THE CROONIAN LECTURES ON ADDISON'S DISEASE.

Delivered at the Royal College of Physicians, London.

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LECTURE III.

(Concluded from p. 440 of last number.)

NEARLY ten years ago, in a paper read before the Pathological Society, I observed that the production of the symptoms of Addison's disease by means of the implication of the nerves, was, after all, a secondary question to that of the origin of the suprarenal disease itself, of which the nerve-lesions were the consequence, not the cause. This is still my opinion; but unfortunately it is even more difficult to throw light upon the question of the etiology of the disease than upon that of its pathological processes: a difficulty owing, not only to the peculiar obscurity of the subject, but to the absence, in a majority of cases, of many of the data required in order to justify any certain conclusions being drawn from them. There are, nevertheless, some pathological conditions recorded in association with Addison's disease in so considerable a number of cases as to leave no doubt in my mind that they are not accidental complications, but have a real and more or less causal connection with the disease; and these conditions I shall now proceed to consider.

In describing the characters of the lesion in the suprarenal capsules, I have purposely avoided the use of the term "tubercular", lest I should convey an erroneous impression; but the product of the chronic inflammatory process has undoubtedly analogies with tubercle, and has been termed tuberculous, strumous, and scrofulous, more often than inflammatory. It may, indeed, be a question whether the distinction between the inflammatory and the tubercular deposits can be so clearly drawn as was formerly thought; for even the giant-cells relied on by Schiöppel as decisive of the presence of tubercle are now stated by Dr. Green, in his recent *Manual of Pathology*, to be merely characteristic of chronic inflammatory processes in lymphatic structures. Be this as it may, it is impossible to resist the evidence of clinical facts as to the existence of some affinity between Addison's disease and the tubercular diathesis. By far the larger proportion of diseases of other organs found in association with Addison's disease of the suprarenal capsules are diseases of tubercular or strumous character. In the typical cases, indeed, these complications are either altogether absent, or are indicated only by small tubercular concretions in the lungs, some of which are described as cheesy, some as calcareous, others as peribronchitic nodules, and others, again, merely as indurations in the apices of the lungs. But a very considerable number of the other genuine cases of Addison's disease are complicated with more or less active tubercular disease, and, in a certain number of cases, the genuine lesion of the capsules has been found coexisting with advanced phthisis or general tuberculosis. This may be explained in two ways. Even if general tubercular disease and the particular lesion of the suprarenal capsules never stand to each other in the relation of cause and effect, it can be no matter of surprise, seeing how a vulnerable constitution, as Virchow calls it, predisposes to the development of low chronic inflammatory processes, that these two diseases should not infrequently be found in the same patient. There have been, however, a very small number of cases in which it does appear to me as if the lesion in the capsules characteristic of Addison's disease had arisen as part of a general chronic tubercular process going on at the same time in several other organs. It will be remembered that, in these cases, which were discussed in my last lecture, the characteristic symptoms and bronzing of skin were altogether undeveloped. Although this is a part of the subject on which I desire to speak with great diffidence, seeing that it can only be determined by careful *post mortem* examination of similar cases, I may say that it seems to me by no means improbable that, in these cases, secondary deposits of tubercle may have taken place in the capsules, to the extent of entirely destroying their structure, without having produced the inflammatory nerve-lesions which I regard as essential factors in the development of Addison's disease.

It is much more certain that Addison's disease of the suprarenal capsules is frequently due to extension of inflammation from diseased

or injured adjacent parts. I have records of eighteen cases in which psoas abscesses arising from caries of the lower vertebrae, and other abscesses in the vicinity of the capsules, have been followed or accompanied by Addison's disease. In several other cases, in which the spine and neighbouring parts were not examined after death, distinct tenderness on pressure was observed over two or more lower dorsal or upper lumbar vertebrae; so that I believe the number I have stated by no means represents all the cases in which this form of the disease has coexisted with inflammatory lesion in the capsules. There is clear evidence, in most of these cases, that the abscesses and vertebral disease have preceded the appearance of Addison's disease by considerable periods of time; and, in some cases, they have even become entirely quiescent for years before the development of the symptoms. A man, aged 24, who died in St. Bartholomew's Hospital under the care of Sir George Burrows, had suffered in childhood from spinal disease, and, two years before death, he had had a spinal abscess, which healed after a few months. His last illness was of eight months' duration, and, after death, the fifth and sixth dorsal vertebrae were found to be destroyed; but there was no active disease. Both the suprarenal capsules contained purulent fluid and yellowish pea-sized nodules, resembling concrete tubercular matter. In a case published by Dr. Cotton of Lynn, the patient, a member of our own profession, had suffered in the year 1847 from an abscess in the right lumbar region, which produced very serious effects upon his health; but, contrary to expectation, he recovered and remained well until 1854. His complexion then underwent a marked change, and somewhat later the constitutional symptoms of Addison's disease supervened. After several alternations of remission and exacerbation the patient died in 1857, and at the necropsy a whitish fibrous-looking obliterated sinus was found proceeding from the cicatrix of the old abscess in the right loin to the site of the structures in which the diseased capsules were firmly imbedded. The disease in the right capsule appeared to be older than that in the left.

This appears to me to be a point of so much importance in its bearing on the etiology of Addison's disease, that I will quote here two other cases exhibiting similar conditions. In the case of a deformed woman, aged 26, who was under the care of Dr. McDonogh of Clapham, and whose case is recorded by Dr. Wilks, the lower dorsal and one or two of the upper lumbar vertebrae were found to be almost destroyed; and surrounding these, adjacent to the suprarenal capsules on either side, was found a quantity of putty-like cretaceous matter—the remains of an old abscess. The capsules presented the characteristic appearances of Addison's disease in a not very advanced stage. Another case, in which an inflammatory process had apparently been the exciting cause of Addison's disease, by reason of its close proximity to the suprarenal capsules, is that of a patient of Niemeyer's, a man aged 37, whose case was diagnosed as one of Addison's disease three or four years before his death. The disease seems to have run a slow, sluggish course, complicated by successive abscesses and fistulae in various parts of the body. The constitutional symptoms and discoloration of skin were both characteristic, and he died in a sudden paroxysm of nerve-paralysis. The capsules were found in the usual conditions, the right one still showing a trace of normal structure, and both were imbedded in much firm tissue. The left capsule and kidney were blended together into one mass with the neighbouring portion of the descending colon by means of a firm tissue traversed by strong fibrous threads. The colon at this part was the seat of an extensive cicatrix of an old ulcer, which had involved the whole tube, and had much contracted it by the thickening of its walls. The colon was adherent to the pancreas by the same mass of hard tissue which bound it to the left suprarenal capsule.

In some of these eighteen cases, the disease which seems to have been the exciting cause of the inflammatory process in the suprarenal capsules, has apparently been due to constitutional tendencies; but, in several of them, there is a distinct history of injury which has obviously produced it, and in apparently healthy subjects. The most striking case of this kind which has come under my own observation is that of a coal-porter, aged 32, who was admitted into the Middlesex Hospital in the year 1866 under Dr. Stewart's care. His health had been robust until about three years before his death, when he suffered a severe strain in the back from pushing a loaded coal-truck, and felt a sensation as of something giving way. From that time, he felt more or less pain in the loins; but the first symptoms of Addison's disease supervened only ten months before his death, or two years after the accident. The case was, like most of those in the class I am discussing, a typical one as regards the constitutional symptoms and the bronzing. At the *post mortem* examination, the suprarenal capsules were both found imbedded in thick fibrous tissue, and adherent to the surrounding parts. The right capsule was much enlarged and nodulated, consisting of semitransparent tissue, yellow cheesy masses, and

small calcareous patches; the left capsule was smaller, and contained more calcareous matter. Adjacent to the capsules, and in front of the lower dorsal and upper lumbar vertebrae, was a largish abscess, bounded by firm fibrous investments. Lastly, on examination of the spine, the intervertebral substance between the lowest dorsal and the first lumbar vertebra was found to be separated from the upper surface of the last-named vertebra, for two-thirds of its depth, on the left side, but the separation did not extend to the spinal canal. The denuded surface of the upper lumbar vertebra was rough and carious. The clinical history and pathological conditions, in this case, scarcely leave room for doubt that the separation of the intervertebral substance took place at the moment of the strain three years before death; and that this injury gave rise, primarily, to the abscess in front of the injured parts; and secondarily, by extension of inflammation from the abscess, to the disease in the suprarenal capsules.

Another remarkable case of the same character is recorded by Dr. Grey Glover in the *Edinburgh Medical Journal* for 1859. The patient, a furnace-man at some chemical works, had hurt his back by a fall. Three years later, he became of a yellow colour, and was supposed to be jaundiced. Notwithstanding medical treatment, the discoloration never left him, and it ultimately deepened into the typical bronzing of Addison's disease. The peculiar constitutional symptoms only began to develop three years after the first appearance of the discoloration, and the patient died after two years' illness. The capsules were entirely destroyed, and consisted of a semitranslucent deposit, with some opaque white material and cretaceous masses; and in this case also there was psoas abscess, with caries of the two lower dorsal and upper lumbar vertebrae. Dr. Wilks, to whom the capsules were sent for examination, pronounced the case to be a capital example of Addison's disease; and, in referring to it in one of his papers in the *Guy's Hospital Reports*, he stated that the fact of caries of the spine being the only disease which had in two or three cases been found preceding Addison's disease, strongly suggested the opinion that the capsules might have been secondarily affected by it.

In ten or twelve other cases, abscesses, frequently connected with disease of bones, or otherwise apparently of scrofulous character, have been found in situations more or less remote from the diseased suprarenal capsules. In several of these, as in many of the cases complicated with tubercle of the lungs, the only connection between the two diseases has probably been the constitutional vice which predisposed to the development of both of them; but in others, in which the local seats of inflammation were not far removed from the suprarenal capsules, the disease probably spread, as in Dr. Cotton's case, by continuity of tissues, although the connection was overlooked at the *post mortem* examination. In a case of my own, that of a man aged 24, who died at the Middlesex Hospital in the year 1864, there had been an abscess in the left hypochondrium about nine months previous to his death. Soon after it healed, he had been attacked with severe pain in the left hip, which never left him. Typical symptoms and discoloration of skin supervened, and he died in a few months of Addison's disease. The capsules exhibited the usual characteristic changes; and a small abscess was found situated underneath the pelvic fascia, containing about half an ounce of pus, and directly communicating with carious bone at the left sacro-iliac synchondrosis. I am now of opinion, from analogy with other cases, that I overlooked a connection between this abscess and the tissues adjacent to the suprarenal capsules. At least, it is certain that, not fully appreciating at that time the important bearings of such a connection, I made no sufficient search for it.

I must now invite your attention to a class of cases in which there is no pathological evidence of the existence of any local lesion from which there could have been an extension of inflammation to the suprarenal capsules, but in which, nevertheless, the clinical history of each case very decidedly points to some severe strain, or blow, or physical shock, usually in the back, as the starting-point of the illness. Unfortunately, the previous history is wanting in so large a proportion of cases, that I can only quote seven unequivocal cases of this class. A woman aged 31, who died under my care in 1858, when I was Physician to the Western General Dispensary, constantly assured me that she had never recovered from a strain in the back received in turning a mangle some years before her last illness. A female servant aged 30, who died in the Middlesex Hospital under the care of Dr. Burdon Sanderson, was laid up for a week with pain in her back from a fall down stairs, and began to fail in health from that time. In like manner, a druggist's assistant, aged 16, fell through a trap-door; and, although Dr. Bristowe, whose patient he was, verified the absence of any disease of the bones of the spine or pelvis, the lad's illness undoubtedly dated from the fall, which he survived sixteen months. Lastly—for it would be tedious to enumerate all these cases—a German factory-manager, whose case is related by Dr. Ploss, dated his illness

from supposed rheumatic pains occasioned by a fall over a bank two years before death. These seven cases were all typical, in the sense of there being no coexisting disease of any importance; but in almost all of them some tubercles are reported in the apices of the lungs, giving evidence of the existence of a tubercular diathesis, with which Addison's disease appears to have so strong an affinity, and which may have predisposed these persons to its development from slighter or more temporary causes than would have given rise to it in persons of different constitution.

In four or five cases, patients have referred their illness to physical over-exertion; in about the same number of cases, to nervous shocks, grief, or anxiety; and in two or three cases, to attacks of intermittent fever. The evidence in such cases is, of course, somewhat vague and questionable; and, due regard being had both to the apparent inadequacy of the supposed causes, and to the occasional latent course of the disease until its symptoms are developed under some external depressing influence, it may fairly be conjectured that, in most of these cases, the lesion of the suprarenal capsules existed antecedently to the supposed cause of illness, which was only the immediate exciting cause of the manifestation of the symptoms. It is well not to overlook any aspect of so obscure a subject; and, therefore, without attaching any undue importance to the alleged facts in the history of these cases, I think it advisable to keep them in view.

There still remain, however, a majority of the whole number of cases, in which neither the clinical history nor the pathological conditions seem to afford any clue to the origin of the disease. In too many cases, indeed, these are imperfectly reported or altogether wanting; but in many others, in which they are recorded, we find no trace of any antecedent cause. Good health until the apparently causeless beginning of the fatal illness is perhaps the most frequent history; and in typical cases, the usual report is, that all other organs were healthy; the exceptions to this rule being, as I have said, the presence of small inactive tubercular deposits in the lungs.

In this absence of all internal conditions, and of all direct evidence of external injuries, which might serve to refer the origin of Addison's disease, in these cases, to any of those causes which have apparently been its starting-point in the cases belonging to the other classes with which I have dealt, we must fall back upon the indirect information to be derived from the very obvious influence of sex, age, and occupation, upon the development of the disease.

Taking the 183 cases which I classed as unequivocal examples of Addison's disease, I find, as regards sex, that in 119 of these cases the patients were of the male sex, whilst in 64 they were females.

As regards age, my analysis shows that by far the larger number of the sufferers were persons in the most active period of adult life. Of the 119 males, 92 died between the ages of twenty and fifty; whilst nineteen boys died under the age of twenty, and eight men over the age of fifty. The two youngest boys were aged eleven and thirteen years respectively, and the oldest man was fifty-eight years of age. Again, of the 64 females, 47 died between the ages of twenty and fifty; ten girls under the age of twenty, and seven women over the age of fifty. The two youngest girls were also aged eleven and thirteen years, and all the seven older women were under sixty, except one, who is stated to have reached the age of sixty-nine.

If we now look to the rank in life, and the occupation of the sufferers, we perceive that more than nine-tenths of the whole number have belonged to those classes which are engaged throughout the active period of life in physically laborious work. Only eight or nine of the male patients have belonged to the classes of gentry, professional men, or merchants, whilst not more than six of the females have been in the position of ladies.

With respect to the occupations of the men, and still more those of the women, the data are very deficient; but the fact that they were apparently almost all in the class of hospital patients speaks for itself as to the probability of their having led a life of active manual labour in some form or other. Of the eighty-five men belonging to the working classes whose occupations are recorded, fifty-one were employed as agricultural labourers, porters, stonemasons, bricklayers, coal-miners, or in similar heavy work; a considerable number were costermongers, hawkers, journeymen-tailors, shoemakers, etc., whilst a few were publicans, shopkeepers, clerks, or had other miscellaneous occupations. With respect to the large majority of women of the working class, we have no information beyond their age. Of the sixty-four female patients, ten are stated to have been servants, maids of all work, laundry-maids, or cooks, six needlewomen, and three out-door labourers. Some, and in all probability very many, of the others, were poor married women, and on no other class of their sex, perhaps, rests a heavier burden of labour.

Lastly, with respect to the extreme rarity of the disease in persons

exempt from the necessity of bodily labour, I may quote my own experience. Although seven or eight cases have been referred to me in private practice, as supposed cases of Addison's disease, only two of these have been true cases of the disease, and I have met with no others amongst persons of the middle and higher classes. I believe, too, that in this respect, the experience of all other physicians will be found to coincide with mine.

From these data, therefore, imperfect as they are, the following deductions may safely be drawn.

The occurrence of Addison's disease takes place almost exclusively in persons employed in active manual labour.

The mortality caused by it is pretty equally distributed over the laborious period of life, and to that period it is almost entirely confined.

The disease is comparatively much more frequent in persons of the male sex, whose employment naturally involves the heaviest kinds of labour.

Lastly, a preponderating number of the cases which occur in persons of the male sex are found amongst those classes of labourers whose occupations are most likely to expose them to bodily injury from accident or over-exertion.

The facts thus brought out cannot fail to suggest obvious inferences as to the probability that, in many of these cases, more or less temporary causes of local inflammation may have existed, similar to those which appear to have been the starting point of the disease in some of the cases to which I have specially referred. In persons of the working classes, strains and falls, which do not involve disabling consequences, are soon forgotten, and therefore seldom reported; whilst the necessity of striving against the weakness induced by a strain or blow may tend to keep up an inflammatory process, which would have naturally subsided under favourable conditions of rest. Without, therefore, venturing to speak dogmatically on a point which can only be cleared up by much future investigation, I may yet say that I incline to believe the origin of Addison's disease, in many of the unexplained cases, to be due to traumatic causes, although its development has probably been favoured by certain constitutional proclivities.

Very few words need be said here with respect to the diagnosis and prognosis of Addison's disease. The diagnosis is founded upon the constitutional symptoms, aided, in a large majority of cases, by the presence of more or less of the peculiar change of colour in the skin. It is not always unattended with difficulty, but, to those who have any practical acquaintance with the disease, it is not, I think, more doubtful than the diagnosis of many other chronic diseases. The prognosis is, of course, invariably grave as regards the ultimate result, though it is impossible to say to what extent life may be prolonged under favourable circumstances. Rest and scrupulous avoidance of bodily or mental excitement, or any other causes of nervous exhaustion, form the essential parts of the therapeutical management of all such cases; whilst the diet and medical treatment must be carefully adapted to the inevitably varying phases of the disease.

It only remains for me to sum up, in conclusion, the objects which I have had in view in the course of lectures which I have had the honour to deliver before you.

In the first, I believe I delineated faithfully all the principal clinical symptoms of Addison's disease, and the remarkable varieties in their course; together with the true characters of the pathological lesions in and around the suprarenal capsules, which have been found to coexist with them.

In the second lecture, I endeavoured to show clearly, on the one hand, the concurrent testimony of facts in proof of the real connection subsisting between these clinical symptoms and the one specific lesion in the suprarenal capsules, and, on the other, the baseless nature of the misconceptions which have prevented the general recognition of its reality.

In to-day's lecture, I have trodden on more difficult ground. No one can feel more strongly than myself that the opinions which I have been led to form, with respect to the obscure pathological and etiological processes in Addison's disease, rest as yet upon an inadequate basis. I can only express the hope that, however problematical their correctness may appear to many, the suggestions I have ventured to make, regarding the probable mode of production of the symptoms of Addison's disease, and the probable means of origin of the suprarenal disease itself, may lead to a thorough investigation, in future cases, of all the facts bearing upon these questions; and thus, to the acquisition of knowledge which may justify positive conclusions, in place of the uncertain inferences which are all that I have been able to draw, from my own necessarily limited personal experience, and the insufficient materials at my command.

THE GERM-THEORY OF DISEASE:

BEING A DISCUSSION OF THE RELATION OF BACTERIA AND ALLIED ORGANISMS TO VIRULENT INFLAMMATIONS AND SPECIFIC CONTAGIOUS FEVERS.

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WHEN honoured by a request from the Council of this Society, a few weeks since, to open a debate during the current session, compliance with such a wish was regarded by me as a professional duty. I was compelled, therefore, to do the best I could with the short time and limited leisure which presented themselves, though these, I regret to say, have proved insufficient to enable me to bestow the attention I should have desired upon the vast accumulation of writings directly or indirectly related to the subject selected for discussion, and quite insufficient also to enable me to throw light upon it, to the extent I should have wished, by certain new observations of my own. The subject, however, large as it is—and consequently difficult to be dealt with satisfactorily in the space of one hour—seemed to recommend itself for several reasons. (1) It is a question lying at the root of the pathology of the most important and most fatal class of diseases to which the human race is liable—diseases which cause nearly one-fourth of the total number of deaths in this country. (2) It is a subject important alike to those engaged in almost every department of our profession. And (3) it is one which I happen to have very carefully considered for several years, and for the elucidation of which I was tempted in 1869 to undertake long and laborious investigations, though these may have seemed to many to have little practical bearing upon the science of medicine.

The subject of the relation of the lower organisms to disease has, moreover, a growing importance. The notion that there is a distinct causal relation between the two—though it has long existed in one form or another—is one which has been spread enormously within the last few years, partly owing to our increase of knowledge concerning these low organisms, and partly because of their ascertained presence in numerous diseased tissues and exudations. Medical literature, both at home and abroad, now in fact teems with papers and memoirs bearing upon this relation, and such communications rapidly increase in number year by year.

In the short time allotted to me to open the debate, I shall be able to make specific allusions to but few of these contributions, as it would seem better to keep the broad issues well in view in my opening statement, and to reserve questions of detail, as these may be taken up by other speakers and subsequently commented upon where necessary.

The one common and distinguishing feature peculiar to all the diseases, whose pathology we are now about to consider, is their "contagiousness". An individual affected by either of them throws off particles from the region specially affected, or from many parts of the body; and these particles, on coming into contact with suitable surfaces in other persons, may incite similar local or general diseases—though such results do not invariably follow. This peculiarity, by means of which such diseases are spread amongst the members of a community, was, even in the time of Hippocrates, compared to the property by which one fermenting mass may communicate its state of change to another mass of fermentable material. Throughout all intervening periods such an analogy has never been lost sight of—it has rather been more and more strongly dwelt upon. Thus, more than two centuries ago, we find, as has been recently pointed out, Robert Boyle, one of our great English philosophers, and himself a pioneer in scientific investigation, giving strong expression to the then current view. "He that thoroughly understands", he says, "the nature of ferments and fermentations, shall probably be much better able than he that ignores them, to give a fair account of several diseases (as well fevers as others) which will perhaps he never thoroughly understood without an insight into the doctrine of fermentation." Again, in more recent times, it was doubtless under the influence of a belief in the same analogy between fermentations and the class of diseases of which I am about to speak, that the term "zymotic" was proposed by Dr. Wm. Farr, and adopted as a general designation, under which nearly all these diseases might be included. The consequence of the adoption of this nomenclature has been, that views as to the nature of the infecting something or *contagium* have since been so powerfully influenced as to

* Read before the Pathological Society of London, April 6th.