Editorial

Clinical Use of Digitalis: Science or Empiricism?

In 1785 Withering reported his observations on the use of foxglove in the treatment of edema, presenting a scientific account of the use of an herb previously administered by lay healers. By the turn of this century pharmacologic and clinical bases were laid for the use of digitalis and its specific action upon cardiac edema was firmly established. Mackenzie and Lewis emphasized the beneficial effect of digitalis in slowing the ventricular rate in atrial fibrillation and questioned its usefulness in patients with regular rhythm, but by 1940 the effectiveness of the drug in heart failure, regardless of rhythm, was generally recognized and interest developed in the purified digitalis glycosides that were thought to be safer and easier to administer than the leaf. The recent development of new research tools and technics led to an unprecedented number of investigations concerning digitalis: between 1951 and 1955 more than 1,300 articles dealing with digitalis and its derivatives were listed.

Technical advances made possible the study of the effect of digitalis on the contractile proteins and myocardial energy release, on ionic exchange and cellular action potential. The fate and distribution of glycosides were investigated in animals and man by use of sensitive bioassay methods and isotope-tagged digitalis. Coronary sinus catheterization in man permitted the assessment of myocardial oxygen consumption and of various metabolites. The effect of digitalis on intracardiac pressures and changes in cardiac output in man were measured by accurate and reliable methods. The information obtained by these and other methods of study brought about better understanding of the fundamental action of the drug.

The purpose of this discussion is to explore the practical significance of the newer concepts of the action of digitalis, specifically, to review three problems connected with the clinical use of digitalis: the prevalent mode of its administration, its use in cardiac failure, and the prophylactic use of digitalis.

The traditional administration of digitalis is its use in large initial dosages until the desired effect is accomplished or mild evidence of toxicity (anorexia, nausea, and bigeminal rhythm) appears. The careful studies of Eggleston and others evolved the widely accepted "cumulative" theory of digitalis action (fig. 1). A large initial dose is administered at once or over a period of a few days in order to enter the therapeutie zone, a dose estimated at 75 to 90 per cent of the total digitalizing amount. Digitalis is thus thought to have an effect close to an "all-or-nothing" phenomenon. Once the therapeutic zone is reached, the drug action is maintained by the addition of smaller doses, equal to those destroyed or excreted. The toxic zone can be entered rapidly by overestimating the initial

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dose, or slowly by too large maintenance doses. Too small maintenance doses lead to loss of digitalis action as the ineffective zone is re-entered. This theory is applicable to all digitalis preparations. Claims of superiority of action of one preparation over another have not been substantiated, for there is no convincing evidence of a qualitative difference among them nor greater safety of any one agent, the effect of cardiotonic agents being determined primarily by rapidity of action, dependency of oral absorption, and speed of elimination.

The cumulative theory was based on observations concerning the effect of digitalis on ventricular rate in atrial fibrillation. Other indices, notably ST-segment displacement in the electrocardiogram, were found to be too variable to be useful. In patients in sinus rhythm no convenient yardstick for the estimation of individual digitalis needs is available. Paradoxically, dosage difficulty for the administration of digitalis in the presence of regular rhythm is even more apparent now than in the past, because the old rule of administering digitalis to the point of mild toxicity applies primarily to leaf: purified glycosides, now most frequently used, are less likely to produce anorexia and nausea or bigeminal rhythm, but may instead cause serious arrhythmias without warning. This unquestionably provides the reason why current medical literature dealing with clinical aspects of digitalis devotes much more space to toxic than to therapeutic effects of this drug. If, on the other hand, one wishes to judge the "effectiveness" of digitalis in patients with sinus rhythm from improvement of clinical signs of cardiac failure, one faces the difficulty of separating drug action from the effects of rest, salt restriction, and other therapeutic maneuvers usually administered concurrently.

The virtual impossibility of proper titration of digitalis in patients with sinus rhythm led to a therapeutic compromise, namely, the average digitalizing and maintenance dosages found effective in slowing ventricular rate in atrial fibrillation have been recommended for treatment of heart failure with sinus rhythm. It is generally overlooked, however, that this widely accepted recommendation is based on equating two pharmacologically different properties of digitalis. In patients in heart failure with sinus rhythm improvement is thought to be due to the inotropic action of this drug, i.e., its ability to strengthen myocardial contraction—the action now believed to be intimately related to its effect upon the contractive mechanism of myosin and actomyosin. In atrial fibrillation, the principal cause for improvement is the dromotropic effect of the drug: impairment of the conduction mechanism, presumably in the atrioventricular node, reducing the ventricular rate and permitting a more efficient function of the heart. The inotropic effect of digitalis is specific to deranged hemodynamics of heart failure. The dromotropic effect controls ventricular rate in atrial fibrillation regardless of whether or not
cardiac failure is present. The dose-effect relationship of the dromotropic and the inotropic effects of digitalis are assumed but not proved to be equivalent, yet at least one important difference between them should be pointed out: inotropic effect is due to direct myocardial action; dromotropic effect is known to be, in part at least, mediated by the vagus nerve. Obviously, the relationship of the two actions needs further study.

The direct myocardial action of digitalis in cardiac failure is now generally accepted. The earlier controversy, as to whether direct inotropic action or peripheral venopressor effect predominates, has been resolved in favor of the former. Hemodynamic improvement, such as increase of the abnormally low cardiac output and fall in the end-diastolic pressure within the failing ventricle, has been consistently found after intravenous administration of a digitalis glycoside, and, in a small number of cases, also after chronic oral digitalization. Yet the contribution of digitalis in the overall management of chronic cardiac failure leaves some unanswered questions. For example, if the cumulative theory of digitalis with its all-or-none implication applies to chronic cardiac failure with regular rhythm, how often does the clinician actually guess the dosage to maintain the patient within the narrow therapeutic zone? It should be pointed out that the use of digitalis is only one of several ways by which improved function of a failing heart can be brought about. Other effective means of controlling heart failure include reduction of overload by medical and surgical means, rest and reduction of blood volume by salt restriction, and diuretic therapy. These alternative methods of treatment are often capable of reversing cardiac failure without the need for continuous therapy. It is conceivable that a single dose of digitalis, or the initial digitalizing dosages, could be effective in cardiac failure by resetting the cardiac performance curve at a more efficient level without need for maintenance therapy. Such a possibility would be in line with the concept that cardiac dilatation is associated with wasteful expenditure of energy and that any factor capable of reducing cardiac size could permanently improve its function. It is noteworthy that intermittent intravenous administration of strophanthin has been popular for many years in various European and Latin American countries, but received no attention here and in England because this method has never been supported by adequate studies and was in conflict with the "cumulative" theory of digitalis. While it is doubtful whether intermittent intravenous strophanthin has a place in cardiac therapy, the effect of single-dose digitalization needs further investigation. It should be pointed out that preliminary observations in our laboratory suggested that acute intravenous administration of digitalis leads to improvement in circulatory dynamics that could not be maintained by continuous digitalis administration, as if acute digitalization produced a "supernormal" circulatory response. Could the "cumulative" theory be incorrect?

One of the controversial aspects of digitalis is its action upon the normal heart and the hypertrophied heart not in failure, which represents the basis for the prophylactic use of this drug. Recent experimental and clinical studies failed to confirm earlier views of the paradoxically harmful effect of digitalis upon the normal heart, and demonstrated that digitalis exerts no consistently detectable action upon the circulation in the absence of hemodynamically evident heart failure. In spite of these findings, a renewed interest in the preventive use of digitalis has been aroused by the demonstration that digitalis increases the contractile force of the normal and the nonfailing, hypertrophied heart. Some studies of cardiac performance under stress also showed better function curves in response to digitalis.

These discrepancies can best be explained by taking into account multiple actions of digitalis. In addition to the inotropic and dromotropic actions, the drug exerts a mild chronotropic effect (slowing of the sinus pacemaker), a venopressor, and an arteriopressor.
action. Each of the circulatory functions affected by digitalis plays an integral part in the regulation of the circulation. In atrial fibrillation with rapid ventricular rate the dromotropic action exerts a specific effect aiding the homeostatic regulation of the circulation. In cardiac failure the inotropic effect of digitalis counteracts a specific deficiency of myocardial performance. In both situations the circulatory system is deranged from its optimal state and the drug action helps to reestablish more normal circumstances. On the other hand, when the circulatory system performs normally, its homeostatic mechanism tends to maintain optimal state. The increased force of cardiac contraction from inotropic drug action could thus be nullified by mechanisms maintaining cardiac output, arterial and venous pressures, and coronary flows at the previous level, so that work and efficiency of the heart would remain unchanged. For similar reasons caution has to be applied in translating experimentally obtained changes in cardiac function curves into clinical medicine. The types of cardiac overload used to plot function curves are often unphysiologic and have no counterpart in human pathology. One would accept as evidence the demonstration that digitalis permits better cardiac performance during customary human overload, such as strenuous exercise. Such evidence is not available, hence the prophylactic administration of digitalis is as speculative today as it was 30 years ago when first suggested by Christian.

In the foregoing discussion some unanswered clinical questions have been raised. It is clear that answers to these questions will not be forthcoming from research at the bio-physical or biochemical levels, but rather from clinical studies, particularly from hemodynamic observations. Yet, hemodynamic studies of digitalis, popular in the early days of cardiac catheterization, have been few in the last decade. A clinician, who wished to examine the evidence upon which clinical use of digitalis is based, finds himself in a web of contradictions and inconclusiveness caused by lack of interest on the part of the investigators, rather than lack of methods of study. He then sadly has to admit that the use of digitalis in clinical medicine today is hardly scientific, but, as in Withering’s time, intuitive and empirical.

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References
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