or the total mass of bacteria producing infection in vivo determines to a great degree the level of activity of streptomycin in the same manner as it does the effect of other antibiotic agents.[26, 46-48] The larger the number of organisms, the greater the concentration of drug required to produce complete suppression of multiplication. This is due, in part, to the fact that the cells in any bacterial population exhibit a wide range of sensitivity to streptomycin.

Bacteria do not produce an antagonist for streptomycin. The drug is not destroyed by organisms or removed from the medium during growth. The effect of serum in inactivating streptomycin varies with different bacteria.[49, 50] With *Staph. aureus* and *E. coli,* serum does not appear to decrease the antibacterial activity of the antibiotic. On the other hand, serum inhibits the effect of the drug against *Streptococcus pyogenes* to a marked degree, and against pneumococci to a moderate extent. A 10 per cent concentration of serum appears to enhance the antimicrobial action of streptomycin against *Sal. typhosa.*[50] It has been suggested that the type of response observed on the addition of serum is dependent, in part, on the need that various organisms may have for this material as a growth stimulant.

The activity of streptomycin is extremely sensitive to salt concentration.[17] The addition of 2 per cent sodium chloride may increase the minimal inhibiting quantity of the antibiotic one hundred–fold. This effect has been observed with all organisms and with a variety of cations and anions, including sodium, potassium, lithium, ammonium, barium, magnesium, and calcium, and chloride, sulfate, tartrate, phosphate, acetate, pyruvate, nitrate, lactate, citrate, fumarate, succinate, formate, and maleate. Antibacterial activity is also reduced by potassium permanganate,[23] thioglycollic acid,[51] vitamin C,[18] semicarbazide, phenylhydrazine, and methylphenylhydrazine.[9]

Unknown constituents of bacterial media, unidentified components of blood and plasma, cellulose, oxidized cellulose, desoxyribonucleic acid, thymonucleoprotein, and various bacteria absorb streptomycin. This phenomenon can be completely inhibited or reversed by the addition of various salts.[24] The absorption of streptomycin by bacteria occurs completely or almost completely at the cell surface and is not related to the degree of sensitivity of the organisms to the antibiotic.[52]

ANTIMICROBIAL ACTIVITY OF STREPTOMYCIN

High concentrations of streptomycin are bactericidal and smaller quantities bacteriostatic in vitro. Resting cells are less susceptible than multiplying ones. Very small amounts of the drug may stimulate bacterial growth. The factors that influence the degree of antimicrobial activity of streptomycin are type of organism, nature of the medium in which bacteria are growing,