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ON DIGITALIS: ITS MODE OF ACTION
AND ITS USE.

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IN bringing forward a subject so debated as digitalis and its action, the only apology the writer can offer is, that for years he has studied its effects clinically, having had patients continuously under its use for no less a period than three years and a half uninterruptedly. He has tried to bring to the inquiry a mind free from prejudice on either side, and impressed with the wish to elicit the truth. Physiological experiment has been largely resorted to and carefully observed; and, finally, the writer has carefully striven to give his results honestly, and to record what he thinks digitalis can do, and what it cannot, and, further, why he thinks so. It may be desirable to commence with an account of the different experiments performed, and the results obtained; and all through the inquiry he will regard digitalis as a member of a group of agents, rather than as possessing any qualities which are unique or peculiar to itself.

On Plants.—Marcet and Brunton have separately tried the effects of digitalis on the haricot bean by watering the plant with an infusion, and found it to kill it by withering it up. The writer injected a strong infusion into the hollow stems of the ordinary bean without effect for days; in time, however, those so treated withered and died, contrasting with those not interfered with. Precisely the same results ensued from similar injections into the orange lily. A lettuce was frequently watered, in a dry season too, with a strong solution, without any perceptible injury to it either soon or late. Another was then dug up by the roots, and placed in a large basin containing a strong infusion of foxglove, and for a day or two grew amazingly; on the fourth day, it commenced to wither, and died in a day or two. The first effect of the drug was to improve the appearance of the plants to which it was administered; an impression to the same effect remains in the minds of friends who witnessed the experiments. Strong infusions were injected into the stem of the rasp, and into holes bored into a plum tree without apparent effect.

On Invertebrata.—Snails, when touched with the tincture or strong infusion, took a contrailic spasm, threw off a coating of mucus, and passed on apparently unaffected. Earth-worms, when placed in an infusion for a short time, did not appear incommoded. Wasps were not affected by it when applied to them.

On Fishes.—Minnows, when placed in an infusion of digitalis, a very weak one, for some minutes were not affected; then commenced a rapid movement of the gills, which lasted till death; they were also drawn to one side in dying. After death, the ventricle was found firmly contracted and glistening like a speck of gristle; and, on being examined under the microscope, no cavity was visible. The auricle was distended and vainly tried to drive any blood into the tightly contracted ventricle, the blood merely regurgitating into the venous sinus behind, and then flowing back again, from the venous distension relieving itself on the auricular diastole. On pricking the venous sinus so as to permit the escape of the contaminated blood, the auricle soon also became firmly contracted, and no cavity was perceptible under the microscope. The quickened action of the gills was probably due to the accumulation of carbonic acid in the blood, giving rise to an increased necessity for breathing, while the firmly contracted ventricle prevented the flow of blood to the branchiæ, and cut it off from oxygenation.

On Birds.—About half a drachm of strong infusion of digitalis was passed down the throats of two sparrows, some being spilled during the process. The animals soon became unable to move much, and gasped for breath most vigorously. The hen died first, and the cock died hard in about half an hour. On opening them immediately on death, the left ventricle in each was found firmly contracted; the lungs so congested as almost to be hepatized; the right ventricle full of blood. It was evident that the condition of the lungs and right ventricle was due to inability to drive the blood into the contracted left ventricle. The gorged condition of the lungs accounted for the gasping respiration observed. Side by side with them, ten drops of Fleming's tincture of aconite were administered to a third sparrow, who became convulsed,

and died in about one minute and a half. In it, the lungs were pale, and the heart completely paralysed and distended, looking like a small Barcelona nut. The contrast between the two conditions was marked.

On Mammals.—Experiments have been made on the higher animals by Handfield Jones and Fuller, with similar effects as regards the state of the heart after death.

On Frogs.—These have purposely been put last, on account of the large number of experiments to which they have been subjected by various writers. Frogs have been made much use of by experimenters, on account of their great susceptibility to medicines, and the ease with which experiments could be carried on. Dybkowsky and Pellikan abroad, and Hilton Fagge and Stevenson in England, experimented largely on them, with uniform results as regards the state of contraction of the heart observed. The manner in which the writer experimented was this. The frog having been firmly secured to a piece of lath by a bandage, leaving the chest exposed, the chest was then opened with a pair of scissors up the middle; the heart usually appeared through the incision, and was readily cleared of its pericardium. It thus beat with much regularity, apparently not much affected by temperature or air. It may not be out of place here to state that, when thus exposed, the cardiac contraction was clearly seen to be a swiftly passing peristaltic action, commencing in the auricle (as first described by Schiff and corroborated by Valentin), and passing rapidly on to the ventricle. The complete distension of the auricle stimulated it to contract in the direction towards the ventricle; this action, driving still more blood into the already distended ventricle, produced such distension of it as stimulated it to contraction; after the systole came a period of muscular rest, during which the blood poured from the distended veins into the lax chambers, until the distension of the auricle led to a general systole. Digitalis was then administered by the mouth, or hypodermically, and its effects were quickly apparent. First, the contractions became somewhat quicker, and the contraction more complete; and here it may be stated that, whatever may be the normal state of the human heart in systole, certainly the frog's is not thoroughly emptied, and is still dark coloured from the colour of the contained blood, showing through the transparent walls, which are quite white when thoroughly contracted. Soon the peristaltic action became more marked, the systole being longer and more perfect. Then the distension became less complete, especially at the apex, which remained white and firmly contracted. Here and there were little sections, apparently belonging each to a separate cardiac ganglion, which did not seem affected, and in the general contraction pouched out, contrasting in colour, too, with the other contracted and whiter portions: these are the crimson pouches of Dybkowsky and Pellikan. The action of the ventricle became almost vermicular in its slowness, and the diastole was most imperfect, till the ventricle came ultimately to a standstill in firm contraction, the heart being much diminished in size—and in size, shape, and colour, much resembled an unripe apple-pip. The frogs did not seem much affected otherwise, the poison seeming to be confined, as regarded its action, purely to the heart. If released, they hopped about unconcernedly, nor did the removal of the contracted heart by scissors cause them any apparent inconvenience. They merely seemed to die ultimately from the arrested respiratory changes: a slow mode of death in cold-blooded animals. In accordance with the observations of the above mentioned experiments, my results were uniform as regards the contracted condition of the ventricle. To other frogs were administered belladonna, caffeine, strychnine, and aconite. The first produced rather marked contraction; caffeine somewhat less so. Strychnine produced no perceptible effect, contrary to anticipation. Aconite produced paralysis and arrest of the heart in diastole. A still more interesting series of experiments was performed. To some frogs, digitalis and aconite were administered, side by side, and the opposite actions contrasted. The experiment was then varied; and, after the action of each drug was well established, the other was administered—i.e., after the effects of digitalis were well established, aconite was administered; and to others, after the action of aconite was well brought out, digitalis was given. Over the action of digitalis, aconite certainly had an influence, but it could scarcely be called a marked one, and did not ultimately arrest the contraction produced, even when pushed. On the contrary, the administration of digitalis was followed by the most marked results, when aconite had been given, and the ventricle had become gradually more and more distended, and its contractions more and more imperfect, each contraction merely expelling a small quantity of blood off the top of the distended ventricle, the contractions becoming slower and slower, and less and less perfect, until a condition of advanced dilatation had been artificially produced; and even when the heart seemed to have given up all action, and remained in diastole, distended with blood and inert. When all action had apparently ceased, the first

effect was to produce an imperfect contraction at long intervals; then the intervals became shorter and the contractions more complete, some irregularity both as to time and amount of contraction being observed. Slowly and gradually, however, the distended ventricle recovered itself under the action of digitalis, the contractions being more rhythmical and perfect, and the distension less and less pronounced, until a return to normal contraction and distension was brought about. If the administration of digitalis were then continued, the same appearances were brought out as when no aconite had been previously given. This interesting experiment was frequently performed before other medical observers, and can be readily repeated. In all the experiments the ventricle was the most affected; in the frog, where there is only one ventricle, the auricle could only remain distended behind it, incapable of getting rid of its contents into the firmly contracted ventricle in front, and of course it could not contract unless its contents could be disposed of: if the venous sinuses behind were pricked, as in the case of the minnows, the auricles soon became contracted. As regards the effects upon the rhythm, the general results may be stated broadly thus: at first there were occasional slow beats, interposed without any exact order; and then, as the effect became more marked, the slow beats preponderated, until the contractions were only occasional before complete cessation in systole. During an experiment on a dog by Brunton and Gamgee, a temporary murmur was observed, which they concluded was due, and apparently with good reason, to an irregular action of the musculi papillares, producing imperfect closure of the mitral valve.

In these experiments on the frog, sometimes the tincture of digitalis was used, and at other times the infusion. In some instances, a solution of digitalin was used, but its effect in producing increased contraction was certainly not so marked as when a preparation was used which contained the other principles. It is not intended that this statement should convey the impression that there exists any good reason for supposing that digitalin is not the active principle in digitalis; but such is the writer's experience.

Hilton Fagge and Stevenson found that, sometimes, the ventricle makes only one pulsation for two of the auricle, the number of its contractions being therefore lessened one half (*Transactions of the Royal Society*, May 1865, Conclusion 3). Reid seems to think that sometimes more than one auricular systole is necessary to produce such ventricular distension as would excite contraction. This seems in accordance with reason and fact.

Composition.—The leaves of digitalis have been subjected to repeated chemical examination, chiefly by foreign investigators. It has been found that there are various substances, which can be separated from one another, contained in them. The principal of these is digitaline. Indeed, by some it is considered the active principle; but of this I am not convinced; certainly it did not act on frogs so powerfully as the tincture of the leaves did. It is, however, frequently used. Digitaline is light yellow, inodorous, and crystallises with difficulty, and presents the appearance of very imperfect crystals, if crystals at all, under a pretty high magnifying power ($\times 250$). It does not contain nitrogen, nor does it neutralise acids. It is a principle, not an alkaloid. It is soluble in sulphuric acid, and also in hydrochloric acid. The solution in hydrochloric acid passes from yellow to a fine green. Homolle considered this reaction sufficiently delicate for medico-legal purposes. It is scarcely necessary to state that it is not generally accepted as being so. There are also digitalic acid, digitalin, digitalose, digitalide, of whose qualities we know nothing. There are also tannic acid, sugar, and a substance named pectin, chlorophyll, and woody fibre.

Chemical Characteristics.—A dark precipitate (tanno-gallate of iron—Pereira) is formed on the addition of sesquichloride of iron to the decoction, or to a mixture of the tincture and water. A solution of gelatine causes a scanty precipitate (tannate of gelatine). Tincture of nutgalls merely causes a slight turbidity. There is no reason to suppose that any of the active principles are affected by these combinations; or that the drug is rendered inert by anything that we know. For a fuller account of its principles, the reader, if curious, can consult Pereira, or the thesis of Brunton.

On the Blood.—Magendie and Thackrah thought the addition of a decoction of digitalis interfered with the coagulation of the blood. Davy states that the addition of a large quantity of watery extract to blood gave it the consistence of paste. So far as I know, no English observers have recently noticed anything peculiar in the blood of animals experimented upon. And in the large number of animals experimented on by me, there never was any appearance about the blood which made it different from any other blood. No scientific observations of any kind have yet been instituted as to the action of digitalis or any of its constituents on the blood, such as have been performed by Harley, Bernard, Fraser, and Crum Brown and Broadbent, on some other therapeutic agents, by which their action has been

much elucidated. At this point, it may be desirable, in order to elucidate the subject thoroughly, to take a bird's-eye view of the manner in which the heart's action is maintained: the manner of its disorder, the mode of production of its affections of its vascular walls, and the mode of action of the drug.

The Heart's Mode of Action.—The heart, as has been shown by Pettigrew, consists of several folds of organic fibre-tubing folded on each other; it is thus capable of distension and rhythmical contraction. For this purpose, a singular system of innervation, motor and co-ordinating, is provided. The real motor power of the heart is under the control of minute ganglia, each with a morsel of muscular fibre under its direction, which are alone capable of carrying on the action of the heart, but only in a tumultuous manner, as seen after section of the vagi. As with all other accumulations of organic fibre, the distension by contents leads at length to contraction in a more or less rhythmical manner. The vagus exercises over this a co-ordinating (von Bezold), or even an inhibitory action; i.e., the application of a stimulus, as electricity, for instance, to the vagus, retards the cardiac contractions, and, if the stimulus be powerful enough, arrests the heart's action in diastole. The vagus then normally acts against the first impressions of distension, and only permits contraction when the distension is sufficient to produce uniform contraction, which then goes on in a truly peristaltic manner, but so swiftly as to be easily mistaken for a simultaneous general contraction. Thus, to some extent, distension and the action of the vagus balance each other; any disturbance of that balance, then, would produce irregularity, no matter in what direction the disturbance might lie. There lies, too, in organic muscular fibre, an inherent power of growth to meet demand; thus, if increased strain be thrown upon the heart, increased growth of muscular tissue, in health, takes place, and again the balance is restored between the blood to be driven and the power to drive it. When, however, from any cause, there is a deficiency in the compensatory nutrition, a species of balance is again struck, but of a lower form, by distension of the fibres, or, in other words, dilatation. In fact, there is planted in this comparatively simple cardiac innervation, a more complex one of contraction and reduction of the ventricular cavity on the one hand, and a species of normal distension on the other. These actions are regulated by nerves which have been dissected out in the rabbit, and experimented on by MM. Cyon, Claude Bernard, and others. The one which calls into action an increased action against obstruction is called the *accelerator nerve*; and the other, which admits a normal distension of the walls, is called the *depressor nerve* of the heart. Claude Bernard has even gone so far as to state it as his opinion that, through the action of the latter, a species of distension may so take place in accommodation to existing circumstances as to convert the cardiac chambers into temporary blood-reservoirs. This their construction as organic fibre would permit; for organic fibre permits great distension without abolition of function. Thus, while carrying on the circulation by expelling a quantity only of the contained blood off the top of the ventricle, and permitting a large portion to remain on each systole, this accommodation is allowed without bad results. This is undoubtedly no rare occurrence, if clinical observation were exact enough. Thus, between the ordinary balancing powers of the obstacle of the blood to be driven, and the muscular power to drive it, of the stimulating effects of distension in producing contraction, and the controlling action of the vagus, the heart's action ordinarily rocks; but, in addition to that, there is a more complex system of accommodating distension on the one hand, and an accelerating contracting action against an obstacle on the other: which exercise a regulating power according to special circumstances. Ordinarily, however, the action lies between the first set of nerves, with the driving power, and the work to be done. With their disturbances of balance, we are now more especially engaged.

Distension.—The first action of disturbance of this balance is engorgement or distension. When much blood has been located in the ventricles, and they are not capable of completely emptying themselves, a portion remains at each systole. At each diastole, however, an equal quantity of blood is again thrown into the ventricle, and thus at the next systole a larger quantity remains unexpelled; and this process goes on until death, or until some compensatory relief is attained. This relief is usually attained by congestion of the veins, and the system suffering. This distension or, if chronic, dilatation is produced in many ways, thus:—1. Pouring in of the blood under increased pressure, as in the enlargement of the left ventricle, which follows in time on mitral regurgitation, and increased action of the right ventricle and thickened pulmonary vessels; 2. Muscular failure from defective nutrition, as in fevers, in coronary atheroma, or pericardial adhesion; 3. Obstruction to the flow of blood forwards, as in deposit of fibrine on the semilunar valves, diseased vessels, etc.; 4. Disorder of innervation, as a disturbance of the balance between the sympathetic ganglia and the action of

the vagus; 5. Excessive exertion and consequent cardiac exhaustion; 6. Valvular insufficiency. This condition may pass on to permanent dilatation.

Mode of Repair.—The ordinary modes of repair of this condition are two: first, relief of the condition on which it depends, where practicable; and, second, hypertrophy, when it is due to increased difficulty in the flow forwards, or to valvular insufficiency, by that power of self-increase which is allowed to all muscular fibre, but with which organic muscular fibre is endowed *par excellence*. Restoration of the balance may take place in three modes, of higher and lower grades: 1. The highest, restoration of the cavity to normal size; 2. Hypertrophy, by increase in number of fibres (Forster) and thickening of existing fibres (Bamberger and Rokitsky)—a compromise; 3. Dilatation, a permanent distension—the lowest restoration of balance, and entailing diminished vital capacity to a point proportioned to the heart's lowered power.

The signs of this disturbance of balance, or partial asthenia, are three—palpitation, irregularity, intermittency.

1. *Palpitation.*—The first evidence of failure of power is palpitation. It is undistinguishable from increased action, except in deficiency of results. When there is excited action, as in exertion or excitement, it is perceptible in the bounding pulse, or, with the sphygmograph, in the increased apex-beat. Palpitation is not so accompanied; and though to auscultation and percussion the heart-stroke may appear identical, it is in the results the real difference lies. Palpitation is a laborious heart-stroke, but not a stronger one. It is the evidence of effort, not of capacity. It is barren in result—a laborious stroke in place of a normal one, but not of more effect, not always of so much. It is intimately associated and commonly mixed up with the next form—irregularity. Palpitation may be engrafted on symptoms of chronic insufficiency as a temporary condition; as, for instance, in the palpitation of Bright's disease, or of slight exertion in a dilated heart from valvular insufficiency. Palpitation is a violent effort of the heart-walls to overcome the action of the vagus, *plus* the obstructed flow.

2. *Irregularity.*—Irregularity of the bulk of blood transmitted into the arteries is one thing, and is due to auriculo-ventricular incompetence. Irregularity in time is another. The latter is under consideration here. Irregularity of rhythm is not due to disordered innervation, but to obvious debility. It is an arrest in the commencement of the peristaltic contraction or heart-stroke. The controlling action of the vagus arrests the contraction until such time as the layers of fibres acting early on the systole ought normally to have acted; and then a sharp, almost simultaneous contraction takes place, with an increased thud against the chest-walls. This action is homologous with the increased action of the muscular fibres, under the control of the cardiac ganglia, when the systole has been retarded by stimulation of the vagus. Sometimes it appears as if the action of these layers, acting early in the systole, had been lost; and there is a perceptible change of action in the heart, as if the contraction were commencing from a new layer or set of fibres. Richardson has compared this to a change in order of a number of strikers on an anvil. It always reminds the writer of a horse changing its feet when cantering. This is a more serious evidence of over-taxation of the heart, and is often found mixed up with palpitation. It is often the result of over-exertion, and affords strong suspicion of ventricular distension. Chronic irregularity may have engrafted upon it a passing palpitation from an intercurrent additional disturbance of balance. Nervous irregularity and palpitation will be considered in a future section.

3. *Intermittency.*—This is sometimes purely nervous, and is inexplicable. When persistent, it is usually associated with an impaired first sound, defective apex-beat, and other signs of degeneration. The occurrence of palpitation during this condition sometimes clouds the diagnosis, and makes it very difficult. Intermittency of ventricular contraction is not identical with intermittency of radial pulse, though related to it. In some cases of intermittency of the radial pulse, if the stethoscope be applied while the pulse is held, a ventricular contraction will be distinguished when there is no evidence in the pulse; but it is a feeble contraction. In other cases, the ventricle does not perceptibly contract. Whether there is a very abortive contraction, or not, is doubtful. Certain it is, that in some cases the ventricular contraction can be detected when too feeble to produce a pulse wave; in other cases, no ventricular contraction can be perceived. Intimately connected with this condition, is true angina pectoris, and, finally, cessation in diastole.

After this brief *resumé*, we can now consider the mode of action of digitalis, in what manner it acts; and from that, again, get an idea of its therapeutical value.

[To be continued.]

CASES OF PLEURITIC EFFUSION MARKED BY VERY FŒTID EXPECTORATION.*

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WHEN we read the descriptions of pleurisy given in our medical textbooks, we cannot well help coming to the conclusion that few diseases ought to be more easy of recognition than pleuritic effusion; and that any one who overlooks an effusion of fluid in the thorax, or who is unable to speak decidedly as to the cause of dulness on percussing the chest, must be quite behind the age in his medical knowledge.

Be this as it may, I expect I do not relate a marvel of medical experience when I say that I have known a case where the treatment of more than one competent man has been energetically directed to the patient's brain for the purpose of arresting convulsions, when after death this organ was found in every respect healthy, while the left side of the thorax was the seat of a well-marked diaphragmatic pleurisy, with copious deposition of lymph and effusion of fluid. This case was related to me by one of the attendants, himself an eye-witness of all the events. Incessant vomiting, followed by convulsions, drew all attention to the brain, and the chest was, it appears, entirely forgotten.

I have, doubtless like many others, been asked to see a case of continued fever, when an examination of the thorax has disclosed the novel fact of one side being dull as a brick from top to bottom. No complaint of pain in the side or of cough had ever been made, hence it had not been deemed necessary to examine the thorax.

In hospital out-patient practice, and in other than hospital practice, too, it is not rare to meet with patients who describe their symptoms in such a way as to lead us not to wonder when they tell us they have been told "it is all stomach" or "all liver", and yet examination shows us a thorax containing more or less of fluid effusion.

These matters teach us the importance of carefully examining every patient who may come under notice, and of not forgetting the precept of the late Matthew Baillie, that the physician, in his examination, should seek to turn his patient inside out before him.

Though ordinary painstaking care will do much to guard us against serious errors in the diagnosis of pleurisy with effusion, still there are forms of pleuritic effusion that come on so gradually and so imperceptibly, presenting also—prominently often—symptoms that we are accustomed to connect with other known forms of chronic pulmonary disease, that the correct diagnosis becomes a matter of peculiar difficulty.

The three cases of pleuritic effusion that I have made the subject of this paper, presented other than the ordinary signs of pleuritis, and hence seem worthy of notice.

In all the cases, the most marked and prominent symptom was extreme fœtor in the expectoration. When the patient makes this his great cause of distress and complaint, the first thought of the physician may tend to old-standing bronchitis with dilated sacculated bronchial tubes, or to chronic phthisis with old cavities and more or less fibrosis, or fibrification, of the surrounding lung-tissue. In the following cases, none of these explanations could be assumed as correct.

CASE I.—Mrs. S., aged about 40, was seen with the late Dr. Cregeen of Rotherhithe on May 11th, 1867. She had been ill five weeks with pain in the right side and cough. Lately this cough had increased, and been attended with some rusty-coloured, very offensive, expectoration. The right side below was dull, and at some parts a distinct rubbing sound was heard; very little respiratory sound was heard. The pulse was 80; the skin was not hot; debility was great. Considering the duration of the illness, and the recent occurrence of the fœtid sanious expectoration, I thought that there must be a subpleural abscess; and I told Dr. Cregeen that we might have hæmoptysis, pneumothorax, or both, as possible events of the future. On May 19th, the patient seemed dying, in a state of collapse, with shivering, profuse sweating, and finally very copious purulent expectoration. On May 21st, I saw her for the second time. She was better; pulse 88. The right side was dull; there was an ægophonic twang in the voice; a friction-sound was audible; there was no blood in the sputa. She gradually recovered. On May 7th, 1868, I examined the chest, and all that I noted was some impaired resonance on the right side and bronchial breathing. The treatment consisted of bark, with sulphuric acid and free nourishment. Carbolic acid made her faint, and she would not continue it.

CASE II.—The notes of this case are fragmentary. The patient was a man in the Victoria Park Hospital, with much cough and expectora-

* An abstract of this paper was read before the Medical Society of London; and, in compliance with the expressed wish of the President, I here publish the paper in a more ample form.—J. C. T.