

## THE HISTORY OF DIGITALIS THERAPY\*

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THE modern development of the use of digitalis is so intimately associated with William Withering that one loses sight of the fact that the plant was known for several centuries before his time.

To trace this knowledge, we must go back to the beginning of the Christian era. There are some references extant which lead to the belief that Dioscorides<sup>1</sup> knew the foxglove, or at least a plant that very closely resembled it. Some would interpret his description of ephemerum as being closely akin to what we now regard as digitalis, if indeed it is not actually the same plant. It would appear that Galen knew and used a similar plant. Mention is also made of its use by the Saxons in the eleventh century.

The distribution of the plant, in a triangular area bounded by Ireland, the Pyrenees, and the Rhine lends color to the theory that it was used by the Welsh about the end of the thirteenth century. Irish and Welsh folklore mentions foxglove not only against the evil eye and the influence of witches but also as an external application against eclampsia.

However, the first indisputable mention of the plant, its accurate description, and indeed its name, we owe to the Bavarian, Leonhard Fuchs (1501-66),<sup>2</sup> one of the pioneer fathers of modern scientific botany. It was he who christened the plant "digitalis," from the German "fingerhut," "because,"

he says, "its flower resembles the thimble used for sewing." He continues: "What the ancients called it I do not know; it was perhaps not known to them. In the meantime, until we find a better name, let's call it 'digitalis,' in Latin, after its German name." It would seem that no better name was found.

Fuchs remarked upon the beauty of the plant and was struck by the fact that it had not had any widespread medicinal application. In his "De historia stirpium" (1542), he directed the attention of physicians to the effects of digitalis, which he recommended to be taken as decoctions or infusions, to scatter dropsy and to relieve swelling of the liver and other internal organs. He suggested its use even in bringing on the menstrual flow. Following this description of the plant, digitalis began to be used on the continent for patients that were waterlogged, as an emetic and purgative.

Professional recognition of the action of digitalis did not become widespread, however. Several writers in the following hundred years, Monardes (1565), Clusius (1601), Hornung (1625), do not mention it among their lists of drugs. Even such a famous naturalist and physician as Theophrastus Bombastus von Hohenheim, called Paracelsus (1603), does not allude to it.

In England, however, it was not quite forgotten, though its use was restricted to the uneducated and those unskilled in its proper application.

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The all-comprehending herbalist, John Parkinson<sup>3</sup> in 1640, speaking of the "vertues" of digitalis, recommended it internally for epilepsy and externally for scrofula. He mentions a patient with "falling sickness" cured after being ill for twenty-six years.

The next progressive stride in the therapeutics of digitalis we find in the monumental work of William Salmon (1710)<sup>4</sup> in the British Herbal. Many marvelous qualities are here ascribed to digitalis. It is advised for tuberculosis, albeit with caution, because "it produces weakness, induces vomiting, and purges; it cleans the body from top to bottom and thereby rids it of tenacious humours." We read further that, "Foxglove is hot and dry, at least in the Second Degree, Sulphureous and Saline, Aperitive, Abstersive, Astringent, Digestive and Vulnerary, Pectoral, Hepatick and Arthritick, Emetick, Cathartick and Analeptick." As Knott has said, "A goodly array of precious 'qualities,' surely!"

A half dozen preparations are listed thus: "1. A Liquid Juice. 2. An Essence. 3. A Syrup. 4. A Decoction or Infusion. 5. An Ointment or Balsam. 6. A Cataplasm." The qualities of the syrup are described as follows:

The Syrup, or Rob of the Juice of the Herb and Flowers made with Honey. It is a specifick which transcends all other Vegetable Medicaments for the cure of Consumptions; cleansing and healing after an admirable manner Ulcers of the Lungs. It opens the Obstructions of all the Viscera, cleanses, carries off, or expels the recrements of the Humors, by which means the daily Nutriment may be conveyed to all Parts of the Body. It may be given Morning and Night, four or five Spoonfuls at a time, according to Age and Strength: some advise Spoonfuls to be given in the Morning fasting in Mead, as much as Ten in the Morning, three Spoonfuls at Four in the

Afternoon, and lastly, as much at going to bed. This Medicine has restored (where the Patient has not been past cure) beyond all Expectation. It cures a Phthisick or Ulceration of the Lungs, when all other medicines have failed, and the Sick esteemed past Cure. It opens the Brest and Lungs, frees them from tough Flegm, cleanses the Ulcer, and heals it, when all other Remedies act without effect. I have known it to do Wonders and speak here from a long Experience. Persons in deep Consumptions, and given over by all Physicians, have by the Use of this Syrup or Rob been strangely recovered as to grow fat again. I commend it as a Secret, and it ought to be kept as a Treasure. These few lines concerning this Medicament alone are worth ten times the Price of the whole Book. I am very confident of it, the deplorable wasted Patient, who has been long languishing in an inveterate and tedious Consumption, or a Phthisis if they make use hereof, will give me Thanks for this Notice, whilst they may have Reason enough to Curse even the Memories of Quacking Blood-suckers, Issue-makers, and Blister-drawers, who, as they may have possible drained them of a fair part of their Estate and Treasures, would, by a continuance under their hands (for all their specious Methods of Cure), have been fooll'd out of their lives too. But here is to be noted, that this Syrup ought chiefly or only to be made of the Flowers.

This warm recommendation might have been responsible for the appearance in the London Pharmacopoeia of 1722 of *D. folia*, *flores*, *semen*, and an unguentum.

In 1744, digitalis appeared in the fourth edition of the Edinburgh Pharmacopoeia, although it was omitted in 1756 and 1774. In the Paris Pharmacopoeia, it appeared in 1748 and 1758, in the Württemberg in 1754 and 1771.

In 1748, Salerne (Saleron?) published his sensational report on the first experiments with digitalis. He overfed turkeys with digitalis leaves. The animals developed signs of intoxi-

cation and convulsions. Later they began to have frequent evacuations. At autopsy he states he found "the heart, lungs, liver, and gall bladder shrunken and dried out, the intestines empty." This demonstration of the toxic effect of digitalis had a profound effect upon the followers of Salmon. The English and French were inclined again to withhold using foxglove except externally as a salve for all kinds of swellings. Its emetic and purgative qualities were, however, not forgotten.

This then was the state of affairs when, in 1775, from the English "midland capital," Birmingham, William Withering\* began his study of the foxglove. About this time, Withering<sup>5</sup> relates, his opinion was asked about an old family receipt for dropsy that was used by a grandame of Shropshire. It appears that she had obtained cures where the regular practitioners had failed. Well versed in botany, it was not difficult for Withering to conclude that the concoction owed its efficacy to foxglove. He thereupon began to experiment with the plant, and, after ten years, in 1785, published his results in the book entitled "An Account of the Foxglove, etc." In this little volume, which is a classic of clinical investigation, he gives his results on the treatment of 163 cases. He calls attention to its diuretic as well as emetic and purgative properties.

During the decade comprised in studying the properties of foxglove, Withering communicated his findings to such men as Cullen, Stokes and Darwin. In 1779, he presented his findings to the Medical Society of Edinburgh at the suggestion of Dr. Stokes, who was also instrumental in having digi-

\* An excellent biography of Withering, by Lieutenant Commander Roddis, appeared in *ANNALS OF MEDICAL HISTORY*, N. S. 8:93; 185 (March, May) 1936; reprinted in book form (N. Y., Hoeber, 1936).

talis replaced in the Edinburgh Pharmacopoeia in 1783.

Besides establishing the indications for the use of digitalis, we owe to Withering a clear understanding of its toxic manifestations which hold today as they did a century and a half ago. We can do no better than to quote his original summary: "Let the medicine therefore be given in the doses and the 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 one of these effects."

He realized it was of great help in what we now regard as cardiac decompensation, that in cases of auricular fibrillation it acts as a sedative and in full doses slows the heart even to the point of producing complete heart block. He was fully aware of these facts and cautioned against its use in excessive doses as being liable to discredit the use of the drug.

Soon thereafter, there followed many enthusiastic testimonials of the effects of digitalis therapy. However, it is interesting to note that Hahnemann, the founder of Homeopathy, wrote very disparagingly about its effects. Among other things he said: "Inasmuch as above all this, digitalis produces severe headaches, dizziness, cramps, marked loss of strength, a feeling of dissolution, and almost death, because of the slowing of the pulse rate and the reduction in body heat by its direct action," its usefulness seems very limited.

Among those who favored digitalis was John Ferriar who wrote in 1799 that foxglove "furnishes us with a means of regulating the pulse to our wish and of supporting a given state of velocity as long as we may judge it proper."

For the next few years, there appeared many contributions to the ac-

tion of digitalis in phthisis, due to the over-sanguine reports of such men as Drake, Beddoes and Fowler, whose work with the arsenicals we remember. In 1799 Beddoes<sup>6</sup> wrote as follows:

In cases of pulmonary diseases, where the presence of tubercles was indicated by every symptom, and where they seemed ready to break out into open ulcers, I have verified the efficacy of digitalis; and I daily see many patients advancing towards recovery, with so firm a pace, that I hope consumption will, henceforward, be as regularly cured by the foxglove, as ague by the Peruvian bark.

Despite Withering's standards laid down in his writings on the uses of digitalis in cardiac weakness, the drug was almost doomed because of its frequent misuse by those who employed it without proper indications or in the proper dosages. They either forgot Withering's teachings or ignored them.

Until the middle of the nineteenth century, the success of every drug was judged solely by its obvious effects on symptoms, without more deeply inquiring into the nature of the disease. The alarming additions to the indications for digitalis therapy afford a sad commentary on the powers of observation and discrimination of the doctors at the beginning of the nineteenth century. Thus all sorts of swellings, even cancerous ones, tuberculosis, strangulated hernias, quinsy, jaundice, gout, and many other diseases were treated with digitalis. Unbelievable confusion reigned. Because slowing of the pulse was the most frequently noted effect of digitalis, it was classed with opium among the sedatives. Bouillaud is credited with having called digitalis the "opium of the heart."

In 1814, Kreysig called attention to this contradiction, that a narcotic, digitalis being then so regarded, should heal through its action on a damaged organ.

A century later (1912) A. A. Meyer, in his monograph on digitalis, recalled that Kreysig had recognized the specific action of digitalis on the heart and blood vessels, and had expressed the opinion that the slowing of the pulse was dependent on a side-effect on the brain, somewhat similar to the waxing and waning of the pulse in apoplexy.

This was the first postulation of a central effect, a vagus effect. Shortly thereafter (1817) Richter, also recognizing the effects of foxglove, joined Kreysig in this opinion. These investigators, however, did not receive any support; on the contrary, Corvisart, personal physician to Napoleon (1811) and his student Laënnec denied its value. Graumiller (1815) declared that digitalis acted because of a narcotic principle not unlike aconite, while Hufeland at this time advised its use externally for all sorts of scrofulous conditions.

This new attitude resulted from two causes: first, ignorance of the diseases of the heart; second, the erroneous conception that existed concerning the action of the heart.

As for diseases of the heart, there is no doubt that they were badly understood over a hundred years ago, and we must confess this fact. It is to be feared that medicine had not yet arrived at a point where diseases were adequately differentiated. Vaquez quotes one authority as saying, "It is sufficient at all events to prescribe the necessary remedies."

Soon afterward appeared the book by Corvisart in which the main lines of cardiac pathology begin to form. Then followed Laënnec who, in 1818, applied auscultation in his study. Confident in his new method, he declared from the very beginning that it was an exact means of determining the precise nature and site of changes in the heart.

There being at this time gross misunderstanding of the physiology and

pathology of the heart, exaggerated importance was given to the increase in volume of the heart, which explains why digitalis, which did not alter the size appreciably, had gradually been abandoned. Corvisart, Laënnec, Bertin did not mention it, and, when Bouillaud, about 1840, did refer to it, it was only to err in regard to its pharmacodynamic action. This grievous and very narrow interpretation of the pharmacodynamic action of digitalis had led physicians to forget its best uses and to expect of it effects it could not produce.

To slacken the pulse was all that was demanded of it about the first half of the last century. For this purpose it was used readily in all diseases where the pulse was accelerated: tuberculosis, typhoid fever, pneumonia, etc. To this power had been added another, that of an "asthenic" medicine, suitable for combating a stimulant. Medical men in France were then under the influence of the ideas of Broussais and of Rason, who taught that diseases being for the most part due to excess stimulation, they could be cured only by antagonists or antiphlogistics. Affections of the heart were no exception, and these were treated by the asthenic method of Albertini and of Valsalva, previously commended by Senac and Morgagni, viz. repeated bloodletting, diet, purgatives given to the point of death, until as Corvisart says, the patient was scarcely able to raise his arms from the bed. It is interesting to note that leeching was so widespread that in 1833 France used about 40,000,000 of the vampires.

It was because of similar aberrations in thought that digitalis reappeared in cardiac treatment. The increase in the volume of the heart, the hypertrophy, the palpitations which ordinarily accompanied it, all these were unmistakable signs of what the French called *erethism* of the heart. Did they not justify, to-

gether with the method of Valsalva, the return to digitalis, a sedative medicine *par excellence*, the "opium of the heart," as it was then called? Bouillaud declared that it was logical to apply it in "lulling to sleep" the principal nerves or "dynamics of the heart" and it was to this that the symptoms requiring digitalis were reduced.

In England, the decline in digitalis therapy was in part due to the custom of giving too large and unregulated doses, even by such men as Corrigan (1831) and Hope (1833) who used the drug in many forms and combinations. They did not heed the teaching of Withering to give it as pill or infusion, but prescribed the decoctions, extracts, acetum, oxysaccharum, or electuary, often mixed with other drugs and inorganic salts.

We thus arrive at the middle of the nineteenth century when physiology came into its own and animal experimentation paved the way for placing digitalis therapy on a sound basis. The German physiologist, Franke, working with Weber and Ludwig recognized, as did Stannius, the effect of the vagus on heart action and emphasized the true nature of the sedative action of digitalis.

Thus, in 1850, Franke concluded:

- (a) In moderate dosage, especially such as would be used therapeutically, digitalis acts on the regulatory nervous mechanism of the heart.
- (b) Larger doses produce paralysis of regulatory nervous mechanism.
- (c) Finally, very large doses produce not only paralysis of the regulatory mechanism but of the musculo-motor system as well.

In France, under the guiding spirit of Debreyne, a monk trained in medicine, many clinical experiments with digitalis were carried out, including the corroboration of the synergism of digitalis and squills which had already been suggested by Withering and which later

was made famous by the addition of blue mass to form Guy's or Niemeyer's Pill. Debreyne deserves credit further for another clinical suggestion, namely the restriction of fluid intake in the presence of severe dropsy.

In 1844, Homolle and Quevenne<sup>7</sup> discovered in digitalis an active principle which was more powerful than the plant itself: amorphous digitalin. This discovery did not at first excite the interest it deserved. Only the physiologists realized its importance. The substitution of a very definite substance for the watery solutions which had until then been used permitted better control of experiments and more exact results.

But the doctors still remained indifferent. It is interesting to read the report presented to the Academy, in 1851, by Bouillaud on Homolle's discovery and the discussion which it engendered. Bouillaud admitted that digitalin, like digitalis, in weak doses, slowed the heart and in strong doses accelerated it. Other clinicians, among them Martin, Solon, Gilbert, agreed in saying that the new digitalin was harmful even in feeble doses; that it was in any case very inferior to other preparations of digitalis.

This discussion had its reverberations in exciting Duroziez to devote his thesis of 1863 to digitalis, a thesis less interesting than some others and which added nothing to the preceding studies on digitalis. The author possesses a "great love," as he says, for digitalis, but it was a very bashful love for he spent the rest of his life in being afraid of it. As to the digitalin of Homolle, he hardly mentioned it. Similarly, Trousseau, who, a little later in this period, gives the formula of a wine with the base of digitalis, or the wine of Hôtel-Dieu, seems never to have resorted to digitalin. Thus, abandoned shortly after its discovery, digitalin does not even appear in the Codex of 1866.

In 1868, new and more important progress was made. Nativelle<sup>8</sup> announced another product, a chloroform extract of constant strength, namely, crystalline digitalin. Later, Schmiedeberg and Kiliani in Germany experimented with digitalis and isolated from it other products equally well defined but less active.

Actually, up to this time, it was only the physiologists who had profited by the discoveries of Homolle and of Nativelle. They devoted much energy to the study of the pharmacodynamic action of digitalis with the help of new substances isolated by the pharmacologists. Significant among these studies was the work of such men as Lauder Brunton, Botkin, Traube and Schmiedeberg. The most important published in 1894 was that of François-Franck, which came from the medical clinic of the Charité Hospital of the famous Potain. François-Franck reappraised all the hypotheses thus far brought forth. He showed the effect of digitalis on the myocardium and on the various parts of the nervous system; the vagus, the sympathetic, the cardiac ganglia. He did not, however, succeed in solving the problem which particularly interested physicians; namely, its diuretic action.

The problem was decidedly difficult, especially with the resources of the laboratory alone. Within its limitations, François-Franck pointed out that direct diuretic action could not be demonstrated. It remained for the clinicians to decide this question. Moreover, this had been foreseen, and, following Withering, all those who had been guided by clinical observation and not by dogmatic idea, e.g. Berlinghieri in Italy, Bedault of Villiers, Kluyskers, never tired of saying that among the patients treated with the drug only those had diuresis who had more or less considerable edema.

Potain's approach to the problem was

then simple. He had the great merit of capitalizing on the knowledge gleaned from his precursors, but sought his inspiration in the clinic. He confirmed the contributions which had been established and added to them. He emphasized that diuresis was proportional to the amount of dropsy. "The use of digitalis is indicated," he said, "whatever the causal lesion, by the frequency, the irregularity, the insufficiency of the cardiac pulsations, and by the edema of the cellular tissues and other evidences of dropsy." François-Franck attempted to prove experimentally the conclusions arrived at clinically. He produced in his experimental animals a state of arrhythmia; this was the only thing he could do. But this arrhythmia was very different from that which we observe in man, besides which it was not accompanied by edema. Thus the mechanism of the diuretic action of digitalis was bound to escape him. For that, it was necessary to come to man.

Mackenzie understood this. Cognizant of the work of the physiologists, but working under the ordinary conditions of clinical observation, he studied the effects of digitalis in the healthy and the sick. He noted the effects, registered them by the graphic method and determined the causes and the conditions of the slackening of the pulse and various modifications which result from the disturbed functioning of the heart.

To return for a moment to the physiologic side. Following Withering and Kreysig, Franke was the first to recognize clearly the fundamental action of digitalis in increasing the strength of the heart's contractions, as an expression of which the slowing of the pulse and increase in blood pressure were used as controls. In 1864, Franke proposed his theory of the action of digitalis on the muscle of the heart itself.

During this time, the English, still fol-

lowing the footsteps of Corrigan (1831) and Hope (1833) were persisting in the use of large doses. Following them came such men as Fothergill (1871) and Balfour (1898) who talked of the dangers of digitalis therapy. Then came Mackenzie who saw as the chief indication for digitalis the total arrhythmias (delirium cordis). During this time, the most important pharmacologic work on digitalis was being carried out. It might be pointed out that Mackenzie's work, based as it was almost wholly on clinical experience, stands almost as monumental as that of his compatriot Withering who introduced the drug. Thus, in his famous "Textbook on the Heart," he says in his inimitable style: "Give digitalis to physiologic effect, e.g., nausea, diarrhea, slowing of the pulse."

In France, because of the development by Homolle of amorphous digitalin in 1848 and two decades later the isolation of the crystallized digitalin (Nativelle), these two substances enjoyed more widespread use and application than elsewhere on the continent or in this country. Huchard sounded a more modern concept when he stated that digitalis was indicated in all cases of decompensated valvular disease and contraindicated if there exist valvular disease without failure.

Franke's discovery of the slowing of the pulse under digitalis therapy led him and his followers on the same false journey traveled by some of his predecessors. He mistook its significance and prescribed digitalis in febrile cases as he saw them in Schönlein's Clinic; inasmuch as he saw in the slowing of the pulse an antiphlogistic action of digitalis. (This showed the strong influence of the French school.) A student of Franke's, Leyden, recognized that the fall in temperature in pneumonia, and the slowing of the pulse were signs of toxic collapse and were not at all benefi-

cent; accordingly he strove hard to show the futility of using digitalis under these circumstances. He was aided in these endeavors by such men as Rohsbach and Nothnagel.

With the turn of the century, renewed interest in the pharmacology and physiology of digitalis engaged the attention of experimenters in this country and abroad. One needs but mention the monumental work of such men as Cushny,<sup>9</sup> Cloetta, Straub, Wyndhaus, Weese and Stolle beyond the Atlantic. In this country, following the attempts at standardization by Hatcher and Brody,<sup>10</sup> came Cary Eggleston's<sup>11</sup> pronouncement that the amount of the drug needed could be accurately ascertained beforehand according to the patient's weight. More recently, Soma Weiss and the Boston school have contributed further to our knowledge of the toxic effects of digitalis.

This increased interest will inevitably lead to a more rational exhibition of one of the most widely used drugs in the pharmacopeia. The recently introduced digitalis lanata with its active principle

digoxin may curtail some of the annoying side-effects which constantly arise in digitalis therapy.

From all of this there finally emerges some semblance of definiteness as to the indications of digitalis. Cardiac decompensation with valvular disease, edema, dropsy, ascites or general anasarca; severe or even moderate failure with irregular and intermittent pulse; severe dyspnea and palpitation; slight failure with cardiac hypertrophy and dilatation: these are a few of the specific indications.

Thus it will be seen that a century and a half following Withering, the wheel has finally come to rest where it started in 1785 when he wrote his classic descriptions. It is fitting to conclude this sketch with a quotation found in Withering's "Botany":

The foxglove's leaves with caution given,  
Another proof of favoring Heav'n  
Will happily display  
The rapid pulse it can abate,  
The hectic flush can moderate  
And, blest by Him whose will is fate,  
May give a lengthen'd day.

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