Pharmacological Basis of Penicillin Therapy

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To Walter J. Meek

Professor Emeritus of Physiology and Dean
Emeritus of The University of Wisconsin
Medical School

Preface

THE PURPOSE of this monograph has been to present briefly the pharmacological basis of penicillin therapy in a concise and reasonably complete form. At this writing there exists no review wherein the broad field of penicillin pharmacology has been summarized. This is understandable for only the barest outlines of this subject have been known for more than the past few years. Within that period many pieces have been fitted into this mosaic until today it seems justifiable to present this pattern as a whole, with the realization that it is still by no means complete.

It would be entirely rational to present a companion monograph on the bacteriological basis of penicillin therapy, for it is not intended to imply that the interrelation of a chemotherapeutic agent and the patient is the more important aspect of treatment. After all, the purpose of administering the antibiotic agent is to cure the patient of his illness as quickly and with as little discomfort and inconvenience as possible. But it is this interrelation of the drug and the host that has influenced penicillin therapy so profoundly.

It is rather remarkable that the body should set up almost every barrier to the admission of this most valuable ally, penicillin, and that the host should use its most effective means to rid itself of the agent once its entrance has been gained. This physical abhorrence of penicillin is a characteristic of all species to which the agent has been administered, and this philosophy summarizes the more important aspects of the pharmacology of penicillin. It would be interesting to speculate from a teleological basis

as to the reason for this estrangement. Possibly it is linked to the defense of the body against micotic infections. Credence for this view is gained from the observation of more astute clinicians that reactions to amorphous penicillin preparations are more common among patients having a history of athelete's foot or some other, not necessarily penicillium, fungous infection. Further speculations relating to the antagonism of the body for this product of a mold's metabolism might better be left at this point to the reader's self-indulgence, since he might be less critical of his own opinions in the matter.

Certainly, no other agent has made such a profound impression on the practice of medicine in recent years. Its remarkable lack of toxicity and its high degree of antibacterial activity have influenced profoundly the treatment of diseases already amenable to sulfonamide therapy, the otherwise protracted treatment of syphilis, and have made possible the clinical cure of certain of the bacterial endocarditities that have not heretofore succumbed to therapy. Some notion of the relative emphasis that the physician has placed on antibiotic therapy may be gained from the fact that in 1948 the combined sales of penicillin and streptomycin were 60 per cent of the total dollar sales of medicinals. The combined costs of anesthetic agents, sulfonamide preparations, narcotics, barbiturates and biological products amounted to little more than half the sales of penicillin products.

In this monograph I have summarized much of the basic pharmacology pertaining to the absorption, distribution and inactivation of penicillin in Chapters I and II. In Chapter III, I have discussed the mode of action of penicillin in sufficient detail to serve as a basis for the presentation of the two current philosophies of dosage regime in therapy. I am indebted to my associate Dr. W. F. Verwey, Director

of Bacteriological Research in this institution, for his criticism of this portion of the manuscript, which necessarily diverges somewhat from the province of the Pharmacologist. Since the repository forms of penicillin products have enjoyed widespread usage in recent years they have been discussed in a separate chapter, Chapter IV.

Chapters V, VI and VII deal with the renal elimination of penicillin and measures that have been developed to suppress reversibly its tubular secretion. This represents the first correlation of the enzymological, the renal physiological and the clinical bases of this new approach to penicillin therapy. The fields of enzymology and modern renal physiology have become so complex in recent years that it has been difficult for others than the specialist in the field to visualize individual mechanisms for tubular secretion or absorption in terms of the enzymological components of the cell's metabolism. Consequently, the clinical utility of this basic integration of knowledge of the two fields can be understood only to the extent that one appreciates that the physiological inhibition of a single transport system in the cells lining the tubules can be divorced entirely from the pathologists' view of generalized cellular damage and repair. Chapter V and particularly Chapter VI deal with this subject from the enzymological and physiological consideration of the renal tubular secretion of penicillin and its inhibition. In Chapter VII the pharmacology and clinical utility of combined carinamide and penicillin therapy have been reviewed, since the former compound was developed by the application of the principles discussed in the preceding chapters.

It is a pleasure to acknowledge in the legends of illustrations and tables the many excellent contributions to research in this field by various investigators. Dr. W. F. Verwey, Dr. W. A. Feirer and Dr. L. E. Arnow have been

good enough to criticize the manuscript both from an authoritative and a general standpoint. I am especially grateful to them since their knowledge of this general field is most intimate. I should like to acknowledge the assistance of Miss Dorothy Brennan who performed the many secretarial duties connected with the monograph, and also the assistance of Miss Mildred Garrett who prepared the original illustrations.

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Chapter I

Penicillin Pharmacology: Part I

Summary—At least five chemically related penicillins have been produced in sufficient amounts to permit their study. They are penicillins F, dihydro F, G, K and X. All of them are quite unstable in the presence of water to extremes of pH, light, heat, and oxidizing agents. Oleagenous preparations of the crystalline materials are quite stable. Penicillins X and G are generally the more active compounds *in vivo* but they all vary relatively when tested *in vitro* and *in vivo* against an array of organisms.

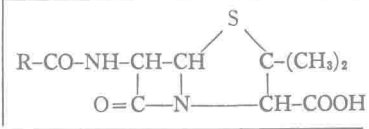
Whereas a tremendous amount of work has been carried out to buffer penicillin against, or carry it past, the acidity of the stomach, it is becoming increasingly clear that absorption *per se* is the limiting factor in its entrance to the body via the gastrointestinal tract. As much as 20 per cent of a given oral dose of penicillin is absorbed and excreted when the drug is administered with or without antacids. Penicillinase produced by intestinal organisms apparently destroys most of the penicillin not absorbed in the intestine. Although locally beneficial the application of penicillin sublingually, and to the skin, eye, external ear, nose, bronchial tree, rectum or vagina results in insufficient absorption to be useful generally as principal routes of administration to combat systemic infections.

FIVE *members of a group of chemically related penicillins* were recognized in a recent report issued by the Antibiotic Study Section of The National Institute of Health.[1] In addition, other types of penicillin chromatographically similar to penicillins G, F and K have been described.[2] The historical development of penicillin syn-

thesis has been described briefly elsewhere.[3] Since the workers in this country have used alphabetical designations and those in Great Britain have used Roman Numerals, I have listed the better known penicillins according to their chemical names, designations, and structures in Table 1.

TABLE 1

The structure and nomenclature of better-known penicillins

Designation of R–			β–lactam structure
Chemical	American	British	
△² pentenyl	F	I	
N–amyl*	dihydro F		
benzyl	G	II	
p-hydroxybenzyl	X	III	
n-heptyl	K	K	

* Formed by the hydrogenation of △² pentenyl penicillin.

In this table, R- represents the chemical designation of the various types of penicillin wherein they differ and the β-lactam heterocyclic nucleus is that which has been most generally accepted to be common to all the penicillins.

The various penicillins are fairly strong acids, forming salts with cations such as sodium and potassium, and with organic bases such as procaine, or forming esters[4] such as the benzyl ester of penicillin G. The salts and esters differ in their solubility and stability. As anhydrous crystalline preparations many of them are stable indefinitely. In anhydrous inert media in which they are insoluble this stability persists. In the presence of water none of the known preparations that is at all soluble is stable for any pharmaceutically useful period of time, unless buffered between pH 6-7 with 0.01 molar sodium citrate or phosphate, and maintained at ice box temperature, whereupon the half-life of sodium penicillin G may be extended to 10 or 14 days.[5] As the pH of the solution is allowed to become