Foxgloves in Medicine

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Written in collaboration with the scientific staff of The Wellcome Research Laboratories, with assistance and clinical advice from Dr A Hollman, University College Hospital London; the National Heart Hospital and Units of The Wellcome Foundation Ltd.

Passages from *An Account of the Foxglove* by William Withering are quoted. Animated diagrams of the beating heart are based in *Electrocardiography* by Dr LN Katz.

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<**Opening credits**>

<**Carleton Hobbs narrates over moving images of fields of foxgloves, images of authors and facsimiles of their publications**>

The foxglove is a plant sufficiently common in this island and the route, the stem, the leaves and the flowers have a bitter herbaceous taste. The numerous purple blossoms hanging down, mottled within, as wide and nearly half as long as the finger

of a common-sized glove, are sufficient marks whereby the most ignorant may distinguish this from every other British plant.

Fuchsius in 1543 is the first author who notices it. He gave it its name of digitalis and used it to purge sharp and sour humours from the lungs and chest, that is for tuberculosis. Fifty years later, Gerard, the Elizabethan herbalist, mentions it as an expectorant and emetic, and in 1640 Parkinson records: “it is effectual against the falling sickness.” But in the 18th century, whatever the learned might say, foxglove tea was known to the country folk of Shropshire and Yorkshire as a cure for the dropsy.

And so the physician William Withering in 1775 began a clinical investigation. Ten years later he published his results. “I soon found” he says, “that the foxglove is a very powerful diuretic of advantage in every species of dropsy except the encysted, and that it has a power over the motion of the heart to a degree yet unobserved in any other medicine, and that this power may be converted to salutary ends.” Here was the first hint of its cardiac action.

<**Hobbs narrates over shots of ink polygraph machine and readings, and clinical signs of heart failure in patients**>

After Withering it was Mackenzie in the 1890s who did most to advance our knowledge of digitalis, for he introduced new methods of analysing the rhythm of the heart. Here is his famous ink polygraph, the instrument which he devised so that he could record simultaneously the venous and arterial pulses for minutes at a time if need be. This is not Mackenzie’s original instrument, but one which was later modified by Lewis. At the top are time markings of one fifth of a second, then the jugular venous pulse and below it the brachial arterial pulse. These are normal recordings. Compare them with the tracings obtained from a patient with auricular fibrillation, with its continuously irregular pulse. Mackenzie concluded that this type of irregular pulse was always associated with paralysis of the auricles, for no auricular wave was present in the venous tracings and he found that digitalis was particularly effective in cardiac failure associated with this condition.

The cyanosis and the distended vein in the neck are outward signs of cardiac failure. Note also the irregular pulsation. And since Mackenzie's time, digitalis has also been found to give excellent results in cardiac failure with systemic congestion and normal rhythm and rate.

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<**Hobbs narrates over animated chemical diagrams, then shots of *Digitalis lanata* plant**>

While all these discoveries were being made, the chemists had been examining the active principles in the leaf. In 1869 they isolated crystalline digitoxin and showed that it had similar medicinal properties. It is a glycoside containing 3 molecules of a sugar called digitoxode, combined with a genin. The gene has a steroid nucleus, like the sex hormones in cortisone, and it is responsible for the cardiac activity. But the sugar carries it to the site of action and enhances its activity more than tenfold. A similar glycoside was discovered in 1928 and called gitoxin. Unlike digitoxin it is too insoluble to be of clinical use.

Then it was reported that the leaf of *Digitalis lanata* had as much as 4 times the activity of standard digitalis. This plant, called lanata because of the woolly hairs which cover it, is found growing wild in the valley of the Danube.

<**Hobbs narrates over exterior shots of Wellcome chemical works and then various activities inside the labs to refine lanata leaves**>

In 1929 some of the dried leaves were brought to the laboratories of the Wellcome Chemical Works. Here, much work had already been done on the purple foxglove. Methods of extracting and purifying the glycoside had been worked out and these same methods were now applied to the lanata leaves. The first step was to extract all the glycosides present so the leaves were finely ground and after maceration with alcohol they were put into a percolator. Then alcohol was allowed to seep slowly

through overnight and at the bottom of the percolator a thick, dark liquid was collected. It was purified, extracted with chloroform and evaporated and so the crude total glycosides were obtained. And then began the tedious process of separation by repeated recrystallisations from different solvents; first from acetone followed by filtration, and boiling the solid with alcohol and filtering again to obtain the first solid fraction, then boiling again to get the second, and so on until the process had been repeated a score of times and more.

They tested each reaction first by the Keller colour reaction which they knew was red with gitoxin but olive brown with digitoxin. And they examined it under polarised light, for both gitoxin and digitoxin are optically active. Then they sorted the fractions according to their properties. Gitoxin was there and so was digitoxin. But they found that there was also a third substance, a substance which had a positive optical rotation like gitoxin but which yet gave the same colour reaction as digitoxin. In those fractions, tiny canoe-shaped crystals were found, quite different from any they had seen before. And with further purification, these chains turned to beautiful five-sided plates.

<**Hobbs narrates over chemical diagram, digoxin product, field of *Digitalis lanata* growing, production and testing of finished digoxin product**>

They had found a new crystalline glycoside, similar to the others in its structure, and they named it digoxin.

This new substance was found to have the same general properties as the standard leaf preparations. It was admitted to the British and United States Pharmacopoeia after extensive pharmacological and clinical trials. Large-scale production began in 1934, and here is a field of *Digitalis lanata* at Beckenham in Kent. The plant is a biennial but the leaves are cut at the end of the first year's growth for the digoxin content is about as high then as it will ever be. Flowers normally come only in the second year but a number of these plants have bolted and flowered before their time. Cutting is usually left until late September, after which the leaves are dried and stored.

The digoxin is later extracted by a process which is essentially the same as the laboratory method we have already seen. In the final stage, pure digoxin is recrystallised from dilute alcohol and spread out to dry. From something like 6 tons of dried leaves come these few kilograms of pure digoxin, but enough nevertheless for about 16,000,000 doses. Finally, the digoxin is made ready for clinical use. As it may be given intravenously in emergency, it is prepared as a sterile alcoholic solution for injection; each ampoule containing half a milligram in solution. And for oral use, in tabloid form – a quarter of a milligram to each product. Digoxin is so well defined both chemically and physically that bile assay is not necessary as it is for the whole leaf preparations. But other routine tests are made to ensure the purity of each batch.

In the works laboratories the sample is chemically assayed using a colourimetric method, and its specific optical rotation is also determined. This must be 13.3 to 13.9 in penidine, using the mercury green line. In these and in other respects, the product conforms to the standard of purity laid down in the pharmacopoeias.

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<Intertitle: Pharmacology and Clinical Use>

<Hobbs narrates over animated illustration of heart>

It has been known for many years now that the glycosides have a selective action on heart muscle. They effect both its powers of contraction and also its conducting mechanism. Normally the heart beat starts in the right auricle at the sino-auricular node, and an excitation wave spreads out over the auricles to the auricular-ventricular node. Then, down the bundle of His, the specialised conducting tissue in the septum between the right and left ventricles, and over the ventricles. The contraction follows in its wake. The glycosides increase the force of contraction and in parallel with this, the rate of conduction down the bundle is slowed.

<**Hobbs narrates over laboratory demonstrations and diagrams showing the effect of digoxin on rabbit hearts** >

These effects may be demonstrated in the laboratory. This rabbit heart is set up in a warm chamber and the coronary vessels are perfused with Locke's solution. The action of the auricles cannot be very easily seen in this preparation for they are empty. But the ventricles are contracting well and the beats are recorded.

The perfusing solution is now changed for a similar one containing a small amount of digoxin. After a few minutes the contractions can be seen to be increasing in size, and they go on increasing until they are about 50% stronger than they were to begin with. But with this type of preparation, the increase might possibly be due to variations in the coronary flow and not to the direct action of the digoxin on the heart muscle. This argument cannot be applied where there is no coronary flow, as in these isolated rabbit auricles. They are beating in Locke's solution with oxygen bubbling through it. A state of artificial failure can be produced by means of chloral hydrate, for this substance causes a decrease in the release of energy from the muscle stores and, more important, it interferes with the conversion of this released energy into work. The chloral hydrate is added, and quite soon the contractions begin to get smaller. Digoxin antagonises this failure. It is added in alcoholic solution. The immediate effect is a further decrease in amplitude due to the alcohol but this is temporary. It can be seen again after a second dose, then the slower stimulating effect of digoxin gradually becomes apparent. Eventually, the contractions are bigger than they were at the beginning of the experiment, due probably to initial inefficiency of the auricular muscle in its artificial surroundings.

At the point marked X the auricles missed 4 beats for no apparent reason. It is inferred from this experiment that digoxin has a direct action on heart muscle, and this action is mainly due to improved energy utilisation.

The action is of value in congestive heart failure and in half an hour after intravenous digoxin, the cardiac output will rise by about 1 litre per minute, as in this typical case.

At the same time, the right auricular pressure falls from 15 to 5 cm of saline and the congestion is relieved. And then the rapid pulse comes back to normal or nearly so.

00:14:34:03

<**Hobbs narrates over laboratory demonstrations of the effects of digoxin on a frog heart, then a mammalian heart**>

The slowing of conduction may be observed on a frog heart preparation, and this is the experimental arrangement. But the effects have to be carried to the toxic stage before they can be seen by direct observation. <*Intertitle: Digoxin is given*> Quite soon we notice a greater systolic contraction and now the conduction effects are beginning to show <*Intertitle: Partial block*> with a 2:1 block and also coupling which is not a conduction effect. Look again: 2:1 block, and again coupling. <*Intertitle: Gross slowing*> Now the slowing is very marked indeed and the heart stopped altogether about 6 minutes after the start of the experiment. <*Intertitle: Second frog heart normal action*> A second heart behaves similarly although it is much more vigorous to begin with. The number of drops per beat gives a measure of the output. <*Intertitle: Digoxin is given*> Toxic effects start quite soon and here the output has already dropped quite considerably. Now the rhythm has become disordered and we have 1, 2, 2:1 block; 1, 2, 3, 3:1 block; 1, 2, 3, 3:1; 1, 2, 2:1 block. <*Intertitle: Complete block*> The degree of block subsequently increased until it became complete and the ventricles stopped in diastole. With a slightly higher dose the heart would pass finally into a state of sustained systolic contraction.

The mammalian heart reacts in much the same manner to toxic doses of digoxin, except for the terminal stage which is usually ventricular fibrillation. <*Intertitle: Ventricular fibrillation*> The auricles can be seen to be still beating. A clinical dose of digoxin, however, produces no obvious outward effect on the normal heart. But it can be measured electrically, in this way <*Shows animated diagram of heart*> The excitation wave gives rise to minute changes in electrical potential at different points on the heart. These changes can be detected by an electrocardiograph which records the variations as the wave advances.

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<**Hobbs narrates over patient having electrocardiograph, then analyses the trace and the effects of digoxin on various heart patterns using animated diagrams**>

The activity of the auricles is represented by the P wave, while the Q, R, S and T waves correspond to the contraction of the ventricles. This rate is about one quarter of that of a normal human heart. A clinical dose of digoxin introduces delay of about one tenth of a second as the wave passes from auricles to ventricles. This is not enough to upset the rhythm of the normal heart but it appears on the electrocardiogram as an increase in the PR interval.

A similar dose of digoxin, however, can have a very different effect in cases of auricular fibrillation. For here the beats of the auricles are extremely rapid and irregular. The AV node is bombarded by numerous impulses and the ventricles respond erratically and usually at more than double the normal rate. The electrocardiogram is characteristic and shows the haphazard ventricular beats. There are no P waves but instead rapid, irregular waves caused by fibrillating auricles. The action of digoxin here is twofold: <*Intertitle: Auricular fibrillation after digoxin*> it affects conduction to diminish the response of the AV node so that the ventricles beat more slowly. This effect is initially due to vagal action but is later due to direct action on the heart itself, this allows more time for the ventricles to fill between beats. And, together with the increased force of contraction, this leads to a much improved performance from the heart.

The electrocardiogram now shows the slower ventricular rate and there has also appeared a characteristic depression in the RT segment, due, it is considered, to the direct action of digoxin on the cardiac muscle.

The primary indication for the use of digoxin is congestive heart failure <*Intertitle: Congestive heart failure*> whether the pulse is fast or slow, or the rhythm normal or

abnormal. But especially so if accompanied by irregular fibrillation <*Intertitle: Congestive Auricular fibrillation*> for this itself may be an indication. It is also of value in auricular flutter <*Intertitle: Auricular flutter*> with or without failure, or to prevent recurrent attacks of paroxysmal tachycardia <*Intertitle: Paroxysmal tachycardia*> after other measures have been tried.

<**Hobbs narrates over shots of female patient with congestive heart failure, before and after the administration of digoxin**>

This patient has congestive heart failure resulting from essential hypertension. She is not seriously ill but the usual signs are present. The venous congestion in the neck, and it may be noted that the rhythm is regular and the rate normal. There is well-marked oedema of the legs which pits on pressure, and marked pulmonary congestion.

In such a case, digoxin is given by mouth. Her dose was 1 milligram per day, that is, 4 tablets to begin with. After 4 days her condition had improved. The venous congestion had disappeared, the oedema of the legs had cleared completely and the pulmonary congestion was no longer present. Marked diuresis accompanied the relief of the oedema – the figures on the columns show the urine output in ounces. One ounce being equivalent to 28 millilitres.

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<**Hobbs narrates over animation of words describing symptoms of digoxin overdose, also highlighted on an electrocardiograph tracing**>

The symptoms of overdosage should be remembered for the digitalis glycosides tend to be excreted slowly and doses may be cumulative. This is less likely to happen with digoxin.

The symptoms may be accompanied by such signs as extra systoles which are recorded here on a polygraph tracing. Or coupling of beats, or extreme slowing below 60.

<**Hobbs narrates over shots of female patient with severe congestive heart failure, before and during the administration of digoxin**>

Severe congestive heart failure requires more rapid digitalisation. This patient has considerable respiratory distress and is cyanosed. The jugular veins are engorged and the rhythm is irregular from auricular fibrillation. Digoxin is especially suitable in such an emergency for it may be given intravenously. It is first diluted with 10 millilitres of saline and then the injection is given slowly, taking 2 minutes.

<**Hobbs narrates over shots of same female patient a few weeks later as she sits painting a still-life of roses**>

The basic mechanism of the action of the digitalis glycoside is still unknown though it has been suggested that the action is primarily concerned with the surface layer of the cardiac muscle fibre.

<**Hobbs narrates over shots of foxgloves growing**>

But the details are still uncertain and there is material here for further study and research.

<**End credits**>