

**DIGITALIS**  
**AND OTHER CARDIOTONIC DRUGS**

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**ELI RODIN MOVITT**

**OXFORD MEDICAL  
PUBLICATIONS**

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# DIGITALIS

## AND OTHER CARDIOTONIC DRUGS

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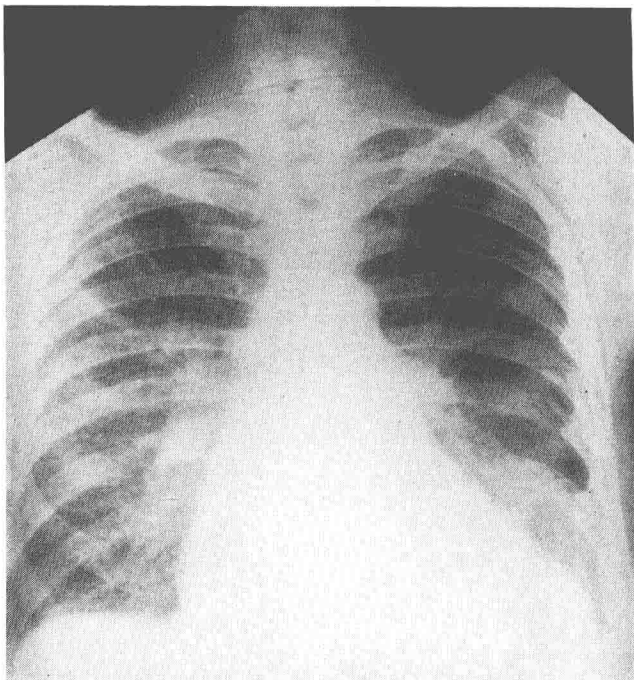
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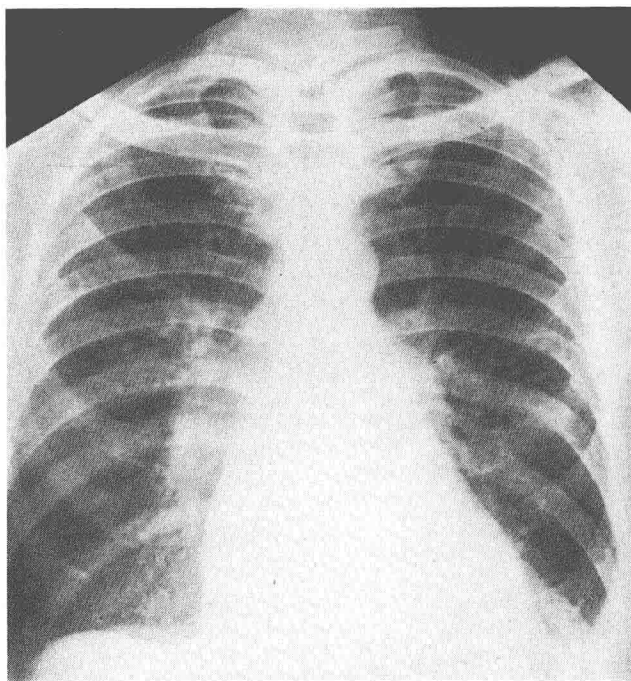
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## DIGITALIS AND OTHER CARDIOTONIC DRUGS

A. BEFORE TREATMENT.



A 6 ft. x-ray film of the chest of a 46-year-old man with rheumatic heart disease, mitral stenosis, auricular fibrillation, and congestive failure.



B. AFTER ORAL ADMINISTRATION OF FULL DOSES OF CEDILANID. NOTE DIMINUTION OF CARDIAC SILHOUETTE.

AFFECTIONATELY  
TO MY WIFE  
JENNIE

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## *Preface to the Second Edition*

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THE need for keeping pace with the newer developments concerning digitalis and the warm reception accorded this book have prompted the publication of a second revised edition.

Recent experimental and clinical research with digitalis, and more specifically the cardiac glycosides, has added much to our knowledge of the mechanisms of action of this group of drugs, although the subject is still controversial. The relative values of the results obtained in the laboratory and those obtained in the clinic are often controversial in any field of investigation, and this is particularly true in the study of the pharmacological action of digitalis. At any rate, whatever be the significance of observations that can now be made with improved techniques in humans, a great debt is owed the pharmacologist, physiologist, and chemist for their contributions which constitute a basis for clinical study.

Catheterization of the heart has made possible a more direct and accurate evaluation of the effect of digitalis on the circulation in man. The cardiac output is measured most accurately by direct application of the Fick principle. This has been done for many years in experimental laboratories, samples of mixed venous blood being obtained by direct puncture of the right cardiac chambers — a procedure impractical in human subjects because of the dangers associated with direct needle puncture of the heart. The advent of venous catheterization has made the application of the direct Fick principle possible in man. The same procedure has enabled investigators to obtain direct records of the alterations in the atrial pressure as conditioned by various physiological functions as well as by the administration of drugs such as digitalis.

The classical studies of Starling on the heart-lung preparation have

demonstrated a relationship between the cardiac output of the heart and the venous pressure, leading to the conclusion that the output of the heart is essentially dependent on venous return. Certain observations with cardiac catheterization on human subjects have tended to render support to this concept, whereas other investigators have discovered a number of circumstances in which venous pressure and cardiac output could not be correlated. Thus, it has become apparent that the regulation of the cardiac output in the human is more complex than is the case in the heart-lung preparation. The application of venous catheterization to the study of heart failure has also led to the discovery that low cardiac output is not present consistently in all instances of congestive heart failure and that under certain circumstances the cardiac output, in fact, may be increased. The latter condition apparently prevails when there is a disproportion between demand for oxygen and its supply. In addition, the theory of Starling concerning the pathogenesis of heart failure does not any longer reign supreme, since newer findings have provided a different explanation for the manifestations of cardiac insufficiency. All these discoveries may have some bearing both on the pharmacological actions of digitalis and its clinical application. It is hoped that the new data incorporated in the current edition will aid the reader in orienting himself with respect to these recent developments.

In the postwar period many additional studies have been made on the clinical application of cardiac glycosides. These have been incorporated in the present volume and, generally speaking, the text has been brought up to date.

The author wishes to acknowledge the many courtesies of the publishers, who have helped to make the revision of this work possible.

E. R. M.



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## *Preface to the First Edition*

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THE literature on digitalis is voluminous but there seems to be a definite need for a treatise which, under one cover, includes not only past achievements but in addition the newer findings, with particular emphasis upon the pure cardiac glycosides that are proving to be so important in the management of heart disease.

In the last century our medicaments consisted almost exclusively of natural substances. The minerals were generally in the form of salts; the organic medicines were principally dried herbs and perhaps purified extracts of vegetable or animal origin. As is evidenced today, chemistry and related sciences are the foundation of medicine and one cannot dispute the important role chemistry plays in influencing medical thought and in developing new medicinal agents. This trend is also apparent in the development of cardiac drugs.

The isolation of the chemically pure glycosides from cardiac glycoside-bearing plants by Stoll, Jacobs, Smith, and their collaborators represents notable achievements in pharmaceuticals. About two decades ago Hatcher prophesied that 'Every discovery of a method for the preparation of a pure principle of this type helps to a better understanding of the way to use these drugs. Such work must eventually lead to the employment of one of the pure principles in the place of the many crude digitalis bodies now employed.' We may see this prophesy fulfilled within the life span of the present generation.

It is hoped that all those who are called upon to treat heart disease may find this small volume helpful.

Material in this monograph has been freely drawn from the literature, including illustrations, and grateful acknowledgment is given to the authors.

I am indebted particularly to Professor William Dock for his criti-

cism of the manuscript; to my wife for her encouragement and careful proofreading; to Mr. Harry Althouse for his valuable help in compiling the bibliography, and to Mrs. Jean Lee and Mrs. May Shaw for assistance in the preparation of the manuscript.

The opinions set forth in this book are strictly those of the author and do not represent the views or policies of the Department of Medicine and Surgery, Veterans Administration.

E. R. M.

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## Foreword

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THE history of the cardiotonic glucosides shows cycles of abuse and neglect, and with each new pharmacologic observation of a property of the drug, new claims arise about how the agent acted in heart failure. Slowing of the pulse, rise in blood pressure (in the dog), systolic arrest of the heart (in the frog), atrioventricular block, decrease in cardiac output (in the dog) — each in turn has been hailed as *the* action on which the therapeutic effects must depend. Pharmacologists were slow in proving that digitalis, almost without effect on the contractions of the normal mammalian ventricle, nevertheless acted in striking fashion to shorten systole, increase the efficiency and diminish fatigue-like changes in the damaged ventricle, whether in the isolated papillary muscle, the heart-lung preparation, or in several of the types of congestive failure in man. They were even slower in making available pure principles, so that these bodies, like morphine, quinine, and other active plant ingredients, could be given in purified uniform preparations at negligible cost.

In this account of our present knowledge of the digitalis bodies and other cardiotonic agents, Dr. Movitt has made available detailed recapitulations of the chemical, pharmacologic, and clinical behavior of a varied and extremely important group of drugs. This is knowledge which will refresh the minds of men who have recently finished their training, and much of it may be new to those who have not paid close attention to this field of medical literature. It is noteworthy that the fundamental chemical and pharmacologic literature has been so fully reviewed, for even doctors whose chemistry is rusty and whose contact with the laboratory is remote need to be aware of the activity which has led to the recent changes in digitalis preparations available for clinical use, and it is only by seeing the structural formulae, read-

ing of the analytical work, and being made conscious of the agreements and disagreements of the specialists that they can appreciate how progress has been made and what lies behind the therapeutic methods of progressive students of heart disease.

While totally dissimilar in chemical and in pharmacological properties, digitalis is much like the Minot fraction of liver so far as its place in medicine is concerned. The crude natural sources were revealed by sagacious clinical observation, the chemistry of the essential fractions long defied the labors of the best investigators, and relatively crude preparations continued in use long after highly concentrated forms were known. Little used in pediatrics, both are invaluable in specific disorders most common in the middle-aged and elderly. The exact nature of the dysfunction for which digitalis is a specific is not understood, but it seems to be a functional failure, often associated with aging and involution; the exact dysfunction in pernicious anemia is also unknown, but it certainly is one of the involutinal disorders. One course of liver extract, or of digitalis, may suffice to restore a sick person to a feeling of complete well-being, but relapses are to be expected sooner or later, and most of those benefited by these agents finally learn that a regular ration is as essential as food and drink. Indeed, for the patient who develops myocardial failure, without any myocarditis, endocrine disorder or vitamin deficiency, digitalis therapy is much like supplying a specific hormone. However, the effects are quickly apparent, and the final failure of the heart to respond, after months or decades of effectiveness, recalls the occasional development of refractoriness to insulin. The serious results of overdosage are as specific as those of desoxycorticosterone, and like them may appear after weeks of cumulation.

The response of the heart to digitalis is a most significant matter in assessing the nature of the disease process in each case. It proves that while coronary disease, hypertension, valvular lesion, hyperthyroidism, or some other condition may be contributing to the burdens borne by the ventricular muscle, an important factor is a metabolic defect, leading to delay in myocardial recovery from contraction. Because such a defect is more and more frequent with aging, old cardiacs respond more often to digitalis than do younger ones. The effects of digitalis on heart failure in a group of young people with rheumatic valve lesions and severe pulmonic hypertension are very much less striking than in old people with arterial hypertension and congestive failure.

If the heart failure of old people were due solely to inadequate blood flow in the myocardium, it is unlikely that digitalis would be of much use, for it is of no value in anginal disorders where myocardial ischemia obviously is the basic defect. The onset of failure usually ends a pre-existent angina, and digitalis therapy of failure may unmask concealed coronary disease by bringing out angina as the myocardial function improves. These phenomena find a parallel in the way in which fatigue of voluntary muscle defers or prevents the pain of the forearm muscles which are exercised after cutting off the arterial inflow.

The brilliant effects of digitalis on heart failure in older people made clinicians suspect that the disorder was not due simply to aging of the cardiac vascular supply, or to hypertrophy of muscle outgrowing the coronary bed. This has been fully confirmed by measuring the capacity of the coronary bed post mortem in cases of cardiac hypertrophy and failure. Heart failure must be a metabolic disorder of the myocardium in all cases in which digitalis produces a definitely favorable response, as it is inconceivable that it could alter fibrosis, anatomical defect, or ischemia of the heart. We have no more idea of what the defect is than we have of the defect in metabolic activity corrected by liver extract or by desoxycorticosterone, but the clinical significance of the response is equally decisive in each case.

The growth of our knowledge of digitalis is so steady and important that every physician who wishes to use these substances effectively and intelligently needs to review the subject every few years in a thorough and painstaking fashion. Dr. Movitt has done this for himself, and made his review available to assist his colleagues in this necessary task. For one reader this has been an entertaining and stimulating experience.

WILLIAM DOCK, M.D.

*New York*

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