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Digitalis

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DIGITALIS

by

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INTRODUCTION

"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." (Winckebach 118) It "is the essential - - - in the treatment of cardiac decompensation". (Christian 18) It was the realization of these facts that prompted the subject of this thesis.

Of the numerous drugs with similar actions, digitalis alone will be considered. The several varieties of foxglove differ slightly in the active principles to which they owe their effect. All of these have essentially the same characteristics so the drug will be dealt with as a whole only.

A short division on the history of the drug will be followed by a section on the effects out of which the beneficial and toxic action of the drug result. Next, administration will be considered followed by a case history that well illustrates one form of digitalis intoxication.

HISTORY OF DIGITALIS*

The use of foxglove as a therapeutic agent is thought of by most people as originating with William Withering. However, as early as Dioscordies, the plant, foxglove, was known. There is good evidence to show that Galen used the plant.

During the eleventh century, it was known to the Saxons, and a century later to the Welsh. Extracts were considered as potent protection against such menaces as witches and the "evil eye".

A Bavarian named Leonard Fuchs (1501-1566) gave the first accurate description of foxglove, and as he thought the flower resembled a thimble, he called the plant the Latin for finger hut or, digitalis. He was a botanist primarily, but he ventured far enough from this field to suggest its use to "scatter dropsy", and to reduce swelling of the internal organs. He also suggested its use in starting the menstrual flow.

That digitalis had only a very limited use at this time is shown by the fact that Paracelsus (1500-1550) did not mention the drug in any of his writings.

In England in 1640, John Parkinson sang the plant's praises in "falling sickness" or epilepsy and in scrofula. In

*(History taken from 24, 62 and 126)

1710, William Salmon in the British Herbal gave the drug a great list of uses. One statement of interest was the following, "It produces weakness, induces vomiting and purges", thus he had observed and set down some of the important toxic symptoms of the drug.

Foxglove appeared intermittently in the Pharmacopeas in England, France and Germany between the years 1700-1775. The first experimental work on animals was performed by Saterene. He over-fed turkeys and noted the resulting frequent evacuations, the convulsions and death. By 1775, the drug had no reputation and had its principal use as an external application for scrofula.

Any thesis on digitalis to be complete should give some account of the man with whom the word is so closely associated. Withering was the son of a Shropshire physician, and it was while living in this section of England as a small town doctor that he made most of his observations. The manner in which Withering happened upon the drug is best narrated in his own words.

"In the year 1755, my opinion was asked concerning a family recipe for the cure of dropsy. I was told that it had long been kept a secret by an old woman in Shropshire who had sometimes made cures where more regular practitioners had failed. -- The medicine was composed of twenty or more different herbs, but it was not very difficult for one conversant in the subject to perceive that the active herb could be no other than foxglove."

As Jenner had seized upon and championed a local remedy so did Withering take up and gain recognition for digitalis. He became very interested in it and used it with ever increasing effectiveness upon his patients. Finally in 1785, he published his classic book upon, "An Account of Foxglove and Its Medical Uses".

In this monograph, he gave an accurate description of the drugs toxic effects. He showed that he well understood the use of the drug. As the ideal indication for its use, he described accurately a patient with cardiac decompensation. His work becomes all the more remarkable when consideration is given the relative scarcity of knowledge and the inadequate methods of study available at that time.

The modesty and genuine scientific attitude of the man are shown in the quotation from his book, "Time alone 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 or mankind".

Withering's clear and concise teaching prevailed for only a relatively short period of time. Ferriar in 1799 and Kinglake in 1801 confirmed his work and concluded that the pulse was slowed and strengthened by the use of digitalis.

Unfortunately the drug so efficient in its indicated field fell down when used in swellings such as hernias and boils. It also failed to cure tuberculosis in spite of the glowing

report of Beddois (1801).

In his words -- "In cases of pulmonary disease where the presence of tubercles was indicated by every symptom and when 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 hence forward be as regularly cured by foxglove as ague by the Peruvian bark".

The drug momentarily fell into such disrepute that Napolean's physician, Crouisart (1806-1818), refused to mention it in any of his books.

With the work of Laennic (1819) valvular lesions began to be diagnosed, and in 1832, Corrigan gave a more positive reason for not using the drug. He reasoned that in lesions of the aortic valve characterized by insufficiency, the drug by prolonging diastole increased the back flow of blood. Bouilland (1824) called digitalis a cardiac sedative, "the opium of the heart", and used it to quiet the heart in fevers. This did little to brighten the drug's reputation.

In 1840, reports of its use again became more numerous in Germany and France. Schoenlein (1842) and Aran (1842), representing these two countries, had much to say in favor of the drug. The English, however, continued to scorn its use. Such men as Stokes (1853) and Fothergill (1871) could find little to recommend foxglove.

As early as 1844, physiologists began active work on the drug. Homalle obtained the first active extract of the foxglove, and Movell in 1860 first crystalized out one of the active principles. The substance he succeeded in isolating was identical with digitoxin.

The method of action of the drug was the subject of much study after 1850. The German physiologist, Franke, showed that the sedative action of digitalis was a result of vagal stimulation. Boehm (1872) showed that there was a direct action of the drug on the heart muscle. Schmiedeberg confirmed this observation. Finally Cushney in 1898 was able to state that in man "in cases of dilatation of the heart with weak and inefficient systole, its action is almost specific; -- the action is very simple -- the increased ventricular systole approaches normal".

In 1899 however, Jurgensen stated that the use for the drug is in the totally irregular and rapid heart.

Thus one school used the drug with the idea that it increased the heart's efficiency through slowing its rate, and the other school with the idea that it strengthened the heart beat through direct action on the muscle.

The former group quickly gained the ascendancy through a series of investigations by Mackenzie (1911). This remarkable clinician ably supported by Thomas Lewis in the laboratory so conclusively showed the value of the drug in auricular fibrilla-

tion that this condition became the indication for digitalis. These men felt that it was through the slowing of the beat in this condition that the improvement was attained.

It remained for Cohn in a series of articles from 1915 to 1924 to recenter the investigators attention on the possibility of digitalis exerting a favorable effect in heart disease by increasing the force of contraction through direct action on the heart muscle.

For our detailed knowledge of the digitalis series, we are chiefly indebted to Cushney (1925) who over a period of twenty-five years worked to unravel this complicated family.

The lack of uniformity in potency of digitalis products was frequently an important factor in producing faulty use of the drug. Hatcher and Brody in 1910 worked out the cat method of bio assay. This plan is the most widely used in this country today, and through its application, it is now possible for any physician to buy a product of known potency.

Two modern methods of attaining the desired therapeutic effect with the drug were set forward by the Englishman, Mackenzie (1911), and by the American, Cary Eggleston (1915). The former achieved his results over a long period while the later showed the way to a rapid accurate means of digitalization.

ACTION OF DIGITALIS

Effect upon the Heart.

There are several avenues by which digitalis may exert its effect upon the heart. The first of these is a direct action. However, it may act indirectly upon the organ first by effecting its autonomic control and second by altering its blood supply through the coronary vessels.

(a) Direct Action upon the Heart. (18)

In connection with the discussion of the effects of digitalis directly on the heart, a short summary of the life history of the drug as it passes through the body will be presented. Digitalis is absorbed readily from the subcutaneous tissue, the intestinal tract or the muscle.

The drug upon entrance into the blood stream is fixed almost immediately by the tissues of the body. The heart muscle binds it to a degree greater than does any other tissue. The ratio compared to other organs is fourteen to one for skeletal muscle, five to one for liver, and two to one for kidney. The degree of absorption in the heart muscle depends upon several factors. It varies directly with the mass of muscle and with the concentration of the drug in the blood stream and inversely with the speed of the circulating blood. The large failing heart which is incapable of keeping up the normal rate of flow will thus take up more of the drug than it will later after the

circulation has improved and the heart size is diminished. This gives a nicely functioning control of the diseased heart according to the degree of need. (108)

After fixation in the heart muscle, there is a short period, a matter of seconds, during which the drug may be washed away. Following this it becomes irreversably fixed in the muscle. The binding action is the result of the formation of a cholesteride.

After the drug is bound, it gradually decomposes into a cardio-active portion, a genin, and an inactive portion, a sugar. The former is slowly removed from the heart muscle and eliminated. This elimination is chiefly through the liver. (33 - 42) The cardio-active principle acts through increasing the hydrophillic phase of the muscle. This increases the ability of the cardiac muscle to swell, and a stronger contraction and a more complete relaxation results.

The gradual breakdown of the drug into its active principle explains the delayed appearance of its effect. Additional doses will lead to fixation of more drug in the heart muscle before previous doses have been eliminated. In this way, digitalis exhibits its well known culminative action.

(b) Action upon Autonomic Control.

The influence of the vagus upon the heart was recognized by the nineteenth century physiologists. These men also recognized that digitalis acted to increase this inhibitory

function of the nerve. Stimulation of the vagus centers was held to be the mode of action of the drug. After the nerve was cut, digitalis no longer slowed the heart. (24)

However, the influence of the vagus may be primarily the result of digitalis action on the heart, for it has been demonstrated that this drug increases the sensitivity of the muscle to vagal tone. (112 - 1)

Experiments devised by Heymans indicate the action is through the carotid and aortic reflex. He was able to perfuse separately the brain and carotid sinus. Perfusion of the former was ineffective in eliciting a vago tonic response. However, the action on the carotid sinus produced the typical inhibitory effect. (60)

Thus digitalis seems to exert its vagal action through direct influence on the heart muscle and through reflex increase in vagal tone as a result of an action upon the carotid sinus.

(c) Effect on Blood Supply.

The effect upon the coronary circulation will be described later. This matter is a subject of much speculation and that any significant change at all is produced is far from accepted.

Now that the means by which digitalis exerts its influence over the heart have been presented, some of the effects of these influences will be discussed.

(1) Effect on the Contraction of the Heart Muscle.

William Withering noted of digitalis -- "It has a power over the motion of the heart to a degree yet unobserved of any other medicine". Since then workers have established an increase in the contractile power of the heart muscle. It has been demonstrated by x-ray that the heart under the influence of digitalis responds with an increased excursion. (24) The heart is able to empty itself against a higher arterial pressure (98), and the same amount of work can be done with less diastolic filling, following a raise in venous pressure. (8)

In the dog, toxic doses can produce the opposite effect through vagal activity with a resulting decrease in strength of ventricular contraction and finally with auricular standstill. (26)

Digitalis alters the speed of contraction through a direct action on the heart muscle. The duration of systole is shortened with a relative increase in diastole. Vagotomy or atropine are ineffective in influencing this response. (123)

(2) Irritability of the Heart.

Digitalis may raise the irritability of the heart muscle so that one or more points in auricles or ventricles may temporarily become the pace maker of the heart for one or more contractions. Extra systoles are the result. This action is important in telling the clinicians that enough drug has been given. (See toxic effects.)

(3) Conduction in the Heart.

Conductivity in the heart is effected by both direct action and indirect vagal control. The prolongation of the P-R interval in the EKG represents a delay in the conduction time through the AV node. This is a vagal effect as atropine will abolish it. (26) However, there is a direct action of digitalis in large doses not affected by atropine. (67) Intraventricular conduction may also be reduced with a resulting bundle branch block. (DeBoer 1919) (36)

(4) Pace Maker.

In the isolated heart, digitalis probably has little influence upon rate. (26) However, it may produce a slight elevation. (117) In the intact animal with normal rhythm, the slowing may be marked and is the result of vagal inhibition upon the SA node. (26)

Effect on the Heart Rate.

The complicated control of the heart rate offers a serious obstacle in the path of any attempt to determine the mechanism by which a drug may alter it.

That digitalis may markedly slow the heart was one of the earliest noted effects of the drug. In the normal human without heart disease, this response is little in evidence prior to the occurrence of toxic effects. (21) However, preceeding the alteration in the T wave, changes up to ten beats per minute

may be observed. (83) This change is due to vagal inhibition of the SA node.

In patients with heart failure, there may be marked slowing of the pulse if tachycardia existed before. That this change is due to action on the SA node primarily can not be assumed for the improvement in the circulation may remove the factor producing the tachycardia. In patients with tachycardia due to fevers, little or no alteration in the pulse rate results. When change does occur, it is as apt to be in the form of an elevation as in the form of a depression. (72)

In auricular fibrillation, the slowing is generally accepted as being due to decrease in conductivity of the AV tissue. In therapeutic doses, this is a vagal effect. There is a group of men, however, that feel that the cardiac muscle in failure exhibits an increased irritability and thus responds more readily to stimuli from the auricles. They point out that the fibrillator not in failure may be beating at a slow rate. (69) The rapid heart in auricular fibrillation is due to this increased irritability coincident with failure. The slowing in rate therefore might be attributed to relief of cardiac failure or a direct sedative action on the heart muscle.

That both a direct action on the muscle and an indirect action through the vagus are factors of importance is very likely the case. The amount of the drug given may determine which factor predominates. (48) Thus in small doses atropine

will abolish the slowing in the fibrillating patient while larger doses will produce a slowing unaffected by atropine.

Very marked slowing may be produced through the production of AV block. (28) However, through the slowing escape rhythms are very apt to occur whereby extra systoles may actually be so numerous as to increase the heart rate. The irritative action of the drug on the heart muscle will amplify this tendency.

Effect on Coronary Flow.

Previously in this paper it was stated that digitalis affected the heart through alteration in coronary flow. Discussion was avoided at that time because the subject being controversial required more discussion.

Digitalis produces constriction in the isolated coronary of a dog. (26) That this may take place in the human heart is suggested by the fact that digitalis when administered to humans with arteriosclerotic heart disease may develope angina pectoris. Several suggestions are submitted to explain this finding. First in a decompensating heart, the patient tends to restrict his activity. However, when digitalis is given, the degree of dyspnoea is lessened and the patient is able to increase his activity. As a result, he may crowd the capacity of his coronary arteries with a resulting ischemia and anginal pain. (Mackenzie 1923) (68)

Fishberg finds the explanation in the study of

patients with angina who decompensate and lose this symtpom. In such cases, there is a decrease in the amount of blood supplied to the left ventricle by the right. As it is the left ventricle that is apt to contain the sclerotic arteries, it is apt to be the source of the pain. Decompensation relieves the load on this chamber due to the decreased supply from the right heart. Digitalis by producing compensation steps up the right heart output and thus the load on the left ventricle with a possible result of return of the anginal pain.

Since Cushney's time, however, much experimental work has been done to prove or disprove alterations in coronary flow as a result of digitalis. In some cases, no effect has been noted. (9 - 52 - 10) Recently in a carefully controlled work, this conclusion has been verified. (34) That there is a definite decrease has also been shown. (3 - 35) The conflicting results may be harmonized. The early effect seems to be one of constriction, reducing coronary flow. Later due to anoxemia the blood vessels dilate, and also the cardiac output may be increased so that an increased coronary flow occurs. (41)

In the final analysis, angina must be looked upon as a subjective finding. In a well controlled series recently reported on, it has been demonstrated that the giving of a placebo is as likely to result in an anginal attack as is the administration of digitalis. (49)

Effect on Cardiac Size.

Digitalis decreases the size of the heart in health and disease. This is perhaps the most constant single effect of the drug. (54 - 110) It is assumed that this is the result of direct action on the heart muscle whereby each fiber is shortened decreasing the size of the whole organ. Extra cardiac factors are of no influence since the change in heart size persists though these be altered. (109) However, decrease in venous pressure and volume of circulating blood may augment this decrease in size. (96 - 64)

Influence on Cardiac Efficiency.

There is probably a marked increase in cardiac efficiency following optimal dosage of digitalis in decompensated heart disease. The heart uses less oxygen for the same amount of work accomplished. This change is due to the decrease in diastolic size of the heart for it is known that the larger the heart the greater becomes the oxygen consumption. (85 -51) Thus following a decrease in size of the heart the functional capacity of the organ will be greatly increased under the same oxygen supply.

Influence on Cardiac Output.

The effect of digitalis on cardiac output is a very complicated problem and from the mere fact that a patient improves

following digitalis therapy, it can not be assumed that the output of blood from the heart has been increased.

The fact that a decrease in cardiac output in the healthy individual takes place was first established by Harrison in 1927. Since then numerous authors have agreed that such a decrease does take place. (13 - 106 - 109)

The effect of digitalis in heart disease is not so clear cut nor so universally accepted. The most recent studies show that given a patient in cardiac failure that a marked elevation in cardiac output will result from the therapeutic administration of digitalis, regardless of whether the heart is fibrillating or not. (110) However, with the patients presenting heart disease but no symptoms of failure, the action is less pronounced. In this group of cases, the output may be increased, unchanged or decreased. In the first case, the heart acts as a decompensated organ and in the last case, as a normal one.

There are those who produce evidence to show that no constant increase does occur in decompensated heart cases. (54)

The question now arises how does the drug produce these effects? In failure, the blood supply to the heart is more than adequate. Venous pressure is high and the output thus depends not on the supply of blood, but upon the heart's capacity to distribute the ample supply. Through the slowing, increased efficiency and increased force of contraction, the functional capacity of the heart is raised. This tends to increase the

volume of blood expelled from the heart.

In the healthy individual, the decreased output is not so easily explained. That the decreased size is an important factor is more than possible. (109) That there is an extra cardiac influence at work must also be given some consideration. (64) Thus it has been shown that digitalis diminished the volume of circulating blood. (79 - 127 - 99) This reduction might be due to a constriction of the hepatic veins pooling blood in the splanchnic area. (27) In heart failure, the blood volume tends to increase from the very nature of the disorder. The segment of the circulation upstream from the failing chamber will show this increase. (53) The relief of failure in itself will thus account for a large decrease in the volume of circulating blood.

Now the findings in health and disease will be harmonized. Two factors are at work. The first is an increased capacity of the heart to do work. This tends to increase cardiac output. The second is a decrease in circulating blood; this tends to decrease cardiac output.

In the healthy individual, the functional capacity of the heart is not a factor to be considered as it can easily manage large variations in blood returned to it. Thus the extra cardiac factors produce a decrease in cardiac output with the possible aid of the decrease in the size of the heart.

It will be remembered that in one group of decompensated patients a constant rise in output existed. Here the in-

crease in functional capacity predominated. In the other group, no constant change in cardiac output was observed. In the cases where a decreased output appeared, the smaller blood volume and the smaller cardiac size were the determining factors.

Relief of Heart Failure by Digitalis.

Now that some of the effects of digitalis have been presented it is interesting to speculate on just how these effects bring about the marked improvement so frequently observed in the failing heart.

Improvement depends on two factors. The first is an increase in functional capacity of the heart, and second a decrease in the load on the heart. The heart fails because the work to be done surpasses the functional limits of the organ. Digitalis alleviates heart failure by attaching both the factors. (36)

The increased functional capacity is brought about by three modes of action. The first is on the AV node. The fibrillating heart is slowed. This gives more time for the chamber to fill and for the heart to rest. The result is a stronger and more efficiently working machine. (76) The second action less definite is an effect upon the SA node slowing the failing heart with tachycardia. Through this action the heart is given a longer rest period. The third action is upon the heart muscle. This results first in an increased strength

of contraction (47); second in an increased mechanical efficiency (54) and third in a lessened fatiguability. (98)

The load of the heart is decreased by decreasing the volume of the circulating blood. (27)

The Effect of Digitalis on the Kidney and Urine.

The apparent effect of digitalis upon the kidney first called William Withering's attention to the drug. He considered the diuretic action to be the principal factor in improving the dropsical patient. That this action is not on the kidney is shown by the fact that digitalis does not aid in reducing edema of any origin other than cardiac.

In heart, lung and kidney preparations of dogs, an increase in urine has been produced through administration of digitalis. (50) However, this does not prove that diuresis in man has a similar origin. The fundamental factor in diuresis is one of improving the circulation. This produces a fall in venous pressure with a decrease in capillary pressure. The blood supply to the tissues is improved so that waste products in the tissues are removed. By this twofold influence, edema fluid is absorbed and carried to the kidney where it is eliminated.

Prior to the diuresis in cardiac patients there is a decrease in the plasma specific gravity. (107) This indicates that absorption of tissue fluid is fundamental in the diuresis

not the reverse.

Effect on the Electrocardiogram.

As early as Cohn's work in 1915, it was known that digitalis effected the electrocardiogram. Since that time, electrocardiographic alterations have become well recognized. The importance of recognition of these changes may be considerable as a digitalis effect may simulate findings of serious coronary disease. The changes are of some importance in determining whether or not a patient has had digitalis recently. Over dosage may be recognized first in the cardiac tracing.

The changes to be found will be listed in some detail.

P Waves. The P wave may become lower or diphasic (95) or may be unaffected. (65 - 120)

P-R Interval. There may be no change in the length of this segment of the electrocardiogram (106) or it may increase anywhere from .01 - .04 sec. where the drug is given in small doses to normal humans. (120 - 114) Changes in the PR interval may vary with respirations following the administration of digitalis. (70) These changes in the undamaged heart are not marked and rarely given an interval above .25 sec. However, in the diseased heart, greater effects may follow small doses. Large doses may produce varying degrees of block up to complete AV disassociation. (28) The lesser degrees of PR prolongation are

probably a vagal effect as atropine will abolish them. However, in larger amounts, atropine will no longer prevent PR prolongation and thus the effect is probably directly upon the AV bundle. (90)

QRS Complex. The height and conformation of the QRS complex may rarely be changed under digitalis. (116 - 12 - 38) The changes, however, are the exception and not the rule. (65)

QT Time. This interval is quite regularly decreased. (15) It is illustrative of the shortened ventricular systole spoken of earlier.

ST Segment and T Waves. The changes in this portion of the cardiograph are most characteristic. They appear quickly after administration of digitalis if given in large doses. The usual alteration is a depression of the ST segment with a coincident lowering or flattening of the T wave. The latter may go on to diphasic state or to complete inversion. (65) The T wave if negative may become positive. (83) When axis deviation is present, the T wave may change so as to become opposite the chief deflection of the QRS. (83) Atropine fails to abolish these changes so they appear to be a result of direct action upon the heart muscle.

Other alterations will be discussed under toxic effects of digitalis.

The changes seen may persist from a few days to as

long as four weeks. The P wave and PR time changes appear to be very transient and last but a few days. (65) However, QT time, ST segment and T wave changes may frequently persist as long as thirty days, usually twelve to twenty. They reach a maximum in from twenty-four to seventy-two hours. (65)

The percentage of the lethal dose at which the various changes appear has been worked out in cats. T changes appear at 24 per cent of the fatal dose; PR changes at 52.5 per cent and ectopic beats at 71.6 per cent with complete AV block occurring at 80 per cent. (90)

ADMINISTRATION OF DIGITALIS

Preparations.

In the United States, digitalis is used mostly in the form of the powdered leaf. The use of other allied preparations is very limited in this country, However in Europe, the tincture is quite popular, and the related drug, strophonthus, has a large following. The isolated components of digitalis are available but are not used a great deal. Infusions and other preparations with the exception of the tincture and powdered leaf are definitely out of date.

The disadvantage of the tincture is that uniformity of dosage is difficult to obtain. The ordinary dropper does not deliver a minim drop; so the drug must be measured out by some other method. Minim droppers have been devised to surmount this difficulty. There is some indication that the absorption from the bowel is more rapid and complete if given in this way than when administered as the powdered leaf. (36)

The use of the powdered leaf has the support of most of the leading men in this country. (66 - 121 - 54 - 18 - 68) This preparation is given either as a pill or in a capsule. Either method insures uniform dosage. The drug is rapidly and nearly completely absorbed from the bowel. None of the more concentrated preparations have been shown to have any marked advantage over it.

Of these active principles of digitalis, there are many on the market in a well standardized and reliable form. However, as has been previously stated, none have any advantage over the whole leaf preparations that will warrant the added expense of their use. The claims that with some of the products there is only a slight tendency to produce toxic symptoms can be discounted. Any preparation that is incapable of producing toxic symptoms is incapable of producing a therapeutic effect. (66) That the various fractions have a similar qualitative effect is now fairly well established. (46)

The properties of digitalis like products will be considered in this thesis only to mention that there are few conditions in which any of them prove to be more efficacious than does digitalis itself.

Any product used should be standardized by bio-assay. The cat method is the most widely used in this country and yields very satisfactory results. (57) Through its application, a standard digitalis preparation can be obtained any where in the country.

Dosage.

Digitalis should -- "be continued until it either acts on the kidneys, stomach, pulse or bowels; let it be stopped upon first appearance of any of these effects". These were the words of William Withering. They are the essence of the rules

used by most clinicians today. The drug should be used until the therapeutic effect is obtained or until toxic manifestations appear.

When these simple rules were disobeyed one hundred years ago, the drug fell into disrepute; and today when they are not followed, poor results are forth coming.

There are two ends to be achieved in digitalis therapeutics. The first is to gain the best possible effect with the initial dose, and the second is to maintain the patient at this optimum level when once it has been established.

The modern era of digitalis administration dates from the work of Mackenzie. The doses given before his work became established were too small. (75) He gained satisfactory results through the use of slightly over the maintenance dose and its continuance over a period of four to seven days.

Dosage since has been placed upon a scientific and exacting basis. The amount of drug to be given to gain the full therapeutic effect can now be roughly estimated before giving. (31) That this full amount can be given over a short time with good results is also well established. (31) By this rapid method, clinical results will be shown within twelve hours, and electrocardiographic changes will be detected within two. (82)

The choice of methods should rest upon the patient. In a case where time may be the deciding factor between life and death, the most rapid means of digitalization is indicated. For

the ambulatory patient, the slow method is admirably suited.

For exact figures to quote, those of Paul White were selected as they seem representative of the thought of a large group of clinicians. (121)

The amount of the drug to be used for a one hundred fifty pound man should be 1.5 to 2.1 grams of powdered leaf, the variation being determined by the length of time over which the drug is to be given. The dose is calculated on the basis of one cat unit or .1 gram per ten pounds of body weight of the patient. In the very urgent cases, .5 grams should be given three times a day at eight hour intervals. This accomplishes digitalization in one day. In less urgent cases, .3 grams given three times a day for two days may be used. While if the patient is in bed and not badly decompensated, .2 grams three times a day for three days may be administered. In the ambulatory patient, .1 gram three times a day for a week is a very satisfactory dose.

There are as many other sets of figures as there are men writing, and there is no point to repeating them.

The calculation of the dose ahead of time should be considered as only a rough guide as there is an individual variation in people as to the effect a given dose will have upon them. Experiments in animals indicate as great as 45 per cent variation in the amount of drug necessary to produce death. (6) Considerable variation in the amount necessary to produce nausea is usually seen. (2) The degree of slowing in fibrillation is a large

variable. (40)

The indication to stop the digitalizing and to start the maintenance dose should be a satisfactory therapeutic response. It is not necessary to reach the level of toxic manifestation before ceasing administration. (68) Withering realized this fact. Too frequently since that time, men have not appreciated it. Calculated doses of Eggleston fall just under this level and should be considered the maximum dose for therapeutic response. There is actually a wide range of therapeutic effectiveness before toxic symptoms appear, and the clinician should be able to place his patient within this limit. (68) It should be remembered that certain patients are beyond improvement, and pushing the drug past the point where untoward effects are observed does nothing but add to the burden of the individual.

The maintenance dose is an extremely important consideration. If this detail is not handled properly, the result can be a swing from reappearance of decompensation up through a picture of digitalis poisoning. The amount usually comes close to a cat unit or .1 gram of the powdered leaf each day. It should be varied to meet the needs of the patient. Some men obtain good results giving two to three .1 gram tablets each day for a limited number of days and then allowing a rest period. (40) The patient who uses the drug over a long time will become very adept at judging the amount of the drug he requires.

The maintenance dose should be such as to match the

amount of the drug destroyed or excreted. By observing the effects of digitalis on the T wave, it has been shown that this amounts to about 1.25 cat units a day. (82) Neither the type of lesion nor degree of compensation has any effect upon this amount. (12) However, the quantity of digitalis in the body may be an important factor in governing the quantity destroyed. The higher the concentration in the body the larger the amount destroyed. (44)

Evidently the amount required for a child is considerably higher in proportion to the body weight than in the adult. This may amount to as much as a 50 per cent increase. (71) This quantity is frequently enough to give toxic symptoms. (63)

Avenue of Administration.

(a) Oral:

In the great proportion of cases, digitalis can be given by mouth. It is the easiest method of administering the drug. The objection to this method as compared to the other avenues is negligible. The cases where the taste of the drug makes this route inhibitory should be non-existent through the use of the powdered leaf in capsules.

The drug passes unchanged through the stomach. (92) and is absorbed slowly and incompletely in the small intestine. (26) Further absorption takes place in the large bowel. Complete removal from the bowel requires from two to six hours. (93)

There is some evidence that congestion of the viscera may limit absorption by mouth or rectum, however, it is generally accepted that digitalis of a high grade will be effectively and evenly absorbed even in such a case. (33)

(b) Rectal:

The rectal use of the drug should be limited to cases where due to vomiting the drug can not be taken by mouth. The dosage of digitalis by rectum is the same as that for oral administration. The tincture may be used in this place (40) if well diluted. Active principals, which dissolve readily, are frequently recommended in this situation. (18) In cases where vomiting prohibits the use of the drug by mouth, this is probably the best avenue of administration.

(c) Parenteral:

Digitalis given intravenously, subcutaneously or intramuscularly is the most efficient means. The drug passes directly to the heart without passing through other organs which could cut down the effect through fixing a portion of it. It thus theoretically should require a comparatively small amount to produce the same result that oral administration would require. (18) In practice, however, this is not carried out. In rapid digitalization by mouth, an initial dose of .5 grams was recommended, and this is the same dose recommended by many for intravenous therapy. (121 - 66- 18) The use of smaller doses lacks rational as it is a rapid effect that is desired whenever this avenue is chosen.

By use of the intravenous route, benefit may be brought about in a matter of minutes. It should only be used in cases where time will be the deciding factor between life and death, as in the case of massive pulmonary edema. (36) It is claimed strophanthus will yield better results than digitalis in this emergency. (121 - 18) However, active fractions of digitalis may be used with excellent results (68) and even the well diluted tincture may accomplish the desired effect. (40) Only the initial dose need by given intravenously as administration by mouth may be begun at the same time and will carry on the initial benefit before a second parenteral dose need be given.

Subcutaneous administration is always painful and should yield to the intramuscular route. This method gives rapid results. However, it is painful and should be replaced by the intravenous method where rapid results are sought. In cases where continued administration of digitalis is required, but the oral route can not be employed, then perhaps intramuscular injections are indicated. (121) Dosage is the same as for intravenous therapy. One of the water soluble active principals is the best product for use although the more irritating tincture is a satisfactory substitute.

Indications.

"Digitalis is indicated in all cases of heart failure, that is, where insufficient functioning of the heart is the cause

of the pathological condition." (118) Thus regardless of etiology, rate or rhythm the indication is heart failure. (68)

Mackenzie's work so clearly showed the drug's value in auricular fibrillation that this condition has been fixed in many clinicians' minds as the criterion for its use. Regular rhythms were not considered to show a similar benefit. Thus in 1926, a well known clinician wrote, "In patients with congestive failure and a normal rhythm, it will be necessary to rely on rest and sedation alone; digitalis is of little value here." (25)

In recent years, however, it has been gradually accepted that a heart with normal rhythm may well be benefited by the use of the remedy. There is considerable evidence available to show that the patient with fibrillation may be no more improved than the one with normal rhythm. (110) Though most men feel that the greatest improvement is seen in the fibrillating patient, heart failure today stands as the essential indication for digitalis therapy.

(1) Significance of Circulatory Dynamics.

The patient suffering from right heart failure with peripheral edema, enlarged liver and ascities was the one that Withering treated, and in such a patient marked improvement does result. However, the patient in whom the left heart is involved who presents dyspnea as a result of pulmonary congestion, will also be markedly relieved. Marked increase in the vital capacity of these patients following digitalization has been impressively

shown. (55)

(2) Significance of Rate and Rhythm.

Tachycardia:

Frequently in cases of congestive failure, the heart beats rapidly until digitalis is given at which time marked slowing occurs and decompensation is relieved. However, it must be reiterated that the preponderance of the benefit to be gained from the drug is in relieving heart failure. As a result of this essential factor, the symptom tachycardia disappears. Thus giving of digitalis to slow the pulse is an improper indication. The only occasion where rapid sinus rhythm exists that the drug is called for is in heart failure.

Fibrillation:

As far as fibrillation itself is concerned, it is not an indication for the drug's use. There are cases where transient fibrillation occurs as a paroxysmal arrhythmia. The action of digitalis in such a case is merely to continue and prolong the attacks. (37) Various infections and toxemias may produce the disorder, but benefit will not follow administration of the drug as long as heart failure is lacking. (68) In fact in these toxic states, digitalis may initiate a fibrillation if it was not present before. (100)

Flutter.

Indications for digitalis in flutter are the same as those for fibrillation. In cases associated with heart disease,

marked improvement may result. Digitalis alone will usually turn the arrythmia into a fibrillation following which, if the drug is stopped, normal rhythm will frequently ensue. In conjunction with quinidine, many flutters will be returned to normal rhythms. (84) At times fibrillation will remain permanently, however.

Paroxysmal Tachycardia:

Paroxysmal tachycardia of supraventricular origin may be treated by digitalis. However, most cases are of short duration and are amendable to other approaches. Persistent paroxysms may be given a trial with the drug and according to several investigators, the cessation of the attack will result. (4 - 5)

The treatment of tachycardia of ventricular origin, however, may be a dangerous undertaking. Cases of ventricular fibrillation have followed such an attempt. (30)

Extra systoles:

Extra systoles, such a common result of digitalis, have in some cases been eradicated by the drug. (101) This has been true of premature beats of whatever origin. The use in this disorder, however, should not be a regular practice; on the other hand, extra systoles should not be considered contraindication to digitalis.

Heart block:

In heart block, partial or complete, if failure is present, digitalis may be of benefit. The earlier notion that it

was a contraindication because it increased the block is now discarded. (97) The improvement may be remarkable and the block even lessened. (33) In some cases which tend to pass from partial to complete block with an insuing Stokes Adams syndrome, digitalis must be used warily. It may in some cases lessen the block or in others produce the complete block. Either state is better than changing back and forth as it is here that the Stokes Adams syndrome tends to appear. (68)

Another condition that may be produced by digitalis or again may be improved by it is the bundle branch block. The finding is in no way a contraindication to the drug's administration.

(3) Use in Acute Infections and Toxic Statis.

If the rule that heart failure is the indication for digitalis is followed, this group of conditions will offer no difficulty. In high fevers, digitalis has less vagal effect than normally, and the toxicity may be increased. In lower fevers, it produces the same effects as in a normal person. (72) The rapid heart in toxemias or infections should not be an indication for the drug, and only when decompensation occurs, may it be used. (68) Several conditions should be mentioned specifically.

In diphtheria, an alteration similar to digitalis effect is seen upon the electrocardiogram. It is possible that the drug given will merely increase this toxic action. However, the test is whether decompensation exists. If it does, the drug is

indicated; if not, it should be withheld. (68)

In rheumatism where active carditis exists, poor response to the drug can be expected. (45) It may even be considered a contraindication, unless the decompensation is severe, as it adds to the toxic effect on the myocardium. (97)

In pneumonia, the heart may be markedly effected by digitalis, (23) and in the past, it has been held to be life saving in many cases and was recommended as a routine measure. (20) Figures were even presented to show a decreased death rate following its use. (111)

As early as 1891, warning was sounded against this measure, (14) and Mackenzie discouraged it. (74) In 1927 and 1930, two studies were published that showed digitalis not only failed to lower mortality statistics, but it showed a definite rise in these figures. This increased death rate was seen in all categories of patients including tachycardia, fibrillation and block. Neither age nor sex showed any difference. It is concluded that its use should be discouraged, and the only possible place in the future for the drug is limited doses in pictures of decompensation. (11 - 128)

The reason for the failure of digitalis in acute infections has several factors in the background. The fact that fever lessens the slowing by digitalis and increases its toxicity has been mentioned. The fact that toxic doses are needed to produce slowing is another. The circulatory breakdown in most of

these cases is peripheral, and this resembles shock. The failure is due to want of blood for the heart to pump. That digitalis decreases the volume of circulating blood has already been shown. With such a consideration in mind, the danger of the drug in any such situation is evident.

In hyperthyroidism, digitalis again produced less effect than would be expected. The presence of fibrillation does not call for the drug, but as before mentioned, it is decompensation that does. Iodine may prove a much better agent than foxglove in such cases. The two together can be quite efficacious. (68) That toxic effects upon the brain are likely to occur is a possibility. (86 - 87) However, failure of the heart in hyperthyroidism should be considered a definite digitalis indication.

(4) As a Preoperative Medicant.

In time gone by, digitalis was used quite regularly as a preoperative medicant by some men. This was an especially common practice in older people. The feeling was that should some emergency arise postoperatively the patient would already have the drug in the body. The usual cause of postoperative circulatory collapse is in the peripheral circulation, and as explained in a preceeding paragraph, digitalis can not aid or may even be dilatorious in this situation. Clinical studies on the matter show a higher mortality rate following its administration. (77) In any condition where there is heart failure or potential heart failure giving of the drug should be considered upon the same

principles as though the operation was not in the picture.

(5) Significance of Etiology.

Given a regular rhythm there is some suggestion that the best results from digitalis obtain in arterial sclerotics and hypertensives. In patients with rheumatic valvular disease, good results are usually forth coming. When the mitral valve alone is involved, an excellent response is likely to follow. Perhaps this is more apparent than real as many of these patients are fibrillators. (36) Hearts with involvement of the aortic valve are usually less beneficially effected. (93) In leutics, this fact is especially apparent and is likely due to the coincident narrowing of the mouths of the coronary arteries. (36) However, in recent years, this has generally been discarded as a contraindication for the drug. (36) The preceding paragraph considers cases where the work to be done by the heart is increased. Considerable improvement is expected in most of these conditions. (78)

In conditions where the amount of work the heart is able to do is decreased, then digitalis is of no avail. Active rheumatism, diphtheria and beri-beri fall into this category. (68)

In coronary artery disease with angina, there has been a discussion previously in this paper, where it was shown that such cases are rare, and angina is not a contraindication to the use of digitalis. In coronary thrombosis, there is quite a different story. Ventricular fibrillation is not an uncommon complication. That digitalis may produce the same condition is recognized. (88)

From this it has been assumed that digitalis in coronary thrombosis will further increase the tendency. Experiments have shown in some cases no change in the heart's response to digitalis following artificial occlusion, but in other studies, a decrease in the tolerance of the muscle for the drug was demonstrated. (43 - 7) Dangers of rupture of the heart are increased by digitalization. Thus in each case, the matter must be settled which plan holds the best chance for the patient. If it is obvious that the patient will die in decompensation, the drug is indicated; however, thrombosis itself is no indication for its use.

(6) As a Prophylactic Measure:

Christian has for some years championed the use of digitalis in cases of potential heart failure. He feels that if digitalis can be used to prevent subsequent attacks of failure following one episode, there is no reason to assume that the proper administration might not postpone the initial failure. His reasoning is based upon the assumption that the hypertrophy is an injurious process. "Cardiac hypertrophy instead of being a beneficial process is an injurious influence upon cardiac function. The heart over enlarged is already on its way to eventual decompensation, to retard hypertrophy is to prolong cardiac efficiency." Dilitation, the forerunner to hypertrophy, is prevented by digitalis, for it is well known that digitalis decreases the heart size. The cases of older people are better effected than those of younger individuals. His conclusions are on a theroretical basis and time

and future clinical experience will determine the value of the drug in this connection. (17)

Toxic Effects of Digitalis.

Even before the time of Withering, the symptoms of digitalis poisoning had been noted. Although it has been intimated that production of toxic symptoms is not necessary nor desirable in treatment; nevertheless it is important to know and recognize these symptoms for at times their production will occur despite all precautions.

Gastro-intestinal Tract.

The earliest recorded signs of foxglove intoxication were those referable to the gastro-intestinal tract. That the action of the drug is not a local one is demonstrated by the fact that nausea and vomiting may occur after the tract has been removed. (32) The action seems to be a reflex stimulation of the vagus centers through a direct action upon the heart. (59)

The effect is manifested in anorexia, nausea, vomiting and diarrhea. There is usually a latent period between giving of the drug and the first symptom, anorexia. The smaller the dose the longer this period. (91) This may be the only symptom. However, nausea and vomiting may follow. The amount of the drug to produce these symptoms is varied, (19) but in a person during a given episode, the amount of nausea and vomiting depends upon the amount given. The symptoms may be persistent over several

days, may appear but once or may come in waves.

Diarrhea more rarely seen may be explained on the basis of increased motility of the intestine and decreased emptying time of the stomach. (115)

Heart and Circulation.

Numerous of the effects referable to the cardia have been mentioned under EKG changes. The small increase in the PR interval and changes in the T waves and ST segments usually occur before the toxic symptoms. Extra systoles may be a manifestation of digitalis poisoning. (122) This may take the form of coupled beats. (68) The number may be numerous enough to produce increased pulse rate in spite of the accompanied slowing. Various grades of block may be produced (122), and complete block has been recorded as the only toxic manifestation. (29) Ventricular paroxysmal tachycardia has been recorded as a result of the drug, (61) and transient (102) to permanent ventricular fibrillation (88) has been seen as an effect of poisoning. Auricular fibrillation may be produced (113) or once present, prolonged. (37) Pulses alternans indicates a severe degree of digitalis poisoning. (125) SA block and auricular standstill are rarely demonstrated due to this drug. (92)

Other Manifestations.

Nervous symptoms are sometimes seen in digitalis poisoning. They may be the only manifestations. Symptoms sometimes produced are head ache, depression excitement, impairment of memory

deep confusion, delirium and convlusions. The occurrence is most common in elderly people and may be partially due to dehydration. (104)

Disturbance of vision may be in the form of blurring, flashes of light, transient blindness or green vision. (105)

Eosinophilia has been observed and is believed a vago tonic effect. (94 - 103)

CASE REPORT

The literature lends numerous reports of digitalis produced heart block. (22 - 33 - 122 - 73) Slight prolongation of the PR interval is a very common occurrence, but lengthening past .3 of a second up to complete block is an indication of well advanced digitalis poisoning. Block is usually accompanied by other severe symptoms, but several cases have been reported in apparently normal people where block was the only finding of the intoxication. (29)

The short case summary is of a patient suspected of having had a heart ailment. Digitalization was carried to a degree of complete block in which state she entered the hospital. The series of tracings illustrate her recovery. The patient left the hospital apparently completely normal with no cardiac findings. Her only treatment was rest and abstinance from digitalis.

History: Patient, a 22 year old single female, entered the University Hospital for the first time 4-8-37 complaining of palpitation, anorexia and loss of weight. The patient had an attack of rheumatic fever at the age of 12 in 1929. Early in 1938, she was in bed with scarlet fever which was followed by no demonstrable complications. In September of 1938, the patient had an attack of palpitation and marked weakness. Following a tonsillectomy, she returned to her usual household duties. In December, the same symptoms recurred.

These have persisted to admission. For six weeks prior to admission, since late in February, she has been in bed. In the last half year, patient has lost 20 to 30 pounds. Occasional spells of vomiting have occurred since February. Digitalis has been administered off and on since early in February.

Physical Examination: Negative except for systolic murmur heard at apex. Pulse 50 regular - marked venous pulsations seen in neck.

Diagnosis: Rheumatic carditis.

Immediate Treatment: Rest - removal from digitalis.

Course in Hospital:

4-9-39 Heart now irregular.

4-10-39 EKG shows digitalis block.

4-11-39 to 5-3-39 Gradual lifting block with disappearance of anorexia, weakness and palpitation. Patient gaining weight.

Dismissed with negative cardiac findings and normal EKG.

Dismissal Diagnosis: Digitalis poisoning.

The EKG tracing taken 4-10-39 (Fig. I) show runs of complete block where the auricles and ventricles are beating independently. However, in places, the ventricle does respond to impulses from the auricle as shown by irregular spacing of ventricular

beats. There is marked depression of the ST segments and flattening of T waves.

4-12-39 (Fig. II) The block is no longer complete. Each auricular beat is followed by a ventricular beat. The PR interval .34 - .38 seconds is extremely prolonged. The ST segments are taking off nearer the base line.

4-14-39, 4-18-39, 4-26-39 (Fig. II) All these records show normal PR time with gradual elevation of ST take off and increased amplitude of T waves.

5-3-39 (Fig.II) The final is a normal tracing with T I, II and IV entirely positive and with the ST segments all iso-electric.

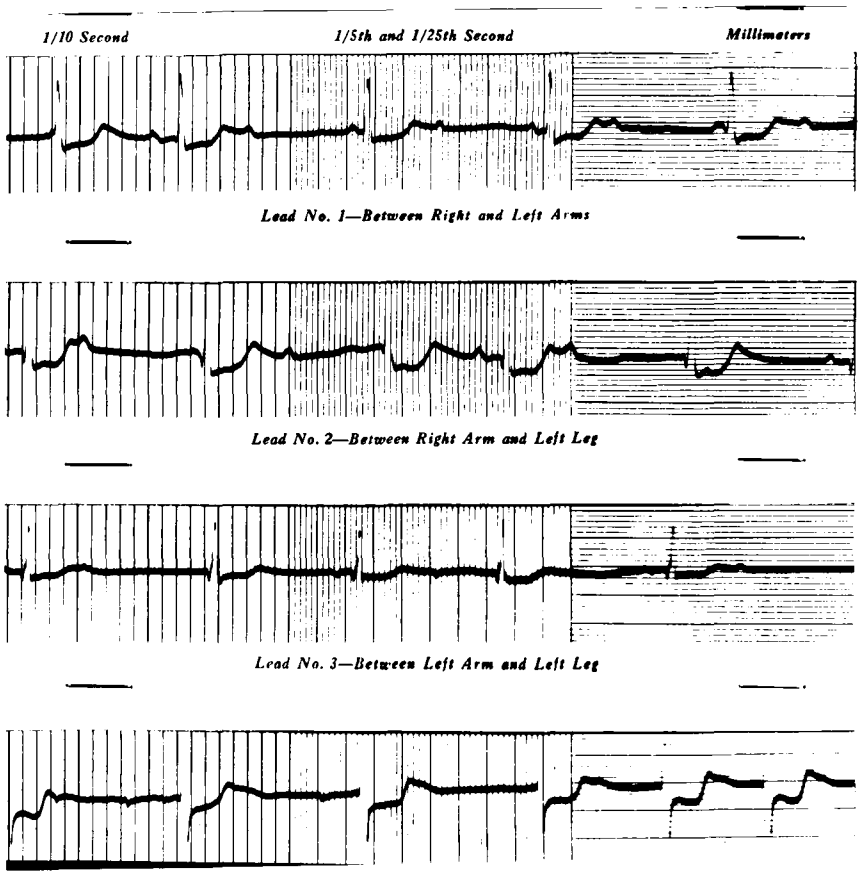
1/10 Second
1/5th and 1/25th Second
Millimeters
Lead No. 1—Between Right and Left Arms
Lead No. 2—Between Right Arm and Left Leg
Lead No. 3—Between Left Arm and Left Leg

Fig. I.

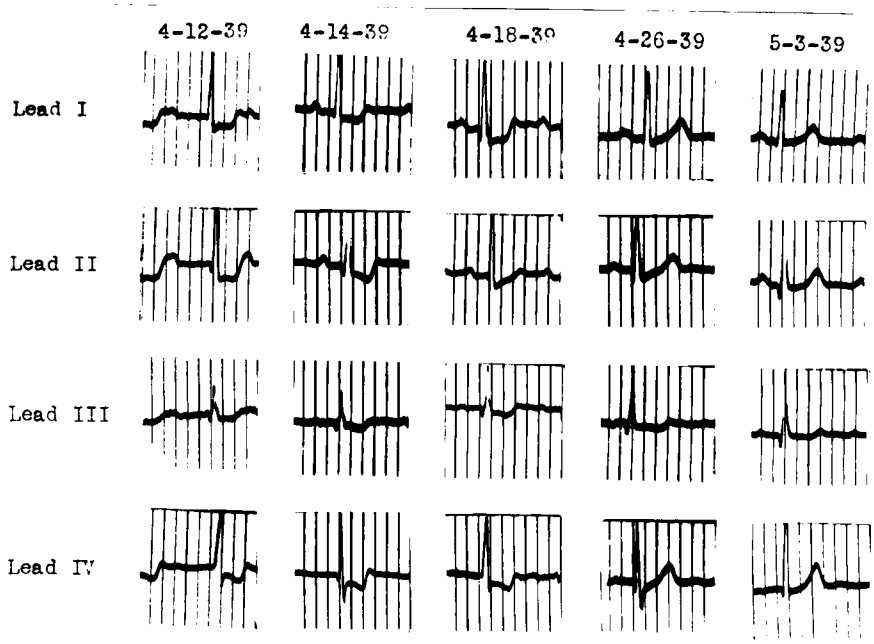

Fig. II.

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