DIGITALIS GLYCOSIDES

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Dedicated to the memory of my father,
Luther David Smith

PREFACE

> It is much easier to write upon a disease than upon a remedy. The former is in the hands of nature, and a faithful observer, with an eye of tolerable judgment, cannot fail to delineate a likeness. The latter will ever be subject to the whims, the inaccuracies, and the blunders of mankind.
>
> *An Account of the Foxglove* (1785)
> William Withering, M.D.

Two hundred years after the publication of Withering's classic treatise on the clinical use of digitalis, the above quotation remains a graceful apology on behalf of all who take pen to hand on the subject of clinical therapeutics. Withering's own trepidations are further reflected in the quotation from the *Ars Poetica* of Horace that he chose for the frontispiece of his monograph: "*nonumque prematur in annum.*" Freely translated, "Let it be suppressed (or held back) until the ninth year," this constituted Horace's admonition to poets to reflect on their work for nine years before publication, and was apropos of the fact that Withering had studied the pharmacology of digitalis for a similar period of time before publishing his famous monograph. To be sure, his active practice as a physician and his broadly based interests in botany, geology, chemistry, and social history* must have left him scant time in which to write up his pharmaceutical and clinical observations. Nevertheless, one can only marvel at his powers of observation and his dedication to the objective reporting of his findings. Withering was clearly a pioneer among a new

* Krickler DM: The foxglove, "The old woman from Shropshire" and William Withering. J Am Coll Cardiol 5 (Suppl A): 3A–9A, 1985

generation of physicians well versed in the basic sciences and able to bring the latter expertise to bear on problems of biomedical consequence.

In the present text, we have tried to provide a timely and selective review of each aspect of cardiac glycosides discussed, and we regret that practical considerations preclude citing many additional pertinent references from the literature. We hope that the background and synthesis provided will be useful to both clinicians and investigators, dedicated as we are to the idea that their interests are inextricably linked both in principle and in practice. Thus, studies of fundamental aspects of ion transport across cell membranes in the basic laboratory have been aided immeasurably by the use of digitalis glycosides, while at the same time the insights thus gained are now providing for the first time a detailed understanding of the cellular and subcellular mechanisms whereby cardiac glycosides enhance the force of myocardial contraction and alter the electrophysiologic properties of the heart.

Finally, despite the impressive mass of accumulated information on digitalis summarized in this book and elsewhere, there are many important gaps in the available data on which therapeutic decisions must be based. One hopes that specific information on the safety and efficacy of cardiac glycosides relative to other current therapeutic approaches (particularly including vasodilators and newer inotropic-vasodilator drugs) will soon be available, and that future clinical trials will allow valid stratification of patients into subsets according to multiple descriptors including the nature, manifestations, and severity of underlying heart disease.

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Introduction

Two centuries ago, Withering concluded from his clinical experience using digitalis that

> . . . it has a power over the motion of the heart, to a degree yet unobserved in any other medicine, and that this power may be converted to salutary ends.
>
> William Withering (1785)

This quotation has been cited frequently in the past 200 years, attesting to the perception of many generations of physicians that digitalis can be used to advantage in the management of selected patients with cardiac disease. Useful reviews of various aspects of cardiac glycoside use include those of Selzer[2] in 1968, Mason et al[3] and Wilson[4] in 1969, Fisch and Knoebel[5] and Kassebaum and Griswold[6] in 1970, Butler[7] in 1972, Ferrier[8] in 1977, and Doherty et al[9] in 1978.

In this book we approach the use of digitalis from a clinical perspective, but we also consider information recently available about the basic mechanisms of digitalis action, since insights into the effects of the drug on such fundamental cellular functions of the heart as ion transport, contraction, and impulse formation and conduction will most likely have eventual clinical implications.

Our citation of references to the literature is not intended to be all inclusive; for purposes of both timeliness and brevity, we have concentrated on selected contributions to the literature since 1975. Recent detailed reviews of specific areas of knowledge regarding the digitalis glycosides will be cited appropriately throughout this discussion.

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Before delving into current areas of progress and controversy, let us reflect—at least briefly—on the colorful past from which our present thinking about digitalis has evolved.

The classic monograph by Withering on the "foxglove,"[10] published in 1785 after nine years of careful clinical observations, contains many penetrating comments but none more astute than the following: "It is much easier to write upon a disease than upon a remedy. The former is in the hands of nature, and a faithful observer, with an eye of tolerable judgment, cannot fail to delineate a likeness. The latter will ever be subject to the whims, the inaccuracies, and the blunders of mankind."

Withering's observations almost immediately met with lively controversy. After a century of continuing debate, clinicians in the early 1900s appear to have been in general agreement with Sir James Mackenzie, who believed that digitalis was of value primarily in patients with atrial fibrillation and who did not advocate its use in patients with congestive heart failure and normal sinus rhythm. In *The Oxford Medicine*, he wrote, "The best effect of digitalis is seen in cases of heart failure with dilatation of the heart and dropsy. Eighty or ninety percent of such cases suffer from auricular fibrillation. . . . If we scrutinize the published records of cases that have benefited by the drug, we find that the great majority of these results occur in one condition, auricular fibrillation, or its allied condition, auricular flutter."[11]

Henry Christian, then physician-in-chief of the Peter Bent Brigham Hospital, took exception to the view that digitalis was of value only in patients with supraventricular tachyarrhythmias. In 1922, he wrote, "My views evidently differ from those of my fellow editor of *The Oxford Medicine*. The views of Sir James Mackenzie . . . have been concurred in by numerous observers, with the result that there is a growing feeling that, unless the pulse is absolutely irregular and rapid, little is to be gained from digitalis therapy. My own experience is so directly contrary to this that it seems worth while to restate the views already expressed by me. . . . My own view with regard to digitalis is that digitalis, as a rule, has a striking effect on those changes in the patient which are brought about by cardiac insufficiency, and this effect appears irrespective of whether or not the pulse is irregular."[12]

Lest it appear that Sir James Mackenzie overlooked important aspects of the action of digitalis, however, elsewhere in his writings can be found a clear awareness of salutary effects of the drug in patients with cardiac rhythms other than atrial fibrillation. The following statement, published in 1911, serves today as an astute summary of the state of the art: "Many years ago I was struck with the variability in the action of digitalis in different patients, and a careful grouping of cases which presented similar effects led me to realize that, to a great extent, the different reactions obtained in different people are due to a difference, not in the drug, but in the nature of the lesion from which the patients suffer."[13]

In any event, Henry Christian must have been a convincing teacher, since the use of digitalis in patients with signs and symptoms of congestive heart failure, irrespective of the presence or absence of atrial fibrillation, became standard and was not seriously questioned—at least in the United States—for the next 50 years.

Between 1969 and 1979, however, a substantial body of literature accumulated that, taken together, convincingly made the point that many patients on chronic maintenance digitalis were not benefiting from the drug commensurate with the known risks of toxicity. In 1969, Starr and Luchi[14] questioned the efficacy of chronic maintenance digitalis treatment on the basis of a placebo-controlled double-blind study of 11 elderly patients with normal sinus rhythm. Later studies of several populations of patients from the United Kingdom on maintenance digoxin therapy showed that a substantial majority of those with normal sinus rhythm showed no deterioration in clinical status upon withdrawal of the drug (see below).[15–18] Similar conclusions have been drawn from studies of geriatric patients in the United States[19] and in Denmark.[20] McHaffie et al[21] studied six patients in sinus rhythm with congestive heart failure resulting from myocardial infarction or cardiomyopathy, and the patients showed no benefit from digoxin over that achieved with diuretic alone, as judged from their response on submaximal exercise testing.

It will come as no surprise to the experienced clinician that a substantial number of patients on maintenance digoxin, including a sizable fraction of those in normal sinus rhythm, do not derive obvious benefit from the use of the drug beyond the extent to which it may offer some enhanced cardiac reserve during periods of stress, such as may be imposed by an episode of anemia, infection, or other intercurrent illness. At the same time, it is clear that there are subsets of patients, including some with normal sinus rhythm, who derive appreciable benefit from long-term digitalis therapy.[22,23]

The challenge to the clinician is to determine which individual patients have a favorable risk/benefit ratio for digitalis use, recognizing that few if any therapies are good for all patients while most are useful in at least selected subsets. In short, then, a critical appraisal of the anticipated benefits of starting or continuing digitalis treatment will ensure that the well-known risks of toxicity are appropriately counterbalanced by the likelihood of such benefits.

> Digitalis treatment is one of the most important and serious duties of the general physician: it demands a great deal of skill, power of observation, keen interest, and experience. A long life is too short to learn enough about this wonderful drug.
>
> K. F. Wenckebach
> 1864–1940

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2

Basic Mechanisms of Cardiac Glycoside Action

INOTROPIC MECHANISMS

Although a major focus of this review is on digitalis toxicity, a broader consideration of the cellular mechanisms of action of cardiac glycosides seems appropriate because the boundary between the "therapeutic" and "toxic" effects of this class of drugs—at least in experimental terms—is so indistinct. In fact, it is widely believed that the difficulty in separating the toxic from the therapeutic effects of digitalis stems from the fact that the toxic effects are actually extensions, in greater degree, of cellular mechanisms that augment the inotropic state or slow atrioventricular conduction.

Essentially all known aspects of myocardial cellular function have been explored in search of the basic mechanism by which cardiac glycosides increase the contractile state of heart muscle.[1] Because studies using clinically relevant concentrations of these drugs have failed to show primary effects on contractile or regulatory proteins, intermediary metabolism, or myocardial energetics, recent investigative efforts have focused on the area of excitation–contraction coupling. It is generally believed that, in some way, digitalis glycosides at "therapeutic" (subtoxic) levels enhance the availability of Ca^{++} to myocardial contractile elements following excitation. This effect must involve an intact sarcolemmal membrane, since Fabiato and Fabiato[2] have shown that the inotropic effects of digitalis are absent in mechanically

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