TWO CLINICAL LECTURES ON ADDISON'S DISEASE,

WITH NOTES OF THREE CASES, IN ONE OF WHICH SUPRARENAL EXTRACT PRODUCED MARKED IMPROVEMENT, AND IN WHICH THE SUPRARENAL BODIES WERE FOUND AFTER DEATH TO BE ABSENT AND REPLACED BY MASSES OF FAT.

Delivered at the Edinburgh Royal Infirmary

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LECTURE II.

The case to which I wish to direct your attention to-day is one of remarkable interest—first, on account of the fact that great improvement resulted from the administration of the extract, the specific treatment of Addison's disease as it may be termed; and, secondly, from the circumstance that after death, which was due to an attack of influenza, both suprarenal capsules were found to be absent, and to be replaced by masses of fat.

But, before referring to the details of this case, let me say a word or two with regard to the pathological physiology of Addison's disease, and the theory on which the administration of suprarenal extract is based.

PATHOLOGICAL PHYSIOLOGY OF ADDISON'S DISEASE.

There can be no doubt whatever that the symptoms of Addison's disease are the result of disease of the suprarenal capsules. In trying to explain the pathological physiology of Addison's disease, the following points in connection with the morbid anatomy must be kept in view:

1. In the great majority of cases of Addison's disease which have been examined after death, both suprarenal capsules have been found extensively diseased—in fact, completely destroyed—by a peculiar fibro-caseous change, which, as I have already told you, is tuberculous in its nature. Some authorities even go so far as to say that this fibro-caseous lesion is the only lesion which can produce Addison's disease. I venture to think that this is a mistake; for in some cases in which all the typical symptoms of Addison's disease were present during life and inactive, and in which the suprarenal capsules were found to be diseased after death, some other lesion than the fibro-caseous (tuberculous) one, which is the common cause of Addison's disease, was present. Cases of this kind are undoubtedly very rare, but they do occur. In some cases of this kind (they are very rare) the capsules were destroyed by malignant disease (cancer or sarcoma). In others, which are also extremely rare, the lesion of the capsules was apparently a simple fibrous atrophy. In still rarer cases, as in the one I shall presently relate to you in detail, the capsules have either been apparently absent, or, as in my case, replaced by fatty deposits.

2. Although, as I have just stated, in the vast majority of cases of Addison's disease both capsules are affected by the lesion, there are, I think, a sufficient number of cases on record in which one capsule only appears to have been affected to warrant the opinion that in very rare and exceptional cases the symptoms of the disease are developed when one capsule only is affected. It must, however, be admitted that this is a disputed point. Some of the best authorities on the subject (such as Dr. Wilks, Dr. Greenhow, Dr. Pye-Smith) doubt whether disease of one capsule is ever sufficient *per se* to produce the disease. This point has a very important bearing upon the theories which have been advanced to account for the mode of production of the disease.

3. In the great majority of cases of Addison's disease the nerves which pass in great abundance between the suprarenal capsules and the solar plexus are inflamed, degenerated, or diseased.

4. In rare cases in which some at least of the symptoms of Addison's disease (such as the pigmentation of the skin) were present during life, the suprarenal capsules were healthy, but the abdominal sympathetic was diseased.

The chief theories which have been advanced to explain the pathology of the disease are:

The Theory of the Arrest of Suprarenal Function.—That the symptoms of Addison's disease are due to destruction of the capsules—that is, to abolition of the functions of the suprarenal bodies or suprarenal glands, as they may be termed.

The Nervous Theory.—That the symptoms of Addison's disease are not directly due to destruction of the suprarenal bodies, but that they result from the derangements in the abdominal sympathetic and, perhaps, other nervous structures which the lesion of the suprarenal capsules produces.

In the present state of our knowledge it is extremely difficult to reconcile all the facts in accordance with either one or other of these theories.

In favour of the first view are the facts (a) that in the vast majority of cases of Addison's disease both capsules are completely destroyed; (b) that in some cases, apparently of simple atrophy or fatty change, in which both suprarenal capsules are completely destroyed, and in which, so far as *post-mortem* examination showed, there was no lesion of the abdominal sympathetic, typical symptoms of Addison's disease are nevertheless developed; and (c) that in some cases of Addison's disease the administration of suprarenal extract is undoubtedly attended with benefit.

Against this view are: (a) the fact that cancerous destruction of both capsules does not (except, perhaps, in very rare instances) produce the symptoms of Addison's disease¹; (b) that in many cases of Addison's disease there is strong pathological evidence to show that the suprarenal capsules have been completely destroyed for months or even years before the death of the patient, and before the symptoms of the disease were developed in a marked degree; and (c) that in many of the cases of this kind (cases in which the capsules are completely destroyed) remarkable temporary improvement may occur.

In favour of the nervous theory of the disease are the facts: (a) That in the great majority of cases of Addison's disease the lesion is one and the same—a fibro-caseous (tuberculous) destruction of both capsules; (b) that cancerous destruction of both capsules rarely (in the opinion of some authorities never) produces the symptoms of Addison's disease;² (c) that in rare cases one capsule only, or (according to two French observers, Drs. Alezais and Arnaud) a part—the peripheral part—of one capsule only is involved; (d) that in almost all cases of Addison's disease the nerves surrounding the capsules, and (in many) the semilunar ganglia and large nerve cords of the solar plexus are embedded in a highly irritative (tuberculous and inflammatory) tissue; (e) that in a considerable number of cases naked-eye and microscopical changes can be demonstrated in the semilunar ganglia and solar plexuses, and that (according to Alezais and Arnaud) microscopical alterations are always present in the pericapsular ganglia; (f) that (according to Alezais and Arnaud) in some cases in which the tuberculosis of the capsule is limited to the centre of the organ (that is, does not invade the cortical portion), and in which the pericapsular ganglia and the abdominal sympathetic are healthy, the symptoms of Addison's disease are not developed; (g) that in a few rare cases in which the symptoms of Addison's disease have been present during life, the suprarenal capsules have been perfectly healthy, but the semilunar plexus and solar ganglia have been diseased (enveloped in a mass of new growth); (h) that in some cases of Addison's disease in which suprarenal extract has been administered no improvement in the symptoms has occurred.

Against this view (the nervous theory of the disease) are:

(a) That in many cases of Addison's disease no changes have been found in the semilunar ganglia or great cords of the solar plexus. It must, however, be remembered that the nerve fibres, which are in the immediate neighbourhood of the capsules, are probably always involved in cases in which the

¹ The question is whether in cases of cancerous destruction of the capsules, in which the symptoms of Addison's disease were present during life, the suprarenal glands were completely destroyed.

² Possibly, as Dr. Rolleston has suggested (the Goulstonian Lectures on the Suprarenal Bodies, BRITISH MEDICAL JOURNAL, March 30th, 1895, page 680), in such cases death has occurred before symptoms characteristic of Addison's disease have had time to develop; or "that some compensation for the destruction of the suprarenal glands is present in accessory suprarenal bodies, and that, as in the case of the thyroid gland, symptoms due to the destruction of the main glands are thus avoided" (*loc. cit.*, April 5th, page 746).

typical fibro-caseous lesion of the capsules is present; and that, as Dr. Dixon Mann had pointed out, it is quite possible that an irritation, which is not sufficiently marked to produce visible (naked eye or microscopic) changes, may nevertheless produce very marked functional disturbances in the nervous system, and so may perhaps produce the symptoms of Addison's disease.

Further, Drs. Alezais and Arnaud, as I have already more than once pointed out, claim that the pericapsular ganglia are affected in all cases of Addison's disease,³ though they allow that in many cases no alterations can be detected in the semilunar ganglia or large nerve cords of the solar plexus.

(b) That simple atrophy and (as my case seems to show) fatty destruction of the capsules (independently of any obvious nerve irritation) is occasionally the cause of the disease, and

(c) That in some cases of Addison's disease—and the one which I am about to relate to you is perhaps the most important which has yet been published—the administration of suprarenal extract is attended with marked benefit.

The theory that the symptoms of Addison's disease are due to arrested or defective secretion of the suprarenal glands is undoubtedly a seductive one, and the knowledge which we have obtained during the past few years regarding the important influence which the thyroid and other ductless glands have in regulating the metabolism and nutrition of the tissues renders it much more probable than it was a few years ago. It cannot, I think, be lightly put aside. As I have stated elsewhere, it is not improbable that both theories (the glandular and the nervous) are correct. It is not improbable, I think, that while some of the symptoms of Addison's disease are the direct result of abolition of the glandular function of the suprarenal capsules, others may be due to the secondary lesions in the abdominal sympathetic, which the primary lesion in the suprarenal capsules, when of the typical fibro-caseous form, seems almost always to be associated with. Cases such as that which I am about to relate afford strong support to the glandular theory of the disease, and I am disposed to argue more strongly in favour of this theory than I did when I published my article on Addison's disease in the year 1892.

Nevertheless, for the reasons already given, it must, I think, be allowed that in most cases of Addison's disease the lesions in the abdominal sympathetic play, at all events, some part, and probably an important part, in the production of some of the symptoms. The facts (a) that in some rare cases in which the characteristic pigmentation and some of the other constitutional symptoms of the disease were present during life, the suprarenal capsules were found to be healthy after death, while the abdominal sympathetic was involved in a mass of new growth; and (b) that in the great majority of the cases which have been recorded in which both suprarenal capsules were completely destroyed by malignant deposits there were no symptoms of Addison's disease, are extremely difficult to reconcile with the purely and exclusively glandular origin of the disease.

Now, the administration of suprarenal extract is based upon the theory that Addison's disease is due to destruction of the suprarenal glands, that is, to abolition of the function of the suprarenal glands and a deficiency of suprarenal secretion; or perhaps it would be more correct, in the present position of our knowledge, to say that some of the symptoms of Addison's disease are due to deficiency of the suprarenal secretion. Let me now give you the particulars of the remarkable case to which I have already referred.

CASE III.—Typical Addison's Disease, characterised by Profound and Causeless Asthenia, deep Pigmentation of the Skin and Buccal Mucous Membrane, Pain in the Back, occasional Vomiting and slight Emaciation: Marked Improvement in all the Symptoms, including the Skin Pigmentation, under the Administration of Suprarenal Extract: Death from Influenza. On Post-mortem Examination, Absence of the Capsules, their place being taken by Masses of Fat: in the position of the Left Suprarenal a peculiar Histological

³It is probable that this statement only holds good for the typical (tuberculous) cases. There is no reason to suppose, in cases of simple fibrous atrophy, apparent absence, or fatty transformation (the condition which seems to have been present in my case No. III) that the pericapsular ganglia are affected.

Change in the Fatty Tissue, probably indicative of the Remains of the Degenerated Suprarenal Capsule.

The patient, a grocer, aged 37, married, was sent to me by Dr. Mossop, of Bradford, on October 8th, 1893, suffering from all the characteristic symptoms of Addison's disease.

Previous History of the Present Illness.—The patient stated that his present illness commenced two years before I saw him, and that it had followed an attack of influenza. During the attack of influenza he was confined to bed for a few days and suffered from cough, but there was no marked pulmonary complication. After the attack of influenza he noticed that his skin was gradually getting darker. He says, however, that the colour is not worse than it was twelve months ago.

Previous History prior to the Present Illness.—The patient stated that he had never been a very strong man. When 22 years of age he had to give up his original employment, that of a compositor, because of "weakness." He had not, however, suffered from any special form of disease. He stated that he had never had a fall or received any injury or strain of the back, and that he had never, during the whole course of his life, been engaged in hard or laborious work.

Family History.—None of his relatives had suffered from consumption or scrofula. His father died, aged 50, from alcoholic excess; his mother, aged 60, is alive and well; one sister died of small-pox; there are no other members of the family. The patient is married and has four children, all of whom are fairly healthy.

PRESENT CONDITION.

The patient states that he is naturally of a pale complexion. He is much pitted with small-pox, the result of a severe attack of that disease thirty years ago. He complains of extreme languor and debility. He says that he has not got appreciably thinner. Since the illness commenced he has felt some pain in the small of the back; this has been worse during the past three months.

On examination, the skin was found to be of a dark, yellowish-brown colour. The small-pox pits on the face, which were very numerous, were much more deeply pigmented than the other parts of the skin; in places they were almost black. This appearance was so peculiar that I photographed him while he was in my consulting room (see Fig. 1). There were also numerous small deep-brown moles on various parts of the skin. The pigmentation was most marked on the face, neck, hands, and genital organs, and it is over these parts that the small black moles and freckles were most abundant. There were also numerous pigmented patches on the lower lip, and on several parts of the buccal mucous membrane.

The patient complained of palpitation, faintness, and giddiness on stooping. He also stated that he was short of breath on exertion, and that on several occasions during the past three months he had vomited. His expression and bearing were suggestive of extreme debility. The heart sounds were so feeble that they could hardly be heard, and the cardiac impulse could not be felt. The blood was quite normal; a drop drawn for microscopical examination had a dark purple colour. The number of red blood corpuscles was 5,600,000 per cubic millimetre, and the hæmoglobin equal to 85 per cent. There was no excess of white corpuscles. No pigment granules could be detected in the specimen of blood which was examined. The urine was normal, specific gravity 1020; no albumen.

In writing to Dr. Mossop regarding the case, I said:

It is one of great interest. The marked pigmentation at the seat of the small-pox cicatrices, and the numerous small pigmented patches, moles, and freckles, are peculiar. Personally I have never seen these moles and freckles so abundant in any case of Addison's disease before; they are described by Dr. Greenhow as highly characteristic of the disease. The case is a typical one in every respect, and the prognosis is consequently most unfavourable. The essential points as regards treatment are to protect the patient from cold, over-fatigue, and everything, such as over-exertion, likely to produce exhaustion, and to carefully regulate the diet and the condition of the bowels. As regards drugs, if arsenic agrees I should feel disposed to give it a fair trial, with, perhaps, in addition the compound syrup of the phosphates. I should also like very much to try the effect of feeding with an extract of suprarenal capsule. I have not as yet had the opportunity of administering the extract in any case of Addison's disease, but I believe it can be got from Messrs. Brady and Martin—at all events, they will make it for you. It would be well, perhaps, to keep the patient in bed during the early stages of the treatment, and to begin with small doses, carefully watching the effect. I shall be glad to hear from you as to the result.

I heard no more of the patient until November 20th, 1894, when Dr. Mossop wrote me:

I have sent you by post the kidneys and capsules from the case of Addison's disease which you saw more than a year ago, together with portions of the spleen and liver.

I carried out the injections with suprarenal extract prepared by Brady and Martin with undoubted benefit. I will send you full notes of the case in the course of a few days. I feel so convinced of the utility of the treatment in this case, that I would confidently look for good results had I another case of Addison's disease to treat. Other medical men who saw the case during the treatment fully bear me out when I say that it was successful throughout. I may mention that shortly before his death he weighed 8 st. 12 lbs., and his weight at the time when the treatment was commenced was 8 st. 5 lbs.

Dr. Mossop subsequently sent me the following notes: "Early in the month of July, 1893, I accidentally met W. H. G.—who had been a patient of mine in Bradford for several years previous to 1891—at a seaside resort. I was so struck with his appearance that it occurred to me that he was the subject of Addison's disease. I requested him to call upon me on his return home, which he did on July 19th. He then gave me the following history:

"He had never been an ailing man, though not robust, until two years previously, when he had an attack of epidemic influenza; since then he had never fairly recovered his wonted strength and energy, and in fact had gradually become weaker and less fit to follow his occupation—that of a grocer. When I met him in July, 1893, he was totally unable to do anything, and had spent a month at the seaside in the hope of recruiting his strength, but he stated that he was worse than when he left home. His chief complaints were extreme weakness, loss of appetite, and sickness on the least exertion. He was so feeble that he was only just able to dress and undress himself, and had to crawl up to his bedroom on his hands and knees.

"His condition was as follows: Has a mournful, emaciated look, as if he was in the last stage of phthisis, stooping gait and listless movement, with breathlessness on walking. Face and neck as far as shoulders deeply bronzed. His face is marked from small-pox from which he suffered in his youth, the pits being deeper in tint than the rest of the skin. The

whole cutaneous surface is discoloured, the backs of the hands contrasting strongly with the whiteness of the palms. The mucous membrane of the lips, mouth, and tongue look mottled and blotched. The conjunctivæ show unmistakably the usual pearly whiteness. There are also a number of small darker petechial spots about the size of a millet seed scattered over the face more particularly, doubtless pigmentary. The finger nails are not affected. The penis and scrotum are also especially discoloured. He first noticed his skin darker a year previously. He does not remember having a fall or a blow. He complains of vertigo, yawning, and sickness, the latter chiefly in the morning; on stooping or exertion he experiences faint feelings. His pulse in the recumbent position was 114, when standing 120; temperature 98°; respirations 24. His bowels are somewhat constipated; urine normal. Had a slight discharge of blood from the anus due to a pile. Tongue clean and moist, appetite indifferent, attacks of indigestion. Heart sounds normal but action weak. Lungs healthy. I advised rest and nourishing diet, with the compound syrup of hypophosphates.

"Three weeks later, on August 5th, I again saw him, and found him a little better. Temperature 99°, pulse 92, respirations 20. I suggested that he should see Dr. Bramwell, to whom I had previously mentioned his case at the Newcastle meeting of the British Medical Association with a view to the treatment by suprarenal capsule juice. He accordingly went to Edinburgh on October 7th, 1893, and my opinion was confirmed and

Fig. 1.—Pigmentation of Small-pox Pits in Addison's Disease.

a line of treatment adopted which I may say proved entirely successful.

"*Treatment and its Results.*—The patient was kept in bed for three weeks, and twice a week I injected with every care and precautions 15 minims of the sterilised suprarenal capsule juice prepared for me by Messrs. Brady and Martin of Newcastle, the glands of one rabbit in 3j of the extract. It was injected alternately over the kidney region, and in a fortnight a manifest improvement took place in the colour of the skin. Towards the end of October I tried the capsules of a sheep minced and put into beef tea. This brought on severe gastric

disturbance. I then ordered him to take 10-drop doses of the sterilised juice every other day by the mouth; this answered admirably. I ordered him also "Levico" water (arsenio-ferrated), for a time the mild and then the strong, which suited him well. His appetite improved, and a marked change in his general health took place. He was able to indulge in a fair amount of physical exertion, and to attend to his business as before. His colour was decidedly better, which fact was observed by other medical men who saw him from time to time casually. Ten days before his death, he took an unusually long walk in the country (about eight miles), and was much fatigued by it.⁴ At that time his wife and children were ill with influenza, his nights were disturbed, and on the Friday night before his death, which occurred on the Sunday morning at 5 o'clock, he slept in the sitting-room on a couch before the fire. He thought that he had caught a chill, and for the rest of the following day appeared in a semi-comatose condition. A medical man who lived near at hand was suddenly sent for; he requested my attendance. At 11 P.M. I found him in a collapsed condition, with pallor of skin, dilated pupils, and temperature 104°, pulse 140, barely conscious, evidently sinking. Restoratives were tried, but he died at 5 A.M. (six hours afterwards)."

Post-mortem Examination by Dr. Mossop.—"The post mortem was made on November 20th, 1894. In addition to myself, Dr. Walter Nenby and Dr. Firth, House-Surgeon to the Children's Hospital, Bradford, were present. I was not allowed to make a complete examination. The abdomen and thorax alone were examined.

"The skin of the body had a bronzed hue. Half an inch of fat was present in the anterior abdominal wall. The patient was well nourished, the muscles being firm and of normal colour. The pericardium and heart were normal. The apex of the left lung was adherent by old pleuritic adhesions to the front of the chest wall, but the lungs were otherwise normal.

"The omentum was adherent on the right side to the adjacent structures. There were also some old adhesions about the liver and spleen. The gall bladder was distended with bile. There were no enlarged glands in the abdomen. The spleen was somewhat enlarged, but to the naked eye the liver and spleen appeared to be normal.

"After removing the liver, spleen, and stomach, each kidney with the whole of the fatty tissue in its neighbourhood (as was supposed) the suprarenal capsule was removed *en masse*, and was immediately forwarded, together with portions of the spleen, to Dr. Bramwell for further observation." Dr. Mossop subsequently wrote saying, "Absolutely nothing was left in the body which could possibly represent a suprarenal capsule."

The Naked-Eye Condition of the Kidneys and Fatty Masses Representing the Suprarenal Capsules.—The tissues received from Dr. Mossop consisted of: (1) The two kidneys and large masses of fat attached to the upper end of each kidney, in which it was supposed the suprarenal capsules were embedded; and (2) portions of the liver and spleen.

The masses of fat which were supposed to contain the suprarenal capsules were first detached from the kidneys and carefully examined. They were of considerable size, measuring 3½ inches by 3 inches and 4 inches by 3½ inches respectively. An incision from above downwards was first made into the mass of fat corresponding to the right suprarenal capsule, but no suprarenal capsule was found. This mass of fat was then cut up into small pieces, but the most careful examination failed to detect any appearance whatever suggestive of a suprarenal gland. The mass of fat corresponding to the left suprarenal capsule was then carefully cut into a series of transverse sections. In the centre of the fat, a faint, brown, wavy discoloration, which seemed to correspond exactly in respect to its shape and size with the outline of a normal suprarenal capsule, was seen. The portions of fat in which this supposed suprarenal was embedded were immediately placed in Müller's fluid, and handed to Dr. Muir, who kindly undertook to make the microscopic examination. The kidney, liver, and

spleen, which were carefully examined both with the naked eye and the microscope, were found to be perfectly normal.

Dr. Muir's Report on the Microscopical Examination of the

Fig. 2.—Untouched microphotograph of a transverse section through the mass of fat in which the left suprarenal capsule was supposed to be embedded (low power). In the centre a vessel surrounded by fat cells is seen. The fat cells in the immediate neighbourhood of the vessel are filled with small globules of oil, between which is a slightly granular material which colours of a brown tint with the rubin-orange stain.

Mass of Fat in which the Left Suprarenal Capsule was Supposed to be Embedded.—"I have examined three separate pieces of the tissues, and all show similar appearances. The tissue is composed of lobules of fatty tissue with vessels running in the central part (see Fig. 2). Some of these vessels are of considerable size. The cells at the periphery do not differ

Fig. 3.—Untouched microphotograph of a portion of the tissue round the vessel seen in Fig. 2 (high power). Numerous small globules are seen within what appear to be fat cells.

from ordinary fat cells, but those arranged around the vessels show a peculiar appearance. They are filled with small

⁴ The fact that after a year's treatment with suprarenal extract the patient could walk a distance of eight miles, whereas before the treatment was commenced "he was so feeble that he was only just able to dress and undress himself, and that he had to crawl up to his bedroom on his hands and knees," speaks volumes in favour of the remarkable improvement which the treatment produced in this case.—B. B.

globules of oil, between which is a slightly granular material, which colours of a brown tint with the rubin-orange stain. These globules are smaller, and there is more granular material in the more centrally-placed cells, whilst towards the periphery they become larger, apparently by coalescence and disappearance of the granular material (see Fig. 3). The appearance is as if cells were becoming filled with droplets of oil, which afterwards run together so as to produce an ordinary fat cell—a condition suggesting the appearances seen in advanced fatty infiltration of the liver. There are no cells which one can identify as being of epithelial type, and there is no arrangement of the cells in columns, etc. All the tissue examined corresponds to this description. Amongst the cells undergoing this change are a few leucocytes here and there, but there is no trace of inflammatory change. There is nothing, therefore, in the sections which would enable one to identify the tissue as part of a suprarenal. If it is so the change is an extreme fatty infiltration, with ultimate transformation into ordinary adipose tissue. I am not familiar with these appearances as occurring in ordinary adipose tissue. I may state further that when Dr. Bramwell brought to me the piece of tissue for examination, the brownish sinuous outline in the fat certainly resembled that of a suprarenal; and I was greatly surprised to find, on microscopic examination, no trace of suprarenal structure. In view of the absence of anything else which could represent the suprarenal, I agree with Dr. Bramwell that the suprarenals were entirely absent or had been replaced by fat, and the facts stated are in favour of the latter view."

COMMENTARY.

From the account which I have now given you of this case, you will see that it was a very remarkable one. The symptoms were typical and characteristic of Addison's disease. Very great improvement resulted from the administration of suprarenal extract. On careful examination after death both suprarenal capsules were absent, the right being entirely, and the left almost entirely, replaced by fat. These are the most important points.

Another feature of clinical interest was the very dark pigmentation of the small-pox cicatrices, and the presence of an unusually large number of small pigmented freckles and flat moles. As Dr. Mossop has pointed out, the improvement which resulted from the administration of suprarenal extract was most marked. This is only what one would expect if Addison's disease is due to suppression of the function of the suprarenal bodies.

As I have already stated, cases such as this, in which the suprarenal bodies seem to have undergone a simple (cirrhotic) or fatty atrophy, have a very important bearing on the pathological physiology of the disease. They can hardly be explained except on the supposition that Addison's disease is due to suppression of the function of the suprarenal bodies, just as myxœdema is due to suppression of the function of the thyroid gland. But I have already referred to this point in detail, and I need not occupy your time by repeating what I have already said.

But the pathological condition merits further consideration. It is well known that in a certain small percentage of the cases of Addison's disease, simple fibrous atrophy of the capsules instead of the ordinary fibro-caseous tuberculous change is found after death. I have given you the details of a case of this kind which came under my observation in this out-patient department a few years ago. In other cases the lesion in the capsules has been described as a fatty change. Dr. Greenhow refers to several cases of this kind, though he seems to doubt whether they were actually cases of Addison's disease. The same authority (Dr. Greenhow) mentions one case in which the suprarenal capsules appeared to be completely absent.

In the case which I have just detailed it must, I think, be allowed either that the capsules were entirely absent or that they were replaced by fat. The only other explanation is that the suprarenal capsules were not removed from the body and were not sent to me, and that the portions of fat which Dr. Muir and I examined were merely portions of the fat in which the kidney is embedded. This explanation was suggested by one of the speakers at a recent meeting of the Edinburgh Pathological Club at which I showed these speci-

mens and detailed the clinical history of the case. This explanation is, in my opinion, quite untenable. It is of course quite possible in making a hurried *post-mortem* examination to miss the suprarenal capsules. I have, for example, often seen the right suprarenal capsule removed with the liver by an inexperienced pathologist, and supposed for the moment to be absent; but in this case the conditions were altogether different. That the fat which was attached to the kidneys did actually represent the remains of the suprarenal capsules cannot, I think, be doubted for the following reasons:

1. The patient had suffered during life from symptoms which were typical and characteristic of Addison's disease, and had been treated for eleven months with suprarenal extract on account of the Addison's disease. The case was, in fact, regarded as a typical case of Addison's disease in which notable improvement had occurred as the result of this treatment.

2. Three qualified medical practitioners made the *post-mortem* examination, with the express object of removing the suprarenal capsules. I am not acquainted with two of these gentlemen, but the third I have known for twenty-five years, and those who know him as well as I do will not doubt his competence and reliability.

3. This gentleman assures me that everything was removed which could possibly represent a suprarenal capsule, and was sent, along with the kidneys, immediately to myself. He states definitely that nothing was left in the body which could possibly represent a suprarenal capsule.

4. In the specimens which I received I found a large mass of fat attached to the upper end of each kidney. These masses of fat exactly occupied the position of the suprarenal capsules. Until I cut into these masses of fat and examined them I never for one moment doubted that the suprarenal capsules would be found in their interior.

5. In the mass of fat which occupied the position of the right suprarenal I did not find anything suggestive of a suprarenal capsule; but in the mass of fat which occupied the position of the left suprarenal, a dark, apparently pigmented, sinuous outline, which exactly resembled in size and shape the outline of a normal suprarenal body, could be seen with the naked eye.

6. Although the microscopical examination subsequently made by Dr. Muir failed to show anything which could be definitely identified as the remains of the suprarenal capsule, it showed appearances which are peculiar, and with which neither Dr. Muir nor myself are familiar as occurring in ordinary adipose tissue. Whether small localised hæmorrhages could produce such appearances or not I do not know.

Now, for the reasons which I have just stated, there can, I think, be little or no doubt that the suprarenal bodies were absent, and that they were replaced by fatty tissue. If this is so, the lesion is, so far as I know, unique; for although fatty changes in the suprarenal capsules have been previously described, I am not acquainted with any case in which there was complete fatty transformation such as existed in this case.

From a practical point of view, the marked improvement which was produced by the administration of suprarenal extract is the most important point in the case. It raises a question of great interest and practical importance—namely, Why does the administration of suprarenal extract prove beneficial in some cases of Addison's disease, whereas in others it seems to do little or no good? As Dr. Muir suggested to me, this case perhaps affords an answer to this question. In cases such as this, in which the function of the suprarenal capsules is simply, as it were, suppressed, and in which there is no tuberculous lesion and no involvement of (lesion in) the abdominal sympathetic, the administration of suprarenal extract would *a priori* be expected to produce more marked benefit than in those cases of Addison's disease in which the lesion of the capsules is tuberculous, and in which the abdominal sympathetic is extensively involved. I may make my meaning perhaps more clear by saying that if the thyroid body were completely destroyed by a tuberculous lesion, symptoms of myxœdema would result; but in cases of complete tuberculous destruction of the thyroid gland (if such a condition occurs), the results of thyroid treatment would in all probability be less satisfactory than in the

ordinary everyday cases in which the tissue of the thyroid gland is simply destroyed by a process of cirrhotic atrophy.

Now in typical cases of Addison's disease there is not only a tuberculous lesion and abolition of the function of the suprarenal capsules, but there is associated disease of the abdominal sympathetic. Hence perhaps the explanation of the fact that while thyroid extract speedily cures myxoedema, suprarenal extract does not as a rule produce marked benefit in cases of Addison's disease.

It remains to be seen whether, as this case seems to suggest, the administration of suprarenal extract is chiefly beneficial in those cases of Addison's disease in which the lesion is a simple atrophy or fatty degeneration. If this should turn out to be the case, we may in future be able to form, by means of this therapeutic test, a more accurate idea as to the exact nature of the lesion of the suprarenal capsules in cases of Addison's disease than is possible by any of our present means of diagnosis.

These therapeutic considerations lend, I think, additional support to the theory which I have for long advocated, that some of the symptoms of typical tuberculous cases of Addison's disease are probably due to the tuberculous character of the lesion, and to the associated disease in the abdominal sympathetic, which the tuberculous lesion in the capsules seems almost invariably to produce, while others are the result of abolition of the function of the suprarenal glands.

NOTE.—In conclusion I have to express my very sincere thanks to Dr. Mossop for having so generously allowed me to record the case; and also to Dr. Muir for the care and time which he has expended on the microscopical examination.

ABSTRACT OF AN ADDRESS ON THE SPREAD OF PLAGUE.

Delivered before the Epidemiological Society.

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TERMINOLOGY.

[AFTER some preliminary observations on the names which had been applied to plague, Dr. Cantlie said:]

The term "bubonic" so frequently applied to the disease is not so appropriate as would at first sight appear. A bubo is essentially the swelling of a gland caused by the entrance of septic materials in the tract of lymphatics over which the gland presides. This cannot be said to obtain in plague, for the so-called bubo of plague can in no sense be regarded as a sympathetic swelling, but merely the outcome of a blood poison. If it is to be classed a bubo at all, it must be distinctly understood to be an "idiopathic" bubo, a true *bubon d'emblée*. One never speaks of the buboes of tertiary syphilis nor of scrofulous buboes. The terms may be clinically correct, but they are not in common use; they have, however, as much right to be called bubonic as the glandular enlargements in plague. With these considerations before us I would venture to name the disease "Malignant Polyadenitis," in the hopes that attention may be drawn to the naming of the disease by more competent students than myself.

Plague or malignant polyadenitis we may define as "an acute febrile disease of an intensely fatal nature, characterised by inflammation of the lymphatic glands, marked cerebral and vascular disturbances, and by the presence of a specific bacillus."

GEOGRAPHICAL DISTRIBUTION.

The basin of the Mediterranean and the strip of country which runs parallel to that sea across the Asian continent from Turkey to China may be roughly taken as its present belt during the nineteenth century, but the Mediterranean part of the belt has disappeared almost wholly within the present generation. A map of the plague-stricken districts within the last fifty years shows plague astride the Hima-

layas with giant limbs reaching on one side the Red Sea and on the other the shores of the Pacific.

THE INFECTION OF ANIMALS.

The animal which above all others is known to be affected by plague is the rat; but the wide geographical area throughout which this animal is met with would seem to frustrate any attempt to determine a collateral distribution. On looking a little more closely, however, we find rats (the murine) divided into two great sections—the mures, inhabiting the Old World (except Madagascar), and the sigmodontes, inhabiting the New World and Madagascar. Of the mures, one subfamily, that of the nesokia, is met with, reaching from Palestine to Formosa across the northern part of India. The southern limit in India seems to be where the great bandicoot, or pig rat, exists, and here plague is unknown. This is the only animal which presents a geographical distribution well-nigh corresponding to the present distribution of plague, and it is the animal above all others which is looked upon as being liable to be attacked by plague.

[Dr. Cantlie discussed the evidence as to the infection of other animals, and summed up the facts as follows:]

We find that pigs, dogs, rats, snakes, jackals, and pigeons are affected by a fatal malady, whilst plague is epidemic among human beings. Pigs and dogs are believed to be attacked only after consumption of plague flesh. Snakes by the swallowing of rats, and possibly jackals, are infected in the same way. None of the purely herbivorous animals, horses, donkeys, oxen, sheep, goats, or rabbits, are attacked. It is the flesh-eating animals which are the sufferers. Of course, the rabbit, guinea-pig, and a number of animals can be inoculated experimentally or made to consume plague-diseased food, but no herbivorous animal acquires it by the natural processes of infection. If it is by consumption of flesh that animals are infected, how do human beings get it? The animals affected seem to become infected from flesh: the snake from the rat, the jackal, pig, and dog from eating the flesh of persons dead from plague; but how does the rat become infected? Could we find that out we should likely know how man is infected. One animal missing in the scale is the cat; if rats perish from plague surely their mortal enemy, the cat, would be diseased. Perhaps the instinct of the cat teaches it to avoid the diseased rat. In Hong Kong during 1894 many cats died in a peculiar way—the chief symptom being paralysis of the hind legs.

PESTIS MINOR.

[With regard to the nature of *pestis minor*, Dr. Cantlie observed:]

Is there a disease of an epidemic character, attended by a low death-rate, characterised by polyadenitis and showing in the blood and tissues a bacillus resembling the bacillus met with in typical plague (malignant polyadenitis), and yet so apart clinically that it is either a separate disease or caused by the same bacillus in a lesser or non-toxic form?

From all hands we have evidence of such a disease—namely, a *pestis minor*, benign polyadenitis. 1. The Russian outbreak at Astrakan in 1877 was probably, nay certainly, of this nature, the low rate of mortality being sufficient to stamp it other than true plague. It is to be noted that the typical plague which ranged in the same province appeared, not amongst the community affected with *pestis minor*, but in a district 150 miles away, where *pestis minor* was unknown. 2. In Calcutta six years ago a form of fever existed among the British troops there which in all points resembled the present form of bubonic fever which exists there now—namely, fever with specific glandular swellings. 3. We have it also from Calcutta that the natives are frequently afflicted with glandular enlargements during malarial fever. 4. In the far east, from Singapore, the Straits, and along the coast of China as far as Shanghai, between the years 1892 and 1896 we have accounts of a singular affection of the inguinal glands which occupied the attention of the Singapore and Hong Kong Branches of the British Medical Association. The correspondence was carried on between the Societies, and there is no doubt the affection at both places was identical in its nature.

I am compelled to draw attention to this subject in consequence of a paper which appeared in the BRITISH MEDICAL