THE LUMLEIAN LECTURES ON THE MUSCULAR ARTERIOLES:

THEIR STRUCTURE AND FUNCTION IN HEALTH
AND IN CERTAIN MORBID STATES.

Delivered at the Royal College of Physicians of London.

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LECTURE II.

The Relation between Renal Disease and Hypertrophy of the Heart.—Various Hypotheses.—Hypertrophy of the Muscular Arterioles: its Relation to Renal Disease and to Cardiac Hypertrophy.—Results of Arterial Tension in Bright's Disease. 1. Degeneration of Arterial Walls. 2. Cerebral Hemorrhage. 3. Reduplication of the First Sound of the Heart: its Cause and its Practical Significance.

I PROPOSE now to discuss the state of the circulation in cases of Bright's disease, and the influence of the muscular arterioles in the causation of the phenomena.

Dr. Bright was the first to point out the frequent association of disease of the kidney with disease of the heart. In a paper published in the first volume of the *Guy's Hospital Reports*, while passing under review the chief morbid appearances observed in one hundred cases of renal disease connected with albuminous urine, he refers to the subject of cardiac disease in the following terms. "The deviations from health in the heart are well worthy of observation; they have been so frequent as to show a most important and intimate connection with the disease of which we are treating; while at the same time there have been twenty-seven cases in which no disease could be detected, and six others which, from not having been noted, lead to the belief that no important deviation from the normal state existed. The obvious structural changes in the heart have consisted chiefly of hypertrophy, with or without valvular disease; and, what is most striking, out of fifty-two cases of hypertrophy, no valvular disease whatsoever could be detected in thirty-four, but in eleven of these thirty-four more or less disease existed in the coats of the aorta; still, however, leaving twenty-three without any probable organic cause for the marked hypertrophy generally affecting the left ventricle. This naturally leads us to look for some less local cause for the unusual efforts to which the heart has been impelled; and the two most ready solutions appear to be, either that the altered quality of the blood affords irregular and unwonted stimulus to the organ immediately, or that it so affects the minute and capillary circulation as to render greater action necessary to force the blood through the distant subdivisions of the vascular system."

Now, the problem to be solved is the relation between disease of the kidney and hypertrophy of the left ventricle, when there exists no disease of the valves or of the large arteries to account for the hypertrophy. This subject has been much discussed of late; and, although I have nothing absolutely new to bring forward on the present occasion, I shall endeavour so to arrange the facts and arguments which bear upon the question as to assist in the formation of a definite opinion with regard to some hitherto debated points.

It is generally admitted that the hypertrophy of the left ventricle in the cases under consideration is the result of some impediment in the course of the circulation, to overcome or counterbalance which the heart has been impelled to unusual efforts; and, when the arterial trunks and the larger branches are in a normal state, it is evident that the impediment must exist somewhere beyond, in what Dr. Bright calls the "distant subdivisions of the vascular system".

One hypothesis may be mentioned and dismissed in a few words as being utterly inadequate. I allude to the suggestion of Traube (*Ueber den Zusammenhang von Herz und Nierenkrankheiten*, Berlin, 1856), that, when the kidney is in an advanced stage of atrophic degeneration, a diminished quantity of blood passes through it; there is, therefore, increased tension of the renal artery and aorta, and consequently more forcible contraction of the left ventricle, with resulting hypertrophy. This explanation is obviously insufficient. The diminished circulation through the kidney alone, even in the most advanced stage of granular degeneration, would not give rise to the great amount of hypertrophy of the left ventricle which is commonly found in these cases; nor

would it cause the high arterial tension throughout the system which is associated with the cardiac hypertrophy.

I believe that one step towards a solution of this problem was made by myself more than a quarter of a century ago, when, in a paper communicated to the Royal Medical and Chirurgical Society and published in the thirty-third volume of the *Transactions*, I described for the first time the remarkable hypertrophy of the muscular walls of the minute renal arteries in the advanced stages of chronic Bright's disease. In that paper, I correctly described and represented in drawings the hypertrophy of the arterial walls; but my physiology was at fault, and I wrongly interpreted the phenomena. The paper in question was read and published in the year 1850—a year, that is, before the publication of Bernard's first memoir describing the results of his experiments on the vaso-motor nerves. At that time, it was very generally supposed—at any rate, I had been taught to believe—that the contraction of the muscular arterioles assists the heart to propel the blood onwards through the capillaries; and, in accordance with that belief, I endeavoured to explain the arterial hypertrophy by the increased muscular contraction required to overcome the impediment resulting from the destruction of the glandular tissue and the inter-tubular capillaries. The researches of Bernard and Brown-Séquard referred to in my first lecture, resulting as they did in demonstrating that the function of the muscular arterioles is to regulate the blood-stream, and not by their contraction to assist in driving the blood onwards, convinced me that my explanation of the hypertrophy of the renal arteries was untenable; but several years elapsed before I ventured upon any other explanation of the facts. Meanwhile, having daily opportunities of confirming Dr. Bright's observation of the very frequent coexistence of chronic renal disease with cardiac hypertrophy—observing, too, the clinical fact, readily ascertained by the finger and confirmed by sphygmographic observation, of high arterial tension in this class of cases—it occurred to me, thoroughly imbued as I had become with the vaso-motor doctrines of Bernard and Brown-Séquard, that we must look to the influence of the muscular arterioles, and what I have ventured to call their stopcock action, for the explanation of that peripheral impediment to the circulation which results in the arterial tension and the cardiac hypertrophy of Bright's disease.

The course of the argument was this. It is an established physiological doctrine, that the contraction of the muscular arterioles diminishes the blood-stream, calls forth more forcible contractions of the left ventricle, and so increases the blood-pressure in the arterial trunks. It is a physiological law, that increased muscular contraction leads, within certain limits, to increased growth—hypertrophy—of muscular tissue; and this is especially true of the involuntary muscles. If, therefore, in the course of chronic Bright's disease, the morbid quality of blood excites such forcible and long continued contraction of the muscular arterioles, and thereby so increases the work of the left ventricle as to cause great hypertrophy of its walls, it is probable that the muscular walls of the arterioles will be found to have become simultaneously and in a corresponding degree hypertrophied. The next step was to make a microscopic search for the arterial hypertrophy in other tissues than the kidney, where I had discovered and described it years before; and the result was, that the arterioles in various tissues, more especially in the subcutaneous and the sub-mucous tissues, in the muscles, and in the pia mater of the brain, were found to have their muscular walls thickened by a true hypertrophy—by an increase, that is, of their muscular tissue, without structural change or degeneration. The general results of these observations are recorded in a paper which was published nine years ago in the fifty-first volume of the *Medico-Chirurgical Transactions*. I have the satisfaction of knowing that the publication of that paper has had the effect of directing the attention of many competent observers to the condition of the minute blood-vessels in connection with Bright's disease; and, although some of my statements and conclusions have been disputed, I believe that, in the main, my record of facts and my inferences will be found to bear the test of time and criticism.

Some writers have gone so far as to deny the existence and even the possibility of hypertrophy of the muscular coat of the arterioles; but, on the other hand, very competent observers have confirmed my observation of this change in the arterial walls. Amongst these, some have asserted very strenuously that not only is the muscular coat thickened, but the other coats also. I have never denied this, but, on the contrary, I have looked upon it as a matter of course. Just as in the hypertrophied left ventricle there is an increased growth not only of the muscular fibres, but also of the connective and other tissues which constitute the walls of the ventricle, so in a hypertrophied arteriole there is a duly proportioned increase of the outer and inner as well as of the middle muscular coat.

We have now to inquire what are the conditions in which this arte-

rial hypertrophy occurs. What is the physiological explanation of its occurrence? And what are the results of this arterial change?

The associated renal and cardiac hypertrophy are found to occur in the last stages of all the forms of chronic Bright's disease—most constantly and conspicuously in cases of the small red granular kidney; but very frequently, too, as the observations of Dr. Grainger Stewart, Dr. Dickinson, and others, have shown, they are found to occur with the large white kidney which has passed on to the stage of more or less advanced granular contraction. My own observations have led me to the conclusion that there is a direct relation between the destruction of the renal gland-cells and the cardio-arterial hypertrophy; and I will presently suggest an explanation of this relationship.

I must here once more insist upon the fact that the primary and essential structural changes in the small red granular kidney are not interstitial, as the term "interstitial nephritis" implies, but glandular. There is no form of Bright's disease in which the gland-cells are so constantly and extensively destroyed as they are in this. The microscopic evidence of the destruction of the renal cells is to be found during life in the numerous granular casts, composed of disintegrated renal epithelium, which appear in the urine, and after death in the more or less general appearance of transparent tubes denuded of their epithelium and in various stages of atrophy or dilatation.

The *clinical evidence* of the destruction of the essential secreting tissues in this form of disease is afforded by the notorious fact that symptoms of uræmic poisoning—poisoning, that is, from the retention within the system of various kinds and combinations of urinary excreta—are more common in this than in any other variety of Bright's disease.

On the other hand, in the cases of chronic Bright's disease associated with a large white kidney, the enlargement of the organ up to a certain point is mainly the result of a kind of hypertrophy of the glandular tissue, and with this there may be little or no evidence of uræmia, of arterial tension, or of cardio-vascular hypertrophy. But when the renal disease passes on to the stage of atrophy, with coarsely granular contraction of the cortical portion of the gland, uræmia and resulting structural changes in the heart and arteries are commonly found to be associated therewith.

There is yet another class of cases which have an important bearing upon the question of the relationship between renal disease and the associated cardio-vascular changes: I mean cases of acute Bright's disease. In 1873, Dr. Galabin published a pamphlet *On the Connection of Bright's Disease with Changes in the Vascular System*, in which he showed, by the evidence of sphygmographic tracings, that, "even in the early stages of acute nephritis, such an impediment to the circulation may occur from altered quality of the blood, that the arterial pressure is increased and the heart's contraction made more laborious"; and he added, "if this be true, it is easy to understand that this state of things, if continued long enough, will cause the muscular walls, both of heart and arteries, to hypertrophy". And our late lamented friend and colleague Dr. Sibson, in the Lumleian Lectures (*Lancet*, March 28th and April 4th, 1874), which he delivered here three years ago, and in two Harveian Lectures (*BRITISH MEDICAL JOURNAL*, January 6th and 13th, and February 10th and 24th), given last year, showed, by a series of elaborate and careful observations, that, in cases of acute Bright's disease, there may occur, as a temporary and transient condition, increase of arterial tension, felt by the finger and demonstrated by the sphygmograph, distension and incipient hypertrophy of the left ventricle, doubling of the first sound of the heart, and an intensified metallic second sound over the aorta: these modifications of the normal cardiac sounds being results and indications of high arterial tension.

The observations of Drs. Galabin and Sibson are entirely in accordance with my own daily experience, and they have been confirmed by many other physicians: What, then, is the explanation of the systemic arterial tension of acute Bright's disease? Without doubt, it is a result of uræmic poisoning; and I believe it to be precisely analogous to the arterial tension, with distension and dilatation of the left cavities of the heart, which have been demonstrated to occur in the early stages of apnoea, when, as I endeavoured to show in my last lecture, the passage of unœrated black blood into the systemic arteries excites, through the vaso-motor nerves and centre, contraction of the muscular arterioles, and thus causes distension of the arterial trunks and of the heart's cavities. We have additional evidence of the close analogy between the uræmic and the apnoeal conditions in the fact that, amongst the results of advanced emphysema of the lungs with chronic bronchitis, and the consequent passage of imperfectly oxygenised blood into the systemic arteries, we find, not uncommonly, a full, tense radial artery, and after death more or less considerable hypertrophy of the left ventricle. In one case of emphysema with chronic bronchitis and hypertrophy of the left ventricle, the subcutaneous arterioles, of which I have a preserved specimen, are very decidedly hypertrophied.

Obviously, then, there are striking analogies between the phenomena of uræmic poisoning and those which attend the passage of unœrated blood into the systemic arteries.

Before I pass on, it may be well to refer briefly to two suggested explanations of the impeded circulation in Bright's disease different from that which I have here given.

One theory is, that the thickening of the vessels which I describe as hypertrophy of the muscular coat, is not hypertrophy at all, but a degeneration of the coats of the arteries. This question is one of microscopic observation, and can be decided only by an appeal to the anatomical facts. But I may remark, in passing, that degeneration of the muscular arterioles would not explain the phenomena, since it is certain that the contraction of the muscular arterioles exerts an influence which, by limiting and retarding the blood-stream, antagonises the heart, and it is obvious that degeneration of their muscular walls would involve, not an increase, but a decrease of resistance; and so, on this hypothesis, the increased arterial tension and the cardiac hypertrophy are inexplicable. It is evident, too, that degeneration of the arterial walls would not explain the rapid onset and the passing away again of the high arterial tension in cases of acute Bright's disease.

The other hypothesis to which I just now referred is that which attributes the impeded circulation in cases of Bright's disease, not to the contraction of the muscular arterioles, but to "an impediment in the capillaries, due to a modification of capillary attraction between the blood and the walls of the vessels; and, the arterial pressure being thus increased, the muscular walls of heart and arteries are both hypertrophied in concert, since both have to act against greater resistance" (Dr. Galabin, *op. cit.*, p. 10). The obvious objection to this hypothesis is, that an imaginary "capillary force" is substituted for the demonstrated physiological function of the muscular arterioles. There was a time when the theory of a capillary force served the useful purpose of linking together a number of facts regarding the circulation through the terminal vessels; but Henle's demonstration of the muscularity of the arterioles, and the physiological discoveries of Bernard and Brown-Séquard, have rendered that hypothesis as untenable as the theory of phlogiston was made by the discovery of oxygen gas.

The substitution of an imaginary subtle capillary attraction for the obviously adequate influence of the muscular arterioles, reminds one of the curious hypothesis by which Riolanus, in opposition to Harvey, endeavoured to explain the passage of the blood from the right to the left side of the heart. Harvey, referring to this, says—"He (Riolanus) would have the blood to make its way into the left ventricle through the septum of the heart by certain invisible and unknown passages, rather than through those ample and abundantly pervious channels the pulmonary vessels, furnished with valves opposing all reflux or regurgitation" (Harvey's *Works*, Sydenham Society's Translation, page 99).

Even if there existed in the capillaries a power of arresting the passage of the blood, mere passive distension of the arterioles, in consequence of an obstruction in front, would not result in hypertrophy of their walls. This is proved by specimens showing no thickening of the arterioles, in the lung of a patient who had chronic incompetence of both the mitral and aortic valves, with much pulmonary engorgement and hæmoptysis.

That a persistent active contraction of the muscular arterioles is the cause of the impeded circulation and of the resulting arterial tension in cases of chronic renal disease, seems to be proved almost to demonstration by the remarkable hypertrophy of the arterial walls; and this view receives confirmation from the influence of nitrite of amyl in lessening the arterial tension. This agent, when inhaled, has the power of causing rapid and extreme relaxation of the arterioles, and consequent injection of the capillaries; and Dr. Broadbent was the first to show that, in a case of contracted kidney, with high arterial tension, the blood-pressure was much lessened by the inhalation of nitrite of amyl. Dr. Sibson repeated this experiment with the same result. He says, "under the influence of the amyl, there was less tension; and, as the tension was removed, the doubling of the first sound was lost".

It is obvious that the nitrite of amyl could not thus influence arterioles rendered rigid by degeneration of their muscular tissue.

An interesting confirmation of the theory that contraction of the muscular arterioles is the cause of the increased arterial tension is afforded by some ophthalmoscopic observations lately recorded by Dr. Gowers (*BRITISH MEDICAL JOURNAL*, Dec. 9th, 1876, p. 743). In five successive cases of Bright's disease, in different stages and with different degrees of arterial tension, Dr. Gowers observed a direct relation between the contraction of the magnified terminal arteries in the retina and the degree of arterial tension at the wrist. And he argues that, "as the immediate effect of contraction of the arterioles must be an in-

crease in the arterial blood-pressure, it is reasonable to conclude that such is the sequence of events in the phenomena under consideration, that, although the two phenomena may be in part the result of a common cause (altered state of the blood), the contraction of the arteries seen in those of the retina, and inferred to exist elsewhere, is, in part at least, the cause of the increased blood-tension."

And now, having, as I believe, adduced sufficient evidence to show that the arterial tension in Bright's disease is a result of the resistance to the blood-stream caused by the contraction of the muscular arterioles, this undue contraction being excited by the influence of contaminated blood upon the vaso-motor nervous system, I pass on to the consideration of some of the results of the increased blood-pressure and arterial tension.

[To be continued.]

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 III.—Concluded.

Respiratory Organs.—In this group, we find that, taken altogether, men are rather more liable to disease than women, and the excess may arise from the greater degree to which men are exposed. Thus, taking the year 1866, we find in the Registrar's report 41,392 males, against 35,917 females. Thus, in *pneumonia*, there are registered 14,136 males, against 10,919 females; and so on through the various forms of acute and fatal disease of the respiratory organs. To *phthisis*, however, more women fall victims than men. Thus, for the same year, 27,192 males died and 28,522 females. However, in cirrhosis of the lungs, Dr. Bristowe has shown that more males die than females. In his 38 cases, there were 22 males and 16 females.

Urinary Organs.—Men suffer twice as severely and fatally from diseases of the urinary organs as females, because of their liability to stricture and retention, to stone and prostatic disease. At the same time, the bladder suffers annoyance and violent pressure in pregnancy and during labour; but from the shortness and dilatibility of the urethra in women, local curative treatment is much more easy and successful; and calculi, which have descended from the kidney, escape generally in a few days.

It was not my intention to allude to the special diseases of the generative system, except so far as affects the general condition. But it is important to notice the much more frequent occurrence of *malignant diseases*, taken as a group, in females. Malignant disease shows itself more frequently in the sexual organs than in any other; and in the female, the high rate of activity and changes to which these organs are liable, no doubt, tends to set up the abnormal actions of malignant disease. Thus, in 1868, we find that there occurred in England 6,137 deaths from cancer in females, while only 2,743 took place in males; in 1866, in females 5,761, and only 2,332 in males. Up to the age of thirty, the sexes are equally affected, but after there is a great variation. Thus, Dr. Tilt (*Change of Life*, 1870) gives this table:

From 30 years to 40—19 females to 6 males.

" 40 "	" 50 "	" 51 "	" 6 "
" 50 "	" 60 "	" 5 "	" 1 "

In 2,781 cases collected by Leroy d'Étoilles, quoted by Dr. Tilt, the uterus was found affected in 30 per cent. and the breast in 24 per cent.

Again, the uterus renders woman very obnoxious to the absorption of irritating matters, whereby peritonitis, septic and otherwise, phlebitis, and septicæmia invade her. Its shape is one particularly adapted to retain secretions, blood, etc.; and thus, by the communication with the atmosphere, these are liable, under the warmth of the body, to decompose. Its structure is also peculiarly adapted for absorption; cavernous in texture, the lymph-spaces large and very numerous, and connected with openings in the peritoneum, it is easy to see how readily irritating matter may be taken in if abrasion exist, as after abortion and delivery

at full term; and this particularly if vascular tension have been previously lessened by hæmorrhages, ill-health, and fatigue, and other depressants, which act also in another manner. For whenever the vital force is depressed, the check it holds against decomposition is lessened, and we find that secretions, which otherwise would have been innocuous, are then more liable to the putrid change. From this special danger the male is exempt.

From the violent uterine hæmorrhages, too, or slow draining of blood, which tells so severely and often fatally on the female, man is free. From the anæmia resulting woman recovers, but slowly; indeed, I should say, never entirely. If you watch these patients, you will find them complaining of the sense of lassitude, imperfect functions, neuroses, emotional excesses, etc., very bitterly; in many for years afterwards, if not for life. Some of them try to get over it by the use of alcoholic stimulants, only to increase the feeling, and ultimately to yield to fatty degeneration.

From these special troubles also man is free; and thus he is more competent to maintain his position as a bread-winner, with muscular, nervous, and mental power, sustained by rich and nourishing food.

Malacosteon.—It is curious to notice and difficult to explain why women, and especially pregnant women, are so much more liable to malacosteon, or mollities ossium, or osteomalacia, than men. The proportion is at three or four times as many in females: always a condition of adult life, and frequently started by pregnancy, or relit by successive ones. Does it derive its virulence from the altered state of the blood, such as occurs in pregnancy? It must be something common to both sexes; but in what point does its cause exceed in women?

Before I conclude, there is one other subject which must not be omitted. I mean the period called "change of life", the "climacteric", "cessation of menses", "turn of life", or, by the French, the "ménopause". These terms are applied to women; but the term "climacteric", "turn of life", is also applied to man. In him the change is more gradual, as puberty is. Virility ceases at a very uncertain time, lasting till at least 80 in some; and though, no doubt, retrograde changes tending to decay take place in him, yet they scarcely can be said to be accelerated at any definite period; they are generally slow, and to himself scarcely noticeable. No doubt, when man has passed the prime of life, and his system is less vigorous than before, he is conscious of this change; and perhaps, if the task he set himself in the world's work be only half-accomplished, and the great struggle is to come; if he have already overtaxed his strength, and then only partly succeeded; or, still more, if he have failed, his mind recognises its position, and the nervous power, losing its sustaining force, is apt to yield; and melancholia, hypochondriasis, dyspepsia, may easily supervene; and, supervening, add to the depression. But this is not the equivalent of the ménopause in women. This is definitely attended by the involution of the ovary; the cessation of its activity, the reverse of the accelerated growth of it at puberty. As the latter was accompanied by the process of menstruation, so this is accompanied by its cessation. In other words, the ovary fails to stimulate the nervous and vascular system generally, and the uterus in particular; and almost invariably the power of conception is lost, just as it commonly ceases upon the occurrence of amenorrhœa earlier in life. We shall not be far wrong probably, if we were to say that the negation of ovarian action occurs in both conditions. But does ovulation cease entirely? It would be difficult to say "Yes" at present, because we saw imperfect ova passed away in childhood, and it may be that imperfect ova pass away after the cessation of the menses. But it is quite certain that all the tendency to various troubles, to which I have partly alluded as belonging to females, principally after puberty, now cease, or at least do so after a time. All the local uterine irritations, engorgements, and fluxes; all the reflex symptoms, neuroses, vomiting, neuralgias, headaches, pass gradually off; and then, when the change is complete, the woman passes much into the state of one who has had her ovaries removed, having a tendency to revert to the neutral man-woman state; yet not entirely so, because there remains impressed upon the mind, memory, and nervous system the reflection of the woman; in manifold ways recalling to her actions and movements that manner and style she had in earlier life.

But, after the change has been completed, we generally find her system improved; not disturbed by the periods, nor pregnancy, nor by the multitudinous reflex symptoms which distracted her attention; losing sexuality and its various impulses, she becomes more capable of rendering herself useful. She is less of the woman she was than a man is a man at the same time of life. The study of the subsidence of menstruation tells us the same physiological facts as those which accompanied its origin; and further, they point out the essence of those complaints which, troubling the woman so long, subside at this epoch,