EDITORIAL

Digitalis and William Withering, The Clinical Investigator

WILLIAM WITHERING began to use digitalis for dropsical cases during 1775. The first recorded use of digitalis was on December 8 of that year when he administered a "decotion of fol. digital." to a man about 50 years of age who complained "of an asthma." As a result of the therapy, the patient "made a large quantity of water," "His breath gradually drew easier, his belly subsided, and in about ten days he began to eat with a keen appetite." This month marks the 200th anniversary of the introduction of this great therapeutic agent into modern clinical practice.

William Withering, the son of a physician, was born on March 17, 1741 in Shropshire, England (fig. 1). At age 25, he obtained a medical degree from Edinburgh University. He was a student of natural history and in 1776 published his first book on the botanical arrangement of all the vegetables naturally growing in Great Britain. In 1783, he had to give up practice for many months because of ill health from pulmonary tuberculosis and used this time to write his classic work "An Account of the Foxglove" which was published in 1785 (fig. 2). During 1785, he is reputed to have traveled over 6000 miles by horse and carriage to visit and consult on patients and also received the great accolade of being elected Fellow of the Royal Society. Ill health continued to plague him and from 1790 through 1793 he could not work for months at a time. He retired prematurely in 1796 and died of pulmonary tuberculosis on October 6, 1799 at the age of 58.

It was Fuchsius who first recognized the plant in 1542 and named it "digitalis," an allusion to the German name of Fingerhut, which signifies a thimble or a finger stall, from the blossoms resembling the finger of a glove (fig. 3). The plant Foxglove, probably from folk's-glove (i.e., fairies' glove), is known by a great variety of names. It is commonly found in many parts of Europe but is a native plant in only some parts of North America, for example the Pacific Northwest. Prior to Withering, experiments had been conducted to evaluate the effects of this plant on turkeys and in man had been used for such ailments as epilepsy, scrofula, and dyspnea. Dr. Withering was introduced to the foxglove when his opinion was asked concerning a family recipe for the cure of dropsy. His genius lay in recognizing the potential of this therapy, in investigating the benefits of its use in patients, and in keeping precise notes of his accurate observations. Therefore, he was able to describe the indications, methods of administration and the toxic effects of the drug. He was afraid of widespread and improper use of this medication and discerned that time alone would prove its value.

Although Withering had used digitalis from 1775 onwards, he was reluctant to write about it until more knowledge had been gathered. It was introduced into the Edinburgh pharmacopoeia in 1783 and the new therapeutic modality was used indiscriminately. Therefore, Withering was "at length compelled" to write his textbook lest "the lives of men should be hazarded by its unguarded exhibition, or that a medicine of so much efficacy should be condemned and rejected as dangerous and unmanageable." Even at the present time, introduction of new therapeutic modalities often initially results in their overenthusiastic use. Withering described 163 well-documented patients, 16 of whom were noted to have been drink-
William Withering, The portrait is by the Swedish artist F. von Breda. 1792. The original is in the National Museum in Stockholm. (Reproduced with permission of Harper & Row Company.)

Figure 1

Withering recommended the use of digitalis in "Ascites, Anasarca, and Hydrops Pectoris," and recognized that the benefits resulted from a removal of water and did not represent a primary cure of the disease. Withering thought he was introducing an efficacious "new diuretic." However, later in his monograph, the ninth and last of his conclusions was "That it has a power over the motion of the heart, to a degree yet unobserved in any other medicine, and this power may be converted to salutary ends." We now know the main action of digitalis is on the heart and much work has been done to show its effects on the specialized conducting tissues of the heart and to demonstrate its inotropic effect. However, the mechanisms and the sites of action are not yet completely understood and continue to be areas of research endeavors.

Withering took several logical steps in arriving at the method of administration of digitalis. At first, he thought it was necessary "to bring on and to continue the sickness, in order to ensure the diuretic effects." Recognizing later that it was unnecessary to continue the medication once nausea had occurred, he recommended his patients "to persist until the nausea came on, and then to stop." He soon observed that the diuretic effect preceded the sickness or the purging and sometimes would be checked by sickness and purging. Therefore, the directions were changed to "Continue the medicine until the urine flows, or sickness or purging take place." He continued with these instructions for two or three years, and at length noted that there were patients in whom the pulse would be slowed to an alarming degree without any other preceding ill effect. Thus, his final directions were "Let the medicine therefore be given in the doses, and at intervals mentioned above: — let it be continued until it either acts on the kidneys, the stomach, the pulse, or the bowels; let it be stopped upon the first appearance of any of these effects, and I will maintain that the patient will not suffer from its exhibition, nor the practitioner be disappointed in any reasonable expectation."

He carefully noted the ill effects of digitalis and wrote "The Foxglove when given in very large and quickly-repeated doses occasions sickness, vomiting, purging, giddiness, confused vision, objects appearing green or yellow; increased secretion of urine, with frequent motions to part with it, and sometimes in-
ability to retain it; slow pulse, even as slow as 35 in a minute, cold sweats, convulsions, syncope, death." He had most accurately observed the toxic effects of digitalis.

Knowledge of the pharmacokinetics and bioavailability of various digitalis preparations is assisting us in working out better methods of managing digitalis therapy. However, even today, digitalis toxicity continues to be a significant clinical problem. Withering acknowledged the desirability of an effective antagonist and felt that such a remedy might perhaps in time be discovered. Unfortunately, his hope is not yet fulfilled, although much exciting research to reverse digitalis toxicity by pharmacological and immunological mechanisms is in progress.

Sir John McMichael, in 1970, reflecting on the lessons of history, made the observation that perhaps digitalis would fail to pass the criteria presently used by various committees which regulate the introduction of new drugs. He considered it a blessing that Withering pursued his work so persistently on afflicted man. Currently, we are in some danger of throwing out much of the good with only a little bit of the undesirable. It is important to recognize the real needs and desires of sick people. Perhaps this can only be determined by working directly among them.

Finally, Withering had considerable wisdom because he recognized that "After all, in spite of opinion, prejudice, or error, Time will fix the real value upon this discovery, and determine whether I have imposed upon myself and others, or contributed to the benefit of science and mankind." Digoxin is the fifth most frequently prescribed drug by physicians in the United States. Clearly, the judgment of time would please Withering. We can be grateful to William Withering and look back with pride to this astute clinical investigator.

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**References**

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