THE GOULSTONIAN LECTURES

ON

PHARMACOLOGY AND ITS RELATION TO THERAPEUTICS.

Delivered at the Royal College of Physicians, London.

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LECTURE II.—*Concluded.*

As a third example of pharmacological investigation, I shall take casca bark, which I have lately been examining with Mr. Pye; and I choose this because it illustrates various methods of examining the action of a drug on the different organs of the body. The methods we employed were not new. I could have found a better investigation of the action of a poison upon the heart and circulation in Von Bezold's admirable work on *Atropia*, of action upon muscles in his examination of veratria, of action upon the stomach in Giannuzzi's investigation of tartar-emetic, and of action upon the kidneys in Ustimovitch's research on urea and potash. In none of these works should I have found all the methods combined. I have selected this drug, moreover, because I believe it to be deserving of attention, and likely to prove of great use in practical medicine. This bark is used as an ordeal poison along the greater part of the coast line of Western Africa, with the exception of Old Calabar. In different districts, it bears the names of "doom", "gedu", "sassy", "saucy", "cassa", and "casca". It is obtained from the *Erythrophloeum Guineense*, which, like the Calabar bean, belongs to the natural order Leguminosæ.

There are two ways in which it is employed by the natives. One is to make the suspected person fast for several hours, and then to give him a few grains of rice and some infusion of the bark. If he vomit all the grains of rice and be not purged, he is said to be innocent. If he be purged, he is pronounced guilty. The other way is to bend several boughs of trees, and stick both ends into the ground, so as to form a long archway, through which the accused walks in a stooping position, after a dose of the infusion has been administered. If he be able to walk through without stumbling, he is considered to be innocent. If he stumble, he is said to be guilty, and at once despatched. The chief effects of the poison, by which the innocence or guilt of the accused is decided, are thus, vomiting, purging, and loss of muscular power or co-ordination.

Some of this bark having been brought from Angola by Mr. Monteiro, I made a few experiments on its action, the results of which he published in his work. These experiments showed that the poison acted upon the heart in much the same way as digitalis; but other engagements prevented me from making at the time an exhaustive investigation. The experiments of others have shown that vomiting and purging may be due either to local action of an irritant substance upon the mucous membrane of the stomach and intestine, or to its effect upon the nervous system regulating the secretion and movements of these organs. In order to ascertain in what manner the casca produced these effects upon the intestinal canal, a quantity of infusion was administered to an animal. Vomiting and purging both took place, just as in the case of the persons subjected to the "ordeal". When the infusion was injected under the skin, or into a serous cavity, equally violent vomiting occurred, but there was no purging. It was, therefore, clear that the purging was due to the local action of the poison upon the intestine, but that the vomiting was caused through the medium of the circulation. The poison, however, is conveyed by the blood to the stomach itself, as well as to the central nervous system. Its effects might, therefore, be produced by irritation of the walls of the stomach, as well as by means of its action on the nervous centres. The connection between the stomach and the nervous centre is kept up chiefly, if not entirely, through the vagi and the splanchnics. If these nerves were divided, a poison, which acted by irritation of the stomach, ought no longer to be capable of producing its usual effect. The vagi were, therefore, divided before the injection of the poison, and then we often found that vomiting or retching either did not occur, or was much less violent than usual. The purging might be due either to increased secretion or increased peristaltic action. If it had been caused by the

former, a quantity of the drug, introduced into an empty loop of intestine, isolated from the rest by two ligatures, ought to have caused a secretion of fluid, as Moreau has shown to result from other purgatives, such as sulphate of magnesia. This, however, was not the case; and we, therefore, concluded that the purgative action was due to increased peristaltic of the bowel.

The second symptom, regarded as a proof of guilt in those subjected to the "ordeal", is want of power to walk properly; those who stumble before they reach the end of the archway of boughs being at once executed. In attempting to ascertain the cause of this loss of power, we excluded the muscles and motor nerves, as we found that neither of them lost their irritability when the poison was applied to them in the same manner as curare in Bernard's experiments. The spinal cord was the next point of the nervous system to which we directed our attention. We noticed that, some time after an injection of casca under the skin of a frog, the movements of the animal became sluggish and were imperfectly performed. When the toes were pinched, the foot either moved lazily or not at all, instead of being promptly drawn up. The reflex activity of the cord was thus seen to be impaired. It would not be wise, however, to conclude hastily that this impairment was due to the effect of the drug upon the nervous tissue itself; for imperfect circulation through the brain and spinal cord quickly deprives these organs of their power. Although arrest of the circulation does not abolish the functions of nervous centres so quickly in the frog as in warm-blooded animals, it nevertheless does so after a time. The effect of the casca upon the cord might, therefore, be due to its action, not upon the nervous tissues, but upon the circulation. On examining the heart of the frog after the drug had begun to act, it was found that its pulsations had ceased. It seemed, therefore, quite possible that loss of power in the spinal cord was due to an arrest of the circulation; but, of course, this was only a hypothesis, as the casca might act both on the heart and the cord itself. To decide this point, we administered casca to one frog, and waited until the heart had stopped. The instant it had done so, we arrested the circulation in another frog, of a similar size, by a ligature drawn round the large vessels close to the heart. The circulation was thus arrested equally and simultaneously in both animals. In one of them, the poison had been previously carried by the blood to the spinal cord, and could still act upon it, although circulation had stopped. If the casca had any paralyzing action upon the nervous substance of the cord, reflex action ought to cease in the poisoned frog first. But this was not the case. In both animals, reflex action ceased almost exactly at the same moment. The diminution of power in the spinal cord seemed, consequently, to result from the action of the drug on the circulation. We, therefore, arrived at the conclusion that alterations in the heart's pulsation were the cause of the staggering gait and want of muscular power exhibited by the victims of the "ordeal".

The action of the drug upon the heart and circulation was the subject of our next inquiry. After its administration to a frog, the first effect observed is that the heart beats more slowly. Then the ventricle contracts irregularly, some parts of it being firmly contracted and white, while others remain partially dilated and filled with blood, so as to present the appearance of little red pouches studding the surface of the organ. Finally, the ventricle stops altogether in systole, while the auricles continue to pulsate for some time. This condition is almost like that produced by digitalis. Further experiments have shown us that casca also resembles this drug in its action upon the cardiac-nerves. When a moderate dose of casca is injected into the jugular-vein, the pulse becomes slow. A further dose, makes it quick; and another large dose again renders it slow. Slow pulsation of the heart indicates that its regulating nerves are in a state of abnormal excitation. This regulating or inhibitory nervous apparatus is partly situated in the heart itself, and partly in the medulla oblongata, and these two are connected by means of the vagi nerves. The medullary or central is more sensitive to the action of many drugs than the cardiac or peripheral portion, and was, therefore, likely to be the one first affected by the poison. If this were so, division of the vagi, through which it acted upon the heart, would remove the slowness of the pulse occasioned by the action of the casca. Experiment confirmed the truth of this. The effect produced by section of the nerves was an immediate quickening of the pulse. The same condition was brought about, as I have already mentioned, by the injection of an additional dose of casca when the nerves were left untouched. This effect rendered it probable that the additional dose paralysed the ends of the nerves in the heart. When an electric current is applied to the nerves, it usually causes immediate stoppage of the heart's pulsations. If, however, this irritation be applied after the casca has quickened the heart, no effect is produced by the galvanism. This clearly shows that the usual power of the nerve over the heart has been completely abolished. Since, then, a moderate

dose of casca destroys the power of the *vagus*, through which slowness of the pulse is usually produced, and, nevertheless, the injection of a further dose still renders the heart's pulsations slow, this slowness must, we think, necessarily be due to an action of the drug upon the ganglionic structures or muscular fibre of the heart itself.

We have hitherto considered its action upon the heart alone; but, on the injection of a small dose, an effect upon the circulation becomes manifest before any change whatever can be noticed in the pulse. This effect is a rise in the blood-pressure. This rise continues after the pulse has become slow, and it does not fall during the intervals between each cardiac systole. This satisfactorily demonstrates that the arterioles through which the blood flows from the arteries into the veins have become contracted. The next question is, How is this contraction induced? It may be that the drug acts upon the muscular walls of the arterioles themselves, upon the nerves which stimulate these walls to contraction, or upon vaso-motor centres situated either in the spinal cord or the medulla oblongata. The chief vaso-motor centre is situated in the medulla; and usually, when its connection with the arterial system is destroyed by cutting across the cord at the occiput, the arterioles dilate and the blood-pressure falls. If any drug should raise the blood-pressure by acting upon this centre in the medulla, its effect will be prevented by such a section of the cord before its administration. On dividing the cord and injecting casca, we found that the blood-pressure rose higher than in any other experiment. The drug, therefore, does not produce contraction of the arterioles by its action upon the general vaso-motor centre in the medulla, but by acting either upon the arterioles themselves or upon vaso-motor nerves or ganglia not contained in the medulla. In order to ascertain, if possible, whether these centres were contained in the spinal cord, or were in the neighbourhood of the vessels themselves, we divided the sympathetic in the neck of a rabbit, and thus cut off the vessels of the ear from their connection with any nervous centre excepting such ganglionic cells as might lie in the immediate neighbourhood. We then injected a dose of casca, which caused the vessels in both ears to become equally pale. Had the contraction depended upon excitation of a vaso-motor centre in the spinal cord, it would have affected that ear the nerves of which had been left entire to a greater extent than the one in which the vaso-motor nerve had been divided.

As the action of casca resembles in many points that of digitalis, it seemed not improbable that it would exert a similar action upon the kidneys also. A dog was, therefore, anaesthetised by chloroform, and a cannula placed in one ureter, so that the urine could be collected as it flowed from the kidney, and the rate of secretion exactly discovered. The experiments of Ludwig and Max Hermann had already shown that this rate depends upon the pressure within the renal glomeruli; and it was to be expected that, as the pressure rose after the injection of casca, the rate of secretion would be increased. On trying the experiment, our expectation was realised, for a single dose both raised the blood-pressure and quickened secretion. Another dose raised the blood-pressure still higher; but the secretion of urine, instead of becoming quicker, began to slacken; and, when the blood-pressure had risen to its maximum, it stopped altogether. But when, after a while, the blood-pressure began to fall, the secretion again commenced. This indicated that the casca had exerted its contracting power to a greater extent upon the arteries of the kidney than upon those of the body generally; so that, notwithstanding the rise of pressure in the arterial system, the contraction of the renal arteries had almost entirely cut off the supply of blood to that organ. As the effect of the drug passed off, the renal arteries relaxed, again allowing the blood free access to the kidneys. In this respect, the action of casca agrees exactly with that of digitalis. It seems likely that, like digitalis, casca will possess a cumulative action; for if, during the course of its administration, it should arrest excretion by the kidneys while it is still being absorbed from the stomach, poisoning will occur, just as in Hermann's experiment with curare. In casca, then, we possess a drug which strengthens and slows the heart, contracts the arterioles, and increases the urine. Having gained this knowledge, how are we practically to apply it? What connection is there between our acquaintance with the parts of the body on which the drug acts, and the symptoms of any disease with which we meet at the bedside? The connecting link between these two, pharmacology and symptomatology, is pathology. This traces back the symptoms of disease to alterations in the structure and functions of the different organs, just as we have seen pharmacological experiment in the hands of Magendie trace back the symptoms produced by strychnia to the spinal cord.

Only too often are we called upon to see cases where, on the least exertion, the heart begins to palpitate; the breathing becomes difficult; and, as the disease progresses, suffocation threatens. The patient

sits upright in bed; the face becomes dusky, the lips livid; the feet swell; and death ends the scene. To what organic changes are these symptoms due? and how are these changes to be remedied? Harvey's discovery and Malpighi's demonstration of the capillaries have made it easy and natural to connect the rosy hue of health and the flush of exertion with full vessels and active circulation, and to attribute the pallor of death to absence of blood. It is to the blood, then, that the skin chiefly owes its hue; and duskiness of the skin indicates darkness of the blood. But the experiments of Lower showed that darkness of the blood was caused by deficient respiration, and was removed by exposure to air. We therefore trace the dusky skin to deficient aëration; but we cannot yet say whether the air has been prevented from reaching the blood, or the blood from reaching the air. Here the discoveries of Avenbrugger, Laennec, Corvisart, Hope, Williams, Corrigan, and many others, come to our aid. We percuss the chest and listen to its sounds. We find, let us suppose, no excessive resonance, and hear no rattling in the bronchial tubes. We thus learn that the air is not prevented by mucus from filling the lungs, nor is the area of contact with the blood lessened by emphysema. The lungs, then, are not in fault, and we pass on to examine the heart. On percussion, we find the organ enlarged; on palpation, we perceive the apex displaced to the left; and on auscultation, we hear the sharp "lubb" of the first cardiac sound replaced by a whiff like that of a bellows. From this, we know that the valve which ought to prevent the backward flow of blood from the left ventricle during its systole is inefficient; and that, like one sliding back at each step while walking on a slippery road, the heart must beat with abnormal power to carry on the circulation. No wonder, then, if it palpitates at the slightest unusual call upon its efforts. But more than this: each pulsation not merely fails of its proper effect in forwarding the circulation, it positively retards it; for each systole sends a jet of blood back into the auricle and obstructs the flow in the pulmonary veins. The blood cannot pass through the lungs with sufficient rapidity; aëration is, therefore, deficient. Thus we learn why the respiration is laboured, the skin dusky, and the lips livid.

How, then, is this to be remedied? First of all, it would be an advantage to make the heart beat more slowly; for, when it pulsates rapidly, there is no time for the pulmonary veins to become well emptied between each systole. By lengthening the interval between them, the ventricle has time to become better filled, and sends a fuller current into the wide aorta, and a proportionately small amount back into the pulmonary veins through the narrow chink in the mitral valves. But, if this were all, why should not a drug like aconite serve our purpose, for it renders the heart's action slow? But at the same time it weakens it; and, in the conditions which we have just been considering, one of the most important factors is weakness of the right ventricle; for it is in the pulmonary circulation that the resistance lies, and one of our most important tasks is to strengthen the propulsive power of the right ventricle, as well as to remove obstruction in front. This end we gain by employing digitalis or casca, which increase the strength at the same time that they diminish the rapidity of the cardiac contractions.

The next symptom is the oedema. This depends upon accumulation of fluid in the cellular tissue, and may be due either to too much being poured out from the blood-vessels or to too little being re-absorbed. It was attributed by Lower, in 1680, to diminished absorption by the veins; his idea being based upon some experiments in which he tied the vena cava, with the effect of producing great oedema of the lower extremities. His opinions were confirmed by the observations of Bouillaud, who noticed a similar condition in patients suffering from thrombosis of the iliac veins. His experiments, however, were repeated by Valsalva, Hewson, and several others, with a different result; and it was not until Ranvier, in 1870, again investigated the question, that the cause of the discrepancy between these observations was ascertained. On tying the vena cava in the abdomen of a dog, Ranvier found that oedema did not come on unless the nerve of the limb was divided at the same time. When the sciatic was cut on one side, the arteries were dilated, so that the leg became warm and oedema came on, while no swelling was perceptible on the opposite limb, although the venous circulation was equally obstructed in both. The reason of this appears to be that, so long as the arteries were not unnaturally dilated, the lymphatic system sufficed to absorb the fluid poured out for the nutrition of the tissues, so that no excess accumulated in them. Whenever section of the vaso-motor nerves allowed the arteries to become dilated, more fluid was poured out than the lymphatics could absorb; and, the veins being prevented from removing the excess as they would have done under ordinary circumstances, it remained in the tissues, producing oedema. That this effect was due to paralysis of the vaso-motor, and not of the motor nerves of

the limb, was shown by Ranvier in another experiment. He divided the roots of the sciatic nerve in the spinal canal before they had been joined by the communicating branches from the great sympathetic. He thus cut the motor without injuring the vaso-motor nerves, and rendered the leg completely powerless, without altering the vessels. In this case, no oedema occurred, although the vena cava had been tied as in the former experiment. We see, then, that contraction of the arterioles may prevent oedema, even although venous obstruction exists; and we are warranted in supposing that it will diminish the oedema after it has already come on. But more than this: stimulation of the vaso-motor centre increases absorption. This was shown by Goltz, who injected a quantity of fluid into the dorsal lymph-sac of a frog, and found that, when he stimulated the vaso-motor centre, this fluid was rapidly absorbed into the circulation. But, when he destroyed the nervous centres, no absorption whatever took place. We do not yet know the exact way in which this increased absorption is effected; nor has it been ascertained whether drugs which contract the arterioles, either by stimulating the vaso-motor centre in the medulla oblongata or other vascular nerves, have a similar action. It seems to me highly probable that digitalis at least has such an action; for, in some experiments which I made many years ago, after the quantity of urine had been very much increased by the action of the drug, an intolerable thirst came on, which I was obliged to satisfy by drinking a quantity of water greatly in excess of the allowance to which I had restricted myself every day for the preceding six months.

By the use, then, of a drug like *casca*, which contracts the vessels, we will almost certainly lessen oedema by diminishing the flow of blood through the arterioles. At the same time, in all probability, we will increase absorption, both by a direct action upon the circulation and tissues and by the secondary effect proceeding from the augmented urinary discharge. Digitalis has hitherto been our great resort in mitral disease, but I think it probable that in *casca* we possess a drug more powerful still; at least, its effect upon the arterioles appears to be greater than that of digitalis, and it is quite possible that it may succeed in those cases of advanced mitral disease when digitalis fails.

From these examples, it will be evident that the use of experiment to the student of medical science is the same as that of a solar observation to the mariner. An unwise sailor may trust to his "dead-reckoning", and thus make shipwreck; but the wise navigator will not be content with calculating his position from his rate of sailing and the direction of his course. He knows that irregular winds and unseen currents may falsify his calculations, and he will use every opportunity of correcting them by actual observation of his latitude and longitude. Day by day, he rectifies any error into which he may have fallen, and thus he can proceed with confidence, knowing he can never be far astray. When, on the other hand, no such correction is made, each erroneous calculation forms a false starting-point for the succeeding one, and the error daily grows. Thus it was that the ancients, founding a great speculation on a small fact, and building one fancy on another, landed themselves in utter confusion. Erasistratus found the arteries empty after death; he therefore concluded that they contained air during life, and then he went on to fancy that when blood got into them it troubled the spirit they contained, and caused fever or inflammation.

Harvey found valves in the veins, and therefore thought it probable that the blood circulated, instead of oscillating backwards and forwards; and the tetanic spasms caused by upas led Magendie to believe that it acted on the spinal cord. But neither was content with mere probability; each walked as on a quaking bog, and tested each step before taking it. If the blood circulated, pressure on the veins must make them empty above and full below the point of constriction. If upas acted on the spinal cord, its action must cease when the cord was destroyed. Every step thus gained affords sure foothold for another, and thus science daily grows. Already the experimental method has done much for medicine, and in my next lecture I purpose to consider the chief gains we have obtained by its use.

MR. CROSS received a deputation on the 15th instant from the Amalgamated Tailors' Society, to lay before him the evils of what is known as the "sweating system", and to ask him to take remedial measures.

VACCINATION.—Mr. Oded Lousley, Public Vaccinator for Reading, has received from the Local Government Board £53:17. This is the second time Mr. Lousley has received an award for successful vaccination.—The Local Government Board have just awarded to Dr. P. S. Fentem £10:10, as the result of the first inspection made since his appointment as Public Vaccinator for the Bakewell District of the Bakewell Union.

THE CROONIAN LECTURES

ON

THE DIFFERENCE BETWEEN THE SEXES IN REGARD TO THE ASPECT AND TREATMENT OF DISEASE.

Delivered at the Royal College of Physicians of London.

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LECTURE I.—*Concluded.*

LET us now follow the relative liability of the sexes as they proceed towards maturity. Now, the records of the relative frequency of disease in the sexes are pretty clear in attributing to the male a much higher rate of susceptibility to *acute hydrocephalus* than the female. I need only quote the statistics of Dr. J. Risdon Bennett, where he shows that, out of equal numbers of each sex, 1,707 males and 1,349 females died of this disease.

In regard to *convulsions* taken as a prominent symptom in the broad idea of the public statistics ending in death, we find, for two years taken as a haphazard, that, in 1866, 12,438 males and 9,353 females were attacked within the first year of life; and, during the second year, 1,668 males, and 1,513 females; after which time the proportion becomes more equal, and later the excess is slightly more on the female side. In 1868, during the first year, 11,689 males and 8,905 females; during the second year, 1,480 males and 1,367 females.

Of course, we must bear in mind that, convulsions being an accompaniment of other conditions, we must take the above rather as an evidence of serious disease, and compare it with the statistics of acute hydrocephalus, from which it is separated in the Registrar's reports.

In regard to liability to *laryngismus stridulus*, convulsion of the larynx, we find males decidedly in excess. In Reynolds's *System of Medicine*, we find Dr. Hughlings Jackson assenting to this and quoting Vogel, Gee, and Mackenzie in confirmation. Thus, he says, "of Gee's cases, 34 were males and 14 females."

It is curious to note here that rachitis, which has been shown by Sir W. Jenner, Gee, and others to be very frequently found with *laryngismus stridulus*, is also more fatal in males than females. Thus, in the Registrar's report for 1866, we find there died, males 66, females 38; and in 1868, males 69, females 49.

It is also to be noticed that the death-rate in males exceeds that of the females in most of the affections of the larynx. Thus, in *croup*, the proportion of deaths was 100 males to 82.89 females, as quoted by Churchill. Trousseau gives 22 males for 8 females, and 17 males to 5 females.

In *pertussis*, we find that the death-rate is about equal.

The same may be said of the diseases classified as *paralysis* by the Registrar-General; though it is difficult to say whether the condition called infantile paralysis is thereby indicated.

Hitherto, in the diseases to which I have alluded, the male has been the most affected; but, in that which will next engage our attention, namely *chorea*, this proportion is reversed, and in a marked degree. The difference is not much up till the end of the fourth year; but after this, on the average, we find from two to four times more females than males. Thus, at the Great Ormond Street Children's Hospital, Dr. Hillier tabulated the sexes and ages of 422 cases occurring up to twelve years of age, of which 122 were males, and 300 females. I need not quote the whole table, but may mention that, between the ages of four and five, the proportion of males to females was as 4 to 16; and, between ten and twelve, as 23 to 81. Again, when chorea occurs after puberty, it is among women that it is principally seen; thus, in Dr. Ogle's cases, there were 16 females and but 3 males. These facts are doubtless well known to my hearers, but I am anxious to contrast this remarkable difference with other diseases of the nervous system.

Yet, like most, if not all, of the other conditions in which we find marked preponderance in one or the other sex, it must be remembered it is not confined exclusively to females; and, therefore, when we seek for the cause, we must seek in a direction where we find a factor common to both, but especially intense or prominent in the female. What is that condition? Looking at the tables, we find the increased proportion of females affected very noticeable at six years old; up to that age, there was very slight difference; but, from that period to the latest at which it has been noticed, namely forty-seven, the excess is strongly