THE CROONIAN LECTURES ON ADDISON'S DISEASE.

Delivered at the Royal College of Physicians, London.

By E. HEADLAM GREENHOW, M.D., F.R.C.P., F.R.S.,
Physician to and Lecturer on Medicine at the Middlesex Hospital.

LECTURE I.—(Concluded.)

BEFORE quitting the description of the constitutional symptoms and discoloration of the skin, I must advert to one remarkable feature common to them both, to which I directed attention in my clinical lectures on the subject in 1866. It has been noted also by several other observers in the reports of typical cases; but, owing no doubt to the shortness of the time that the majority of patients have remained under treatment, it has never hitherto been classed in its true place as one of the characteristic features of the disease. I mean its paroxysmal mode of progress. The asthenia, the constitutional symptoms generally, the change of colour in the skin, are all, it is true, progressive, but not steadily so. The course of the disease, on the whole, is slow and chronic; but it is subject to alternate exacerbations and remissions, usually dependent in some degree upon favourable and unfavourable circumstances, but sometimes also apparently independent of them. During the remissions, strength is in a great degree recovered, appetite is improved, sickness is abated, the discoloration pales; and, above all, the patient's whole aspect betokens that a heavy weight has been lifted from his head. After each fresh exacerbation, however, the patient remains upon a lower level than during the previous remission; the recovery of strength and the abatement of the other symptoms are less marked; the skin, though paler than during the last exacerbation, is visibly darker than before it. The alternations may occur several times before the onset of the fatal paroxysm; but, on each occasion, the patient takes one downward step that he never regains. In the case of two of my own patients, these alternations were well marked, though they died in one and two years respectively after they came under my care; and in the case of two others, who were under my care five and eight years respectively, the remissions in the symptoms and the paling of the discoloration were most striking. Dr. van den Corput relates, in the case of a woman aged thirty, who died under his care in St. John's Hospital at Brussels, that during four years she had three considerable periods of remission, and that the colour regularly alternated with the symptoms. Dr. Severini records that a woman, who was under his care for some months in the Hospital at Bologna, had, before her death, several alternations of health; and that the discoloration of the skin was darker or lighter, according to her state. Drs. Löwe and Wolff have noted similar alternations in two characteristic cases. Dr. Ringer also states, in the report of a case sent to me for exhibition to the Pathological Society in 1873, that with each slight improvement the discoloration of the skin grew less, but in each relapse it became darker than before.

But although slow chronic progress, with alternate exacerbations and remissions, is the usual course of the disease, it is by no means the only one. In many cases, especially in young subjects, the disease runs what may be termed a latent course; that is, the constitutional symptoms first appear suddenly in a fully developed form, producing death in a few days. This occurred in the case of Dr. Seth Thompson's patient, a man aged 20, who, although the skin was becoming dusky for six weeks, had exhibited no symptoms of illness until two days before admission into the hospital, and grew worse so rapidly that he died on the following day. The girl, E. W., who died under my care in 1865, is another illustration of this occasionally latent course of the disease. She returned home after an absence of six weeks in the country, apparently quite well, though her parents said she seemed rather sunburnt. This dinginess of complexion never left her; but she remained well for some months. Her father then regarded her as drooping for three or four weeks, but she had no symptoms of illness. She attended school until two days before her admission to the hospital, when she presented all the constitutional symptoms of disease in so fully developed a form that I diagnosed the case at first sight, although the discoloration was scarcely observable. She had suddenly become sick and cold; and, notwithstanding all possible restoratives, she died in a week. Dr. Schotte relates almost a parallel case of a girl, aged 15. She had been doing heavy work in the country, and complained for about four weeks of debility and powerlessness of limbs, and a tendency to fall asleep. She was admitted into hospital with symptoms of the disease in an advanced stage, and died the same night. Without doubt, these differences in the mode of onset and course of the disease are

partly due to differences in the mode of progress of the suprarenal lesion. The suddenly fatal termination in the first paroxysm is, however, like the accession of successive paroxysms, partly due also to some depressing external influence. In the case of my little patient, this was apparently an aperient administered by the mother, and in Dr. Schotte's case, a dose of calomel and jalap given in the hospital.

One other peculiarity in the course of the disease must not be overlooked—the very variable date of the appearance of bronzing of the skin, as compared with that of the constitutional symptoms. In a large proportion of cases, as might be expected in a disease prevailing chiefly among a class of persons who become hospital patients, no notice has been taken of this point; and in a great many other cases it is reported that the appearance of the constitutional symptoms and of the discoloration of the skin were simultaneous, or nearly so. Sometimes the discoloration is mentioned as soon following the characteristic symptoms, and sometimes as slightly preceding them. But in a certain number of cases, chiefly among the few that have occurred in the middle and higher classes, or have been longer than usual under observation, the interval between the appearance of the constitutional symptoms and that of the bronzing of the skin has been more accurately recorded. In a typical case recorded by Dr. Addison and Dr. Wilks, the patient, a young lady, aged 18, was ill only four months; but the bronzing had existed a year. In a case of Mr. Jonathan Hutchinson's, the patient, a boy aged 11, felt ill only a few weeks; but the bronzing had been noticed for six months. (I omit for want of time other illustrations of the same point.) These were all typical cases of the disease, no lesion being found of the slightest importance except that of the suprarenal capsules. Again, in about an equal number of cases of the same class, the development of the constitutional symptoms is recorded as having preceded the discoloration of the skin by several months, and sometimes by even a longer period of time. In a typical case related by Mr. John Moore, the patient, a clerk, had been in failing health for two years with the characteristic symptoms of the disease; but the discoloration only became visible during the last six months. In a case of Dr. Spender's, the patient, a young woman aged 21, was ill for a year with fully developed typical symptoms; but the discoloration only began to make its appearance three months before death. Dr. Robertson relates the case of a labourer who suffered from the characteristic symptoms of the disease twenty-two months, never having had any previous illness, but in whom the bronzing of the skin only began on the face, arms, hands, and chest, a year before death. (I must omit some other striking examples.)

I now turn to the consideration of the pathological lesion which Dr. Addison's observation of the clinical phenomena he described led him to seek for as necessary to explain them, and which he only briefly mentions as a diseased condition of the suprarenal capsules. He evidently believed that any diseased condition of these organs might produce the same effects; for he recorded in his monograph, in connection with the spurious cases to which I have referred, other diseased conditions of the suprarenal capsules totally different from the particular diseased condition which he had found in his own cases. This particular condition is nevertheless well described, as regards its naked appearance, in the report on the *post mortem* examination of one of his most typical cases. Each suprarenal capsule, he records, was completely destroyed, and converted into a mass of strumous disease—the latter of all degrees of consistency. The left suprarenal capsule had formed at the upper part a close connection with the outer coat of the stomach. The upper part of this capsule seemed fluid, and of the colour of pus; the lower firm, and of the consistency of putty. The right capsule had all degrees of consistency from the bottom to the top; the lower part being almost fluid, resembling pus; the centre putty-like; and the top was quite earthy, separate angular pieces being easily detached. Dr. Addison, however, gives no description of the microscopical appearances in this case, nor in any other case except one which was submitted to Dr. Hodgkin for examination.

I shall now proceed to describe more fully the pathological changes in the suprarenal capsules, as I have observed them in careful *post mortem* examinations of the same typical cases from which I have drawn the clinical picture of the disease. The capsules are generally enlarged, hard, and nodulated, though in rare cases they are of normal or less than normal size. On section, they scarcely ever present any trace of the distinction between the cortex and the medulla, so obvious in the normal condition of the organs. In all the fresh specimens I have seen, the cut surfaces have presented a marbled appearance, from the mixture of two materials of different colour and consistency. One of these materials is a semitransparent tissue of firm consistence, and grey or greenish grey in colour, at least when fresh cut; but, on being exposed to the air, it assumes a pink hue. The other material is opaque yellow, or

cream-coloured, and it assumes the form of irregular roundish masses embedded in the translucent tissue, from which they can often be easily enucleated. (This drawing shows better than any other that I have been able to procure, the appearance of a capsule freshly cut. The fact that I have stated, that on exposure to the air the greyish translucent tissue becomes pink, renders it difficult to obtain good drawings of the capsules when fresh. This is a copy of the original drawing that Dr. Addison had made for his book. I exhibit also another drawing, a very peculiar one, of a case in which the capsule has already begun to turn pink. There are two other drawings: one of a case in a very advanced stage, when the capsule is shrinking and the parts become hard; and another showing the same condition as that represented in a previous drawing.)

On close examination, intermediate gradations will often be seen between the translucent parts and the opaque cheesy nodules, and sometimes cretaceous granules, or small masses formed by the hardening of the cheesy matter, are felt to grate under the knife. (There are specimens here illustrating all these changes.) More rarely, the whole of the cheesy material dries up and hardens into calcareous masses, and it is in these rare cases that the capsules are smallest. Not unfrequently, on the other hand, the caseous matter softens down into collections of creamy fluid, called abscesses by some observers, and is found to occupy the larger or smaller cavities in the diseased capsules. In some cases, the whole central part of the organ constitutes one large cavity filled with creamy fluid, but more commonly there are, if any, several small cavities, the fluid in which is of the same character, but of various degrees of thickness.

It follows obviously from this description, that the proportions of the translucent and opaque materials, found in the diseased capsules, differ greatly in different cases. In some few cases, the translucent substance constitutes nearly the whole of the mass; in others, the yellow friable matter greatly predominates; whilst in others the normal tissue is almost entirely replaced by calcareous masses or creamy fluid. All these gradations, however, depend solely upon the duration and the more or less acute or chronic course of the disease. The morbid process is identical in them all—a fact which, as Dr. Wilks pointed out, gives a greater definiteness to the disease than Dr. Addison himself conceived it to possess.

On microscopical examination, the translucent substance is seen to consist of a fibrillated stroma containing numerous lymphoid corpuscles. In some cases, these corpuscles are arranged in rows between bundles of fibres; in others, they are contained in a delicate reticular stroma. The opaque cheesy material is formed of amorphous granular matter mixed in variable proportions with irregularly shaped shrunken cells, nuclei, and oil. Dr. Sidney Coupland found, on a microscopical examination of the capsules in my last case, some masses corresponding with giant-cells, which Schüppel considers distinctive of tubercle. The creamy-looking fluid consists mainly of oily *débris*. It is evident from these microscopical appearances that the morbid process in the capsules consists primarily in their infiltration by an inflammatory exudation of low type, which first becomes converted into fibrous tissue destroying the normal structure of the organs, and finally undergoes caseous degeneration.

In every one of my own cases, and in many of those carefully examined and reported on by others, clear evidence of inflammation in the cellular envelopes of the capsules has been afforded by great proliferation of their connective tissue, and also by the existence of firm adhesions to the neighbouring organs, such as the diaphragm, liver, pancreas, vena cava, kidney or stomach. It is probable, therefore, that in many other cases these conditions have been overlooked or have remained unreported, their significance not being understood. Of course, such extensive overgrowth of connective tissue round the capsules cannot fail to invest the nerves of both the suprarenal and the solar plexuses with dense indurated tissue; and accordingly, when these nerves have been examined, their fibrous investment has been found to be hypertrophied. The first careful dissection of the nerves in the neighbourhood of the capsules in a case of Addison's disease was made by Dr. Habershon, who had published in the *Guy's Hospital Reports* in 1856 a very valuable paper on the abdominal sympathetic and its connections with the phrenic and pneumogastric nerves. The results of the dissection of the nerves in the case to which I refer, were published in 1864 in the same series of reports. He found the semilunar ganglia, and the branches of the nerves proceeding to the capsules, surrounded by an unusual quantity of dense fibrous tissue. In several of my own cases, the same condition has been found, though they have not been dissected out of the mass of hard tissue in which they were imbedded. My colleague Dr. Cayley, several years ago, at my request, carefully examined the suprarenal nerves in the body of a man who died of Addison's disease in the Middlesex Hospital, under Dr. Stewart's care.

He found the nerves proceeding from the semilunar ganglia to the suprarenal capsules, and especially one branch of the great splanchnic, twice the size of the same nerves in a healthy subject dissected at the same time. A microscopical examination showed that the increased size was due to the increase of the fibrous investment of the nerve-bundles. Dr. Tuckwell of Oxford also made a complete dissection of the nerves in a case of Addison's disease, recorded by him in *St. Bartholomew's Hospital Reports* for 1873, in which case, as in two others that he had previously dissected, he found decided evidence of thickening, extending from the surface of the capsule to the suprarenal plexus, the semilunar ganglia, and thence up the great splanchnic nerve. The thickening of the nerves was found on examination to be caused by hypertrophy of their fibrous investment, and not by any apparent change in the nerve-fibres themselves. A similar condition of these nerve-plexuses in cases of Addison's disease has also been verified by several eminent foreign pathologists. Rindfleisch, in his report on the microscopical examination of the nerves in a case of Kuhlmann's, found two large nerve-trunks, the fibres of which were undergoing fatty degeneration, bound up in firm adhesions which attached the diseased capsules to neighbouring parts. Professor Tigri found the semilunar ganglia considerably enlarged, and the nerve-fibres forming the solar plexus thickened by hypertrophy of the neurilemma. Hertz also reports that he found the coeliac plexus, and particularly the semilunar ganglia, enclosed in hard connective tissue, with considerable thickening of the connective tissue sheaths of the nerve-fibres going off from the ganglia; and Wolff observed the nerves of the solar plexus and the semilunar ganglia enclosed in a thick envelope of connective tissue. Bartsch, Van Anstel, and others have reported similar conditions of the nerves.

In almost every case I have seen, the dense connective tissue surrounding the capsules has contained some enlarged lymphatic glands, and the same circumstance has been frequently reported by others. The mesenteric and retroperitoneal glands in the neighbourhood of the capsules are also generally enlarged. On section, these enlarged glands sometimes present only the normal appearances, but more commonly they are firm, glistening, of a pale colour, and not unfrequently in process of caseation. Microscopic examination sometimes reveals no obvious change of structure; in other instances, the nerves have been hard and glistening. There is another morbid appearance which has been so frequently observed by myself and others in cases of Addison's disease, that I feel justified in ranking it among the characteristic, though not, perhaps, quite invariable lesions incident to the disease: I mean enlargement of the solitary glands of the small intestine, sometimes likewise of the large intestine. In many cases also the mucous membrane of the stomach, especially towards the pylorus, has presented a mammillated appearance, and the mucous surface has not unfrequently been covered with tenacious grey mucus. Small ecchymoses, and more rarely superficial abrasions or small ulcers, are also found on the mucous membrane of the stomach, and in a few instances on that of the large intestines. Careful microscopic examination of the mucous membrane of the stomach in two different cases by Dr. Sidney Coupland and Mr. Schäfer have shown that the mammillations are caused by overgrowth of lymphoid tissue. Some of these mammillations presented small depressions in their centres, which were ascertained by Mr. Schäfer to be due to a breaking down and opening into the surface of the summits of the patches. Probably these depressions indicate the first stage of the small ulcers which have been reported by other observers as occurring in the gastric mucous membrane.

Lastly, I must not omit to mention one other morbid organic change too often recorded in cases of this disease to be passed over here, although I have had no personal experience of its presence. In a very considerable number of genuine cases, including cases reported by Dr. Addison and Dr. Habershon, the spleen has been found to be enlarged, sometimes greatly enlarged, and usually also dark coloured and soft. It is worthy of remark that in very few of these cases have the patients, so far as is known, suffered from intermittent fever. There has, however, been no enlargement of the spleen in any of the cases which have been under my own care. It is, therefore, quite certain that the disease may run its most typical course without presenting this lesion, and that consequently an enlarged spleen, though undoubtedly an occasional, is by no means an essential feature in the morbid anatomy of Addison's disease.

Having thus delineated, as I believe, the true clinical and pathological features of Addison's disease, I must, in conclusion, observe, to prevent misunderstanding, that it is only in a certain number even of the typical cases that the striking clinical phenomena which I have described are all fully developed. The progressive asthenia, muscular debility, feeble circulation, and low temperature, are invariably present; and in my experience neither loss of appetite, nor vomiting nor dyspnoea,

nor faintness on exertion, has ever been absent in the later stages of the disease. But there is not perhaps one of the other peculiar symptoms which is invariably observed. Every physician is sufficiently aware that this is equally true with respect to every other organic disease. It is only in the comparatively small number of cases in which an organic disease runs a long uncomplicated chronic course, that we can look for the full development of all its peculiar symptoms. The absence of some of these, therefore, in complicated cases, or in cases of short duration, cannot be regarded in Addison's disease, more than in any other organic disease, as militating against the connection between such symptoms and the pathological conditions with which they are associated.

THE GOULSTONIAN LECTURES ON PUERPERAL FEVER.

Delivered at the Royal College of Physicians, London.

By ROBERT J. LEE, M.D., F.R.C.P.,

Assistant Physician at the Hospital for Sick Children, Great Ormond Street.

LECTURE II.—(Concluded.)

THE interval between Gordon and Semmelweiss of half a century was occupied chiefly by those important investigations into morbid anatomy and pathology, both general and microscopical, which have contributed to the improvement of every department of our profession, and particularly to the practical knowledge of diagnosis and etiology. It is to this source that we must look for modifications in general opinion concerning some of the phenomena of puerperal fever; and it will be, I think, most convenient to defer our inquiry into the value of Semmelweiss's observations till we have reviewed the progress of pathological research. The real reason why there was such an universal movement in that direction about the end of last century may be easily traced to a few powerful minds, like the two Hunters and those nearly associated with them, who clearly perceived that the pathological study of the effects of disease promised more than the study of symptoms.

The result of this method, as far as it influenced the subject of puerperal fever, was the introduction of several new terms into our nosology which were intended to describe the pathological conditions of different organs, structures, and tissues. Thus originated puerperal peritonitis, phlebitis, metritis, and some others. These terms, as we know, did not include any explanation of the remote cause which induced the changes observed by the pathologist. They all more or less involved the assumption, that what is termed inflammation was their exciting cause, and the practical object of these terms was to connect local inflammatory processes with local and constitutional symptoms.

The subject of the pathology of puerperal fever is an extensive one, and I shall not attempt to treat it in the same manner as that of the etiology of the disease. There may be some excuse for doing this, as I feel more equal to deal with this part from personal experience and observation than with the other, which we have regarded as a matter of history. There is one point which would not be difficult to prove, if it were not self-apparent, and that is the fact, that neither morbid anatomy nor pathology assisted the theory of Gordon: I mean to say, that the idea of a specific poison would never have been evolved from such pathological work.

It was of very great value, however, in another way. Such theories as that which accounted for the swelling of the leg, or phlegmasia dolens; by supposed metastasis of lacteal secretion, very soon retired before the scalpel of the pathologist. The result of all this is, that we have some chance now of succeeding, after the separation of many pieces which would not fit together, in completing a puzzle of really no great complexity.

If it were asked why Gordon's theory did not find acceptance with pathological investigators (for we may observe that there were some of these who were distinguished for an extensive knowledge of the disease in all its forms, and had studied carefully all its symptoms), we must look for an answer in the supposition, that the pathological mind is of such a character as never to feel satisfied of the existence of anything without direct evidence, and then only when the method of demonstration employed is one with which it is familiar. The pathological mind is not a credulous one. It has a good deal of confidence in its own powers, and it likes to use its own visual organs. It would meet such a theory as Gordon's with an avowal of the greatest willingness to believe in the existence of a specific poison, provided only it could be shown the poison. To imagine that it could be contented with less is to do

injustice to its common sense and acuteness. For such a mind to conceive of an atom is almost impossible; it appears to it practically useless to do so, and to range beyond the sharply defined cordon of the demonstrable is scientifically reprehensible.

Let us examine to what pathology led. The principal effect was a very excellent classification of morbid changes, which has been followed closely by continental authors, and is still preserved by systematic writers in all countries. When it was found that descriptions of particular forms of inflammation were true for the particular cases in which they occurred, but not for all forms of the fever, we can understand that general views would soon embrace the apparently unconnected series of various morbid appearances which have been recorded. It soon appeared quite possible for various structures in the abdomen to be severally or simultaneously affected, or even that there might be well marked, though very different, pathological alterations, and yet that the cases were correctly described as forms of puerperal fever. Thus a simple classification was adopted under the general term uterine or puerperal inflammation, which included: 1. Inflammation of the peritoneal covering of the uterus and the peritoneal sac; 2. Inflammation of the uterine appendages; viz., the ovaria, Fallopian tubes, and broad ligaments; 3. Inflammation and softening of the proper or muscular tissue of the uterus; 4. Inflammation and suppuration of the absorbents and veins of the uterus. Each separate structure was thus carefully examined, and its alterations recorded.

There is a great deal to admire in the very exact and truthful descriptions, which make the works of the pathologists, to whom we are indebted for these valuable aids to our knowledge of puerperal fever, so well deserving of our regard. Probably the very fact, that a rigid exclusion of etiological influences in connection with these pathological conditions was observed by the school of pathologists to which I have referred, may be the cause of their work being so valuable. That publication of Dr. Baillie's, which contained nothing but careful and elaborate engravings, with the simplest descriptions possible, was the type of scholarly composition and masterly anatomical and pathological skill. There can be no doubt that, since the productions of that period from which we have traced the commencement of our history, nothing has ever appeared to compare with those of our own country. There were no uncertainty as to facts, no hasty generalisation, and no attempts at artificial classification, amongst those that followed close upon Baillie's model. So carefully did they attach themselves to the firm rock of certain truth, and so sure were they of the ground on which they stood, that they would have wondered at many since their day who have been looking so long into the hazy atmosphere that surrounds those difficult regions of the origin of life and disease, as to have forgotten to move on whilst dreamingly attempting to define the misty outlines of forms of things beyond their power of perception or comprehension. Such is the feeling they would have experienced, combined with one of pity, if they had heard some of us say that the very foundations of pathology are uncertain; that we know not quite where we are, or what next we may see. This brings me back to an urgent claim for the careful preservation amongst us of our peculiarly national method of observation, which, while accurate in detail and cautious in expression, still considers the best proof of its value to be the benefit it confers by its practical application.

To return to our subject, we have to notice the important extension of the theory of inflammation to the explanation of the connection between that condition which was known as phlegmasia dolens, and certain morbid changes in the structures of the venous system of the uterus; that is to say, when the symptoms which had previously been referred to metastatic lacteal secretion or pressure upon the lymphatics, were found to depend upon obstruction to the venous circulation.

The term phlebitis assumes the possibility of the veins, as separate structures, being affected by inflammation. Various changes of their lining membrane, and the existence of pus within the vessels, were considered satisfactory evidence of inflammatory action; and then followed the theory of pyæmia or puerperal purulent infection, arising from suppurative phlebitis. We will not stop to discuss just now whether these views were altogether correct. There is no doubt that, as far as the facts were concerned, they led to very important results.

It was shown that phlebitis might occur, not only in the puerperal condition, but also as a consequence of suppressed menstruation; in cases, too, of malignant ulceration of the os and cervix of the uterus; in certain forms of tuberculous disease; also as a consequence of abortion, and after operations for fibrous and other tumours of the uterus. The theory of puerperal purulent infection was supported by the popular school of medicine in France, and was ably argued by the late Professor Trousseau. It never was very generally received amongst ourselves, for the reason that we did not find it in accordance with clinical experience.