Nomenclature of Streptomycin Preparations

Selman A. Waksman

New Jersey Agricultural Experiment Station, New Brunswick

ANTIBIOTIC SUBSTANCES ARE PRODUCTS of living systems. They are formed mostly under artificial conditions of cultivation upon complex organic or synthetic media. Methods for their isolation from the medium vary greatly. Most of the antibiotics have been named and described on the basis of crude preparations, or long before they have been isolated in a pure state and their chemical nature determined. The designations and descriptions of antibiotics are based largely upon their formation and certain important properties. These are:

(1) Origin—that is, the nature of the organisms producing them. Most of the antibiotics have been named after the genera or species of these organisms.

(2) Antibacterial or antibiotic spectrum, namely, the selective action of the antibiotic against various bacteria and other microorganisms. This is one of the most important properties of the antibiotic, since its nature and possible utilization are thus characterized. The differences in sensitivity of the various bacteria to a given antibiotic may be both qualitative and quantitative. The nature of the test medium for making the bioassays is, thus, of primary importance. Frequently, bacteria made resistant to one or more known antibiotics are used to establish the identity of an unknown substance.

(3) Toxicity of the antibiotic to animals and its *in vivo* activity. These properties are most significant from the point of view of establishing the possible chemotherapeutic utilization of the antibiotic.

(4) Chemical and physical characteristics, notably elementary composition and chemical structure. The last property is the culminating point in the identification of a new antibiotic.

Although the chemical composition of an antibiotic is frequently used for establishing its further subdivisions, if such are required, it is the biological criteria which are the most significant in describing and defining a new antibiotic. It has even been suggested (*6*) that a new antibiotic not be named or described until it has been isolated in a chemically pure state. Though this procedure would be highly desirable in principle, it has not always been followed in the past, nor would it be possible to bind all investigators to its observance. Thus, penicillin and streptomycin were named, described, and even used for therapeutic purposes long before they were crystallized and their chemical nature established.

An illustration of how the above criteria apply to the isolation of a single antibiotic is provided by the data presented in the announcement of the isolation of streptomycin (*8*): (1) The organism producing this antibiotic was identified as *Streptomyces griseus*; the generic name of the organism contributed to the naming of the antibiotic. (2) Streptomycin was found to be active against various gram-negative and gram-positive bacteria, including *Mycobacterium tuberculosis*. Compared to streptothricin, a closely related antibiotic, it was much more active against certain bacteria, notably *Bacillus mycoides* and *Serratia marcescens*. (3) Streptomycin was found to have little toxicity to animals and was active *in vivo*. (4) It was isolated from the culture filtrate of *S. griseus* by the method previously developed for the isolation of streptothricin, namely, adsorption on Norite A, elution with acid-alcohol, neutralization of the acid, and removal of the alcohol. Further details of the production of the substance, its *in vitro* and *in vivo* activity, and purification procedures were reported in subsequent papers (*9*).

More recent studies of the nature of the antibiotic produced by *S. griseus* brought out two important facts: (a) the organism produces, in addition to streptomycin, two and possibly three or more antibiotics: one is present in the mycelium, and another, designated as "actidione," is found in the culture filtrate and is active only against fungi; (b) streptomycin itself, as originally defined on the basis of biological and certain chemical criteria, is not a single chemical entity, but a mixture of at least two chemically related substances. The major constituent of this mixture is undoubtedly the substance which is now known, from the degradation studies, to possess the structure of an o-glycoside of the disaccharide streptobiosamine (N-methyl-L-glucosaminido-streptose) with streptidine (1,3-diguanido-2,4,5,6-tetrahydroxycyclohexane) (*5*). The only other representative of this type which has been isolated in pure form and chemically characterized is streptomycin B (*2*); it always seems to occur in association with the previous compound, and differs

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The contents of this paper were discussed with O. Wintersteiner, of the Squibb Institute, K. Folkers, of Merck & Co., H. E. Carter, of the University of Illinois, and M. L. Wolfrom, of Ohio State University, who have made a number of constructive suggestions and corrections.

from it by the presence of an additional D-mannose moiety in the molecule (*1*). Streptomycin B is characterized by an antibiotic spectrum (*7*) which differs quantitatively from that of the pure chemical entity originally isolated.

Thus, the elucidation of the nature of the "streptomycin complex" presents a close parallel to the advances in our knowledge of the "penicillin complex." *Penicillium notatum* and *P. chrysogenum* produce, in addition to penicillin, another, chemically unrelated antibiotic possessing entirely different antibacterial properties (penatin, notatin). Penicillin itself, even in the crystalline state, may be composed of several chemically closely related substances (F,dihydro-F,G,X,K). As a further analogy to penicillin, crude streptomycin preparations contain impurities, some of which may act as "enhancement factors" (*3*).

It need hardly be emphasized that the isolation of several chemical entities from the "streptomycin complex" introduces considerable uncertainty in the interpretation of data obtained with impure preparations containing both of the above compounds in unknown proportions; this is true especially in the correlation of chemical with biological assay data and of *in vitro* activities with therapeutic and toxicity effects in animals.

Pending the establishment and acceptance of reliable biological and chemical differential assay methods for the determination of the various compounds in mixtures, it would seem desirable to reach an agreement at least on the definition and naming of the antibiotically active materials and entities concerned. It is suggested, therefore, that the following nomenclature be adopted for products possessing streptomycin activity:

Streptomycin complex. This term should be used, in a sense originally proposed for streptomycin (*8*), to designate that group of antibiotics which is characterized by the antibacterial spectrum and certain chemical and physical properties assigned to it. This term would, therefore, have to be applied to all crude or partly purified preparations containing various forms of streptomycin and inactive impurities in unknown proportions.

Streptomycin. This term designates the compound, chemically defined as N-methyl-L-glucosaminido-streptosido-streptidine. Accordingly, the term "streptomycin A," which has been suggested for this entity by implications (*2*), is not to be used.

Mannosidostreptomycin. This term designates the entity formerly named streptomycin B and now chemically defined as D-mannosido-N-methyl-L-glucosaminido-streptosido-streptidine.[2]

Streptomycin residue. It is suggested that this term be applied to any residues which exist after the removal of highly purified streptomycin from impure streptomycin preparations and which may either have inherent antibiotic properties or act as enhancement factors.

Streptomycin-like substances. Any preparations, produced by organisms other than *Streptomycin griseus,* which show an antibiotic spectrum and other biological and chemical properties similar to those of streptomycin should be so designated. When they are crystallized and their chemical composition is determined, their exact nature may be established. This is true, for example, of streptomycin II (*4*).

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[2] Though the Squibb investigators concerned (Fried, Stavely, Titus, and Wintersteiner) took exception to the system of nomenclature here proposed, they cooperated by suggesting the new term "mannosidostreptomycin" and by agreeing to use it henceforth in their publications. The correctness of the structure given above and implied in the new term will be evident from data soon to be published in a paper by Drs. Stavely and Fried, of the Squibb Institute for Medical Research in the *Journal of the American Chemical Society.*