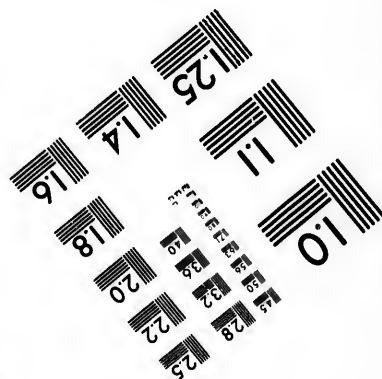
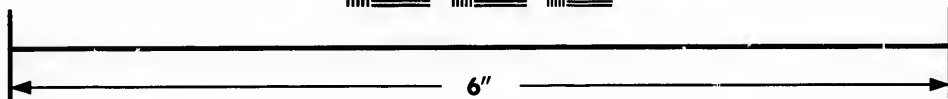
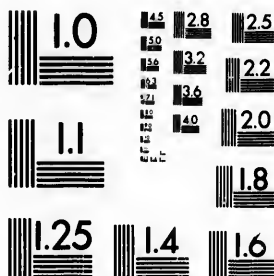


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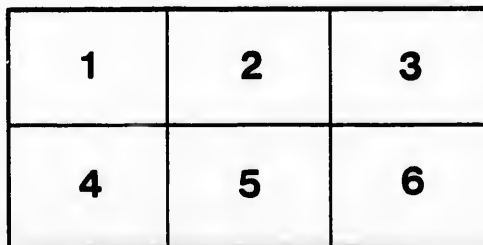
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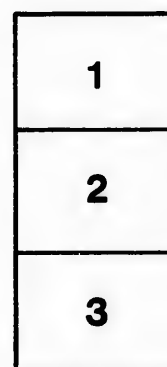
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ON DIGITALIS.

A LECTURE DELIVERED BEFORE THE MATERIA MEDICA
CLASS, MCGILL UNIVERSITY, MONTREAL,
NOVEMBER, 1884.

BY

JAMES STEWART, M.D.,

PROFESSOR OF MATERIA MEDICA AND THERAPEUTICS, MCGILL UNIVERSITY,
PHYSICIAN TO THE MONTREAL DISPENSARY, AND DIRECTOR OF THE
UNIVERSITY DISPENSARY FOR DISEASES OF THE NERVOUS SYSTEM.

Montreal:

GAZETTE PRINTING COMPANY.

1884.

ON DIGITALIS.

DIGITALIS.*

By JAMES STEWART, M.D.,

Professor of Materia Medica and Therapeutics, McGill University; Physician to the Montreal Dispensary, and Director of the University Dispensary for Diseases of the Nervous System.

GENTLEMEN,- The leaves of the digitalis plant contain three glucosides, each of which possesses active cardiac physiological actions. These are digitalin, digitaleïn and digitoxin.

In addition there is a fourth glucoside called digitonin destitute of any cardiac properties, but having an action very similar to saponin, the active principle of senega root. Digitalis leaves also contain a resin which closely resembles picrotoxin in its actions.

The active principles commonly known as Quévenne's and Nativelle's digitaline have been proved to be mixtures of the various glucosides above mentioned. None of the glucosides possess any advantage over a preparation of the leaves, and owing to the great difficulty in isolating them it is always preferable to use a tincture or infusion of the leaves.

Pharmacology.—There is no medicinal agent whose physiological actions it is more important that you should thoroughly understand than digitalis, for when used in proper cases and in proper doses it is capable of accomplishing a great deal of good. Although not, except in very exceptional cases, a curative agent† in the narrowest sense of that term, it is capable in many cases of not only giving great relief, but of prolonging life, frequently

*Lecture delivered before the Materia Medica class, November, 1884.

†In cases of acute dilatation of the heart occurring as the result of anæmia it is a directly curative agent.

for very many months, and at times even for many years. The good that is obtained by mercury in syphilis, by salicylic acid in acute rheumatism, by quinine in malarial fevers is no more striking than the action which digitalis possesses in steady-ing and contracting an irregular and dilated heart.

Digitalis preparations have a disagreeable bitter taste, and when taken in large medicinal doses may give rise to nausea and vomiting and even to purging. The last effect, however, is very unusual.

The active constituents diffuse readily into the blood, but what if any influence they exert on it is not known.

Action on the Circulation.—The effect of small medicinal doses (10 minims of the tincture every twelve hours) of digitalis is to make the heart beat with an increased vigour. The left ventricle especially beats more powerfully. Coupled with this increased vigour of the heart's contractions, there is a slight rise in the blood pressure, which has the direct effect of sending more blood to the ventricles and the indirect effect of further stimulating them in their contractions. If larger medicinal doses are administered, we have in addition to an increase in the effects already described, a slowing of the heart. The ventricles now beat not only more vigorously, but also slower. This slowing from full medicinal doses may amount to forty or even fifty beats per minute, but it is only in cases of cardiac failure that such a marked reduction takes place, and then only when the patient is confined to bed. Slight exercise readily quickens the pulse reduced by digitalis. That digitalis can slow the movements of a healthy heart to a considerable extent there is no doubt, but just to what extent it can do this, short of too high doses, I am not able to tell you. Some people's pulses are much easier reduced than those of others. The pulse of the feeble is much more easily reduced than the pulse of the robust. It has very little power in reducing the pulse of fever. If the temperature is high it practically may be said to have no influence at all. The reason of this will be referred to presently, when I come to discuss through what mechanisms it produces its different effects on the circulation. If the dose of digitalis be

still increased, the vigour of the contractions becomes still greater and the slowing more decided until finally the ventricles come to a standstill in contraction.

A state of tetanus of the cardiac muscle is induced ; this is quite different from the effects of aconite which also slows the heart, and finally brings it to a standstill in dilatation. No better method can be employed to demonstrate the action of digitalis on the heart than to take a frog and bring its heart to a standstill in dilatation by injecting aconite. When this has happened, if we inject digitalis the distended ventricle slowly recovers itself, and soon returns to its normal condition. If we still continue injecting digitalis the systole becomes longer and the diastole less complete, especially at the apex which remains white and firmly contracted. This gradually extends over the whole ventricle, the heart finally comes to a standstill in firm contraction.

When either digitalis or aconite are given in such doses as to produce standstill of the heart, the pulse becomes quick and the blood pressure falls.

"In aconite poisoning the aortic pressure falls because the over distended ventricle is unable to contract upon its contents. Each contraction only sends a small quantity of blood from the upper portion of the ventricle. In digitalis poisoning the aortic pressure falls, because the over-contracted ventricle permits but little blood to get into it and can consequently send but little forward. The result is similar in both cases, but the cause in one case is just the reverse of that in the other."—Balfour.

The action of digitalis on the circulation in full medicinal doses may be summarized as follows :—

1. It makes the ventricles beat more powerfully.
2. It makes them beat slower.
3. It contracts the arterioles.
4. It raises the blood pressure.

These effects take place even after the vagi are divided and the spinal cord destroyed. It therefore follows that they are due (necessarily for the most part) to a direct action on the structures of the heart itself and on the vessels. This is further

confirmed by the fact that when digitalis is directly applied to the isolated frog's heart it slows and renders its movements more powerful.

The increased vigour of the contraction is due to a stimulation of the intra-cardiac motor ganglia, while the slowing is principally brought about by stimulation of the peripheral terminations of the vagus in the heart. Digitalis also has a stimulating action on the vagus centre in the medulla.

Dr. Lauder Brunton has quite recently shown that the reason the pulse of fever is not slowed by this drug is that the increased temperature has a paralyzing effect on the inhibitory influence of the vagus on the heart. The cause of the contractions of the arterioles has been a very much disputed point, and even yet it is not definitely settled. Some maintain that it is owing to stimulation of the central vaso-motor centre or centres, while others ascribe it wholly to a stimulation of the vaso-motor fibres in the blood vessels. That the latter is a factor in the production of the contraction there appears to be no doubt, but that the former is the principal agent in the causation seems very probable.

It follows as a result of the increased contractions and the marked resistance to the blood stream by the contracted arterioles, that the aortic pressure is increased.

The quickening of the pulse brought about by poisonous doses of digitalis is due to paralysis of the inhibitory fibres of the vagus and the final fall in the blood pressure is due to the arteries being imperfectly filled, owing to the contracted state of the heart allowing but little blood to get into it.

Action on the Temperature.—It is generally admitted that digitalis has some influence in reducing a febrile temperature. It has been experimentally shown by Ackermann, that after it raises the pressure in the arteries, it lowers the temperature in the vena cava, and at the same time raises the temperature of the external parts. It diminishes the internal temperature, and increases the external or surface temperature. It is only antipyretic from its action on the circulation. It is not antipyretic in the same sense that quinine and salicylic acid are antipyretics.

Action on the Nervous System.—Any effect produced by digitalis on the nervous system is indirectly brought about by its influence on the circulation. From full medicinal doses it is not uncommon to hear patients complain of headache, a band like feeling around the forehead, dizziness and also of colored vision, together with a sense of faintness, nausea or even actual sickness.

Action on the Secretion of Urine.—Digitalis has very little influence in increasing the quantity of urine in health, but in cardiac disease attended with dropsy, where there is a diminished outflow owing to the failing heart, it then acts powerfully as a diuretic. The diuretic power is solely due to its influence on the blood pressure. In order to bring about the full diuretic effects of digitalis it is necessary to give it in full doses. The effect of small and even of moderate doses is to increase the general blood pressure, including the pressure in the arterioles of the kidneys. While the general pressure is increased the quantity of urine is not increased. After, however, a certain quantity of digitalis has been introduced into the blood, the pressure in the arterioles of the kidneys gives away with the result of a rapid and great increase in the quantity of urine. This may last for several days, depending on the amount administered. If the drug is still continued, the fall in pressure which commenced in the arterioles of the kidney, extends throughout the whole arterial system with the result of a marked decrease in the secretion of urine.

It follows from this that there are three stages in the action of digitalis on the arterioles of the kidneys, and each separate action is attended by a difference in the amount of urine secreted.

1. From the action of small doses (tonic) we have a general increase of the arterial pressure. This stage is not attended by an increase in the quantity of urine.

2. From the effects of large medicinal doses when continued for two or three days, we have a fall in the arterial pressure in the kidneys, while the increased pressure throughout the rest of the arterial system remains. The result of this action is a great increase in the quantity of urine.

3. When the drug is pushed until the fall in the arterial pressure which commenced in the kidney arterioles has extended so to take in the whole of the arterial system, there is a marked decrease in the quantity of urine.

Uses.—The great use of digitalis is in cases of heart failure, especially in cases of heart failure occurring as the result of organic changes in the valves of the heart. It is also useful before actual or pronounced failure has set in. If given in proper doses it is able to delay, often for a long period, the appearance of failure.

It makes but little difference what particular orifice may be narrowed or leaking, whether it is the mitral or aortic, digitalis is indicated. It certainly is more efficacious in some conditions than others, but in a general way the truth of the statement that it is indicated in all forms of heart failure is practically correct.

To have clear ideas as to what digitalis can do in restoring a failing heart it is necessary that you should understand what cardiac failure means, and how it is brought about as the result of a valvular lesion.

I have here the heart of a man, who died a few days ago from the effects produced by incompetence of his aortic valves. Through the kindness of Dr. R. L. Macdonnell he has been under my care at the University Dispensary for the diseases of the nervous system for the past seven months. During this time I had repeated opportunities of observing the marked relief that he obtained from digitalis. I will first point out the differences between this heart and a normal heart, and afterwards show how these differences came about, and finally I will refer to the influence digitalis has in preventing and relieving such changes, and what particular influence it had in relieving the symptoms and delaying the end of the case under consideration. By adopting this method I think I can make the actions and uses of digitalis plain to you.

The man at the time of his death was 35 years of age. Since his fifteenth year he had five distinct attacks of acute rheumatism. He distinctly remembers that his "heart was affected"

during the first seizure, but it never gave him any trouble until four years ago. This was shortly after his fifth and last attack. We have here a period of twenty years during which he undoubtedly had a heart lesion, but it is only during the past four years that he suffered from the effects of this lesion. The compensation during the first sixteen years of the life of the diseased heart was so perfect that it gave rise to no marked symptoms. Four years ago, however, this compensation began to fail, and we have from this time onwards a history of all that results from such failure.

You see that the aortic valves are badly deformed and their surfaces studded with a great number of vegetations.* You can readily understand how incompetent these valves were during life to fulfill their functions of closing the aortic orifice. On further examining the heart we find it greatly enlarged, and that this enlargement is due for the most part to hypertrophy of the muscular fibres of the left ventricle. In addition to an increase in the thickness of the ventricular walls, we have also a great increase in the size of its cavity. The left ventricle is both hypertrophied and dilated. For our purposes there is no need of noticing any further changes, with the exception of dilatation of the mitral valve, present in this heart. I will now endeavour to explain how these different pathological conditions were induced.

The thickening, the vegetations and the deformity of the aortic valves were caused by rheumatic inflammation of their structures during the first and probably also during the subsequent attacks of acute rheumatism. As a result of the incompetency of the valves, the left ventricle received during its dilatation blood from two sources, in place of from one—from the aorta as well as from the left auricle. The result was an over-filling of the ventricle. The immediate result of the over filling was dilatation of the ventricular cavity. This dilatation, however, could only for a very short time relieve the altered conditions. If it were all that had taken place the man would not have lived

*About a year ago he was suddenly seized with left hemiplegia, due as was proved at the post-mortem by Dr. Sutherland to plugging of his right middle cerebral artery by an embolus carried from his warty aortic valves.

at the longest more than a few weeks. What did take place was an hypertrophy of the muscular fibres of the left ventricle, and it was this increased power of the ventricular muscle that enabled the circulation to be carried on in spite of the leaking valves. The causes of the three prominent changes in the heart are plain. They may be thus summarized: 1st. The valvular distortion, &c., is the result of the rheumatic inflammation of the endocardium. 2nd. The dilatation of the ventricle is owing to it receiving an undue supply of blood into its cavity. 3rd. The hypertrophy is the result of the increased efforts made by the heart to overcome the dilating powers of the column of blood. We have finally to enquire, what brought about the cardiac failure in this heart? Why did the hypertrophied ventricle fail at last to propel the blood forward? In all cases like the one we are considering there arrives a time when the heart is no longer able to do its work. A very frequent reason of this failure is a degeneration of the muscular structure as a result of the long continued over-work, or it may be brought about acutely as the result of a severe illness, especially when attended by a high temperature. In the heart before us, the prominent factor in bringing about failure was not degeneration of its muscular structure, for on closely examining it you will find its walls firm, and not, at least to the naked eye, the seat of advanced fatty degeneration. The main factor in the production of the failure was a purely physical one. In cases of aortic incompetency dilatation is ever slightly in advance of hypertrophy. Compensation is never so perfect that a little blood does not regurgitate, and as there is necessarily a limit to hypertrophy, so there necessarily arrives a time when further hypertrophy is not possible. The result is that heart failure sets in. There are two periods in the life history of a diseased heart such as this where digitalis would be useful. The same is true of any valvular lesion, but it is especially true of mitral valve lesions.

Digitalis is useful during the period of compensation, but it is especially useful after compensation has failed. It is very exceptional to find a case of any valvular lesion where the

compensation is so perfect that it would not be benefited by digitalis. During the compensation period it should be given only in tonic doses, that is in quantities just sufficient to slightly increase the vigour of the ventricular contractions, but not large enough to slow the pulse. Given in tonic doses it aids the ventricle in better overcoming the ever acting dilating force of the column of blood. It therefore delays the inevitable cardiac failure.

The other period where digitalis is of use, is when compensation fails—when cardiac failure has set in. The contractile power of the heart is diminished, and when extreme only the upper portion of the ventricle empties itself, just barely enough blood is poured out to sustain life.

The first effect of heart failure is diminution in the aortic pressure, and this at once shows itself in diminution in the amount of urine excreted.

When compensation fails it may be restored by the judicious use of digitalis so completely that it will last for several years.

In cases of aortic incompetency, what we want to produce when compensation fails or is about failing, is sufficient contraction of the ventricle to overcome the dilating powers of the column of blood, and this we can accomplish if the case is not too far advanced. To effect this, however, it is necessary to give the drug in what is called cumulative doses. By this is meant the administration of a second dose before the effects of the first have passed away, and continuing the administration in this way until certain definite effects are brought about. Nothing but the greatest good can arise from the use of digitalis in such quantities, provided its actions are closely watched, and its administration suspended when the symptoms presently to be described make their appearance.

Many practitioners dread giving digitalis in full medicinal doses. The idea is not uncommon, that it may act in an explosive sort of way and bring about that which it is intended to combat. Now, there is nothing whatever of the mysterious in its actions. When given in a scientific manner its actions can be foretold with a certainty, not excelled by that of any medi-

cinal agent. If there are some practitioners who have a dread of this drug, there are on the other hand others who have not a sufficient fear of it. Any one who has witnessed the reckless way in which it is sometimes given to advanced cardiac cases, must be convinced that not all cases of cardiac diseases die from the effects of their disease, but that some deaths are indirectly, if not directly, due to the too lavish or too long continued use of this agent. The mistakes of the unscientific physician are hidden even from himself in these cases.

So long as digitalis increases the quantity of urine it is quite safe to proceed with its administration, but when the amount commences rapidly to diminish then it is a sign that the increased blood pressure is giving place to a diminished pressure and that the saturation point has been reached. If in spite of this warning the drug be continued, the quantity of urine will still continue to decrease, until finally it becomes almost completely arrested. The pulse from being slow becomes weak, frequent and irregular, and the heart sounds are reduced to a "toneless tic-tac." When the condition of things just described has been reached, you can readily understand that a few more doses are all that is necessary to bring the heart to a standstill.

Digitalis should never be pushed to the extent of quickening the pulse after it has considerably slowed it. A preternatural slowing of the pulse should be as much a warning of saturation as the diminished quantity of urine. The occurrence of nausea or vomiting after the physiological effects are induced should also be taken as a symptom denoting that the safe saturation dose has been reached.

A diminution in the quantity of urine excreted, an unusual slowing of the pulse and the occurrence of nausea or vomiting, are then the symptoms that indicate that the point has been reached, past which it is not safe to go. Up to the production of these symptoms, nothing but good is obtainable. The first symptom usually of saturation is the slowing of the pulse, and it may be even twenty-four or forty-eight hours after the drug is stopped before its diuretic effects are manifested. It may

take four or even five days to bring this about. It is, however, more common to find that the urine commences to increase in quantity during the third day. The duration of the diuresis depends solely on the dose.

The changes for the better that are effected by digitalis in persons with irretrievably damaged hearts is very striking. The urine from being scanty and high coloured becomes copious and pale. The dropsy disappears. The breathing becomes easier. The pulse from being weak, frequent and irregular becomes strong, slow and regular. These marked results are, however, only obtainable from the use of cumulative doses.

Now as to the quantity of digitalis necessary to bring about saturation. You should always remember that different persons vary considerably in their susceptibility to its action. Forty minims four times daily for a period of three days will, in the majority of cases of heart failure from valvular disease in adults bring about one or more of the saturation symptoms. That is, a quantity slightly short of an ounce of the tincture will, in divided doses, bring about saturation in three days. In exceptional cases it is necessary to give even larger doses before the desired result is obtainable. One drachm of the tincture four or even six times in the twenty-four hours may be necessary.

Tonic doses should, on the other hand, not exceed twenty minims of the tincture in the twenty-four hours. When these quantities are given the only noticeable effect is a slight increase in the vigour of the heart's contractions together with an appreciable rise in the aortic pressure.

I will now give a brief account of what digitalis did for the man whose heart you have been examining. When he came under observation seven months ago he was suffering from the symptoms of pronounced heart failure. He was dropsical, short of breath and passed but a small quantity of urine. His pulse was very rapid and low in tension. He was troubled with a profuse serous diarrhoea, and his stomach was in a catarrhal condition. Without confinement to bed, twenty minims of the tincture of digitalis four times daily for four days, caused a marked increase in the secretion of urine, with the subsequent

disappearance of the dropsy. He was able to breath much easier. His diarrhoea was arrested and his appetite greatly improved. He expressed himself as feeling greatly relieved, and compared to his former distressing condition he was comfortable. He continued in this amended condition for four or five weeks, all the while taking digitalis but only in tonic doses. The ever progressive heart failure even in spite of the support from the digitalis, shewed itself again, but on this occasion in a much more pronounced form. As before it was attended by the usual symptoms, but on this occasion they were present in an aggravated degree. They indicated such a very serious rupture of the compensation that death appeared to be imminent. Rest in the recumbent position, and the tincture of digitalis in doses of two drachms daily for four days made another marvellous change for the better in his condition. The dropsy again rapidly diminished, but never entirely disappeared. His breathing became much easier and his pulse fuller. So much did he improve that he was once more able to go about. The improvement did not on this occasion last more than two weeks. Once more all the symptoms of advanced cardiac failure made their appearance. He was now removed to the General Hospital, where he remained until his death, which occurred a few days after his admission. The immediate cause of death was an "infective" endocarditis. Even after his admission into the hospital he experienced relief from digitalis, ordered him by Dr. Ross, the attending physician.

I think I have laid before you evidence enough to prove the inestimable value of digitalis in cardiac therapeutics. It is not alone the power it has of prolonging life that should make us prize it highly, but also its marked efficacy in relieving some of the most distressing symptoms that can afflict humanity. The present knowledge that we possess of the actions of digitalis was only acquired by slow degrees. Its scientific application in the treatment of heart failure was not understood until the pharmacology of the drug had been worked out by experiments on the lower animals. If vivisection had done nothing more than give us digitalis, it could be truly said of it that it had

accomplished a great deal. We are principally indebted for our present knowledge of the actions of this drug to Traube and Schmiedeberg of Germany, G. W. Balfour of Edinburgh, and Lauder Brunton of London. Brunton's and Balfour's names deserve especially to be remembered, the former for the elaborate and painstaking experiments by means of which he demonstrated its true physiological actions, the latter for showing us how to use it to the best advantage in cases of cardiac failure.

Mode of Administration.—In prescribing the tincture of digitalis it is as a rule better to give it alone. Its combination with an iron preparation forms not only an unsightly looking mixture, but it is much more apt to disagree with the stomach than when given alone. If, therefore, iron is indicated in a cardiac case, and it frequently is, it is advisable not to combine it with digitalis, but to order it in a separate mixture.

Powdered digitalis can be prescribed in the pilular form. There is a famous combination known as Baly's pill, which is much relied upon by many physicians to remove a dropsy. The following is the composition of this pill:—

R Pulv. Digitalis
Pulv. Scillae
Pil. Hydrarg $\bar{a}\bar{a}$ gr. i.

S. One pill two or three times daily.

The use of the so-called active principle, Nativelle's or Quévenne's digitaline, is not to be recommended when we wish to bring about saturation symptoms, on account of the uncertainty of its action. It, however, can be employed with safety to produce the tonic effects of the drug.

