the wound, and which was accredited with exerting a sympathetic influence upon it, while the wound itself was simply covered up and left to itself. The beneficial effects of this surreptitiously, as it were, introduced method can scarcely be overestimated, and it is an illustration of the manner in which long-standing and erroneous impressions are, now and then, by counter and equally erroneous, though less mischievous impressions, summarily dislodged.

THE GOULSTONIAN LECTURES ON THE SUPRARENAL BODIES.

Delivered before the Royal College of Physicians of London,

By H. D. ROLLESTON, M.A., M.D., F.R.C.P.,
Fellow of St. John's College, Cambridge; Assistant-Physician and
Lecturer on Pathology at St. George's Hospital.

LECTURE II.

PHYSIOLOGY OF THE SUPRARENAL BODIES.

BROWN-SÉQUARD, stimulated by the pathological researches of Addison, investigated the physiology of the suprarenal capsules in dogs, cats, rabbits, and guinea-pigs, by removing them and noting the results. From a series of sixty experiments on animals he came to the following conclusions:

1. That the suprarenal capsules are absolutely essential to life.
2. That suppression of their functions is more rapidly fatal than suppression of the secretion of urine.
3. That the function of the suprarenal bodies was to modify or to destroy a substance which had the property of transforming itself into pigment. When the suprarenal capsules are removed or destroyed the pigment collects in the blood, but there is no pigmentation of the skin.
4. That in an animal from whom the suprarenal capsules have been removed the blood becomes poisonous, and when injected into other animals of the same species often produces death.

Dominicis¹ quite recently has found removal of the suprarenal capsules invariably fatal in a very few hours. Gratiolet² repeated Brown-Séquad's experiments; he often removed the left suprarenal capsule in guinea-pigs without any serious symptoms resulting, but the additional removal of the right one was fatal in three days, and since peritonitis and hepatitis were present, the fatal result was thus explained by him.

Philippeaux³ removed both the suprarenal capsules from rats without producing any symptoms, and therefore considered that death, when it follows this experiment, is due to lesions of other organs. Tizzoni⁴ criticises these results, and considers that a sufficient time was not allowed to elapse after the operation, and that because the animals did not die soon after the removal of the suprarenal capsules it was too hurriedly assumed that they had recovered.

George Harley⁵ came to the conclusion that the suprarenals are not absolutely necessary to life; that when death follows their removal it is in most cases due to injury to neighbouring tissues, chiefly the sympathetic. He successfully removed both suprarenals from rats which survived the operation without ill effects for months.⁶

Schiff, Nothnagel,⁷ Martin-Magron, Chatelain,⁸ and recently Pal⁹ and Berdach,¹⁰ obtained results in favour of the view that the suprarenal bodies were not necessary to life. In a later paper Brown-Séquad expressed himself as convinced of the correctness of his views, and further stated that the results of removal could not be explained by any concomitant lesions such as peritonitis, hepatitis, damage to kidneys, renal veins, inferior vena cava or sympathetic.

In addition to Tizzoni's criticism there is this objection that even when both suprarenal bodies have been completely removed the presence of accessory suprarenal bodies in various situations mentioned above may compensate for the removal of the normal glands. Stilling has shown that under such conditions the accessory adrenals may undergo a compensatory hypertrophy. Alexander points out that, owing to the very close connection of the right suprarenal capsule with

the inferior vena cava it is not improbable that fragments of it might be left behind, and by compensatory hypertrophy might prevent the development of symptoms due to complete removal.

MacMunn,¹¹ by means of spectroscopic examination, found a histohæmatin in the cortex and free hæmochromogen in the medulla of the suprarenal capsules. Hæmochromogen, the writer considers, is an excretory stage in the history of of blood pigment, and is probably formed by a downward metabolism from hæmoglobin and histohæmatins. He put forward the hypothesis that the function of the suprarenals is to pick out of the circulation the effete or worn-out pigments of the blood and their accompanying proteids. He further stated that when these pigment-metabolising organs are diseased there should be present in the urine incompletely metabolised pigments. This he found in a body he called urohæmatoporphyrin.

Foa and Pellacani¹² found injection of aqueous and alcoholic extracts of suprarenal bodies fatal to frogs, rabbits, and dogs. Alexander¹³ believed that in the preparation of these extracts artificial poisons were produced. Schäfer and Oliver¹⁴, by injection of large quantities (equal to 50 grains of the gland) of aqueous suprarenal extract, produced death in rabbits in twenty-four hours.

The poisonous body has been thought to be neurine, which, being continually formed by the activity of the muscular and nervous systems, is eliminated or destroyed by the suprarenal bodies (Marino Zucco,¹⁵ Carbone¹⁶); it is said to have been found in urine of Addison's disease.¹⁷

It was suggested that the toxic effects were due not so much to neurine as to combinations of phosphoric acids with that base (Marino Zucco¹⁸), the toxic properties of the extract being destroyed by the addition of hydrochloric acid, which broke up the phosphate of neurine.

Oliver and Schäfer showed that the symptoms of toxic doses of suprarenal extract do not correspond to those of neurine, and that the phosphate and hydrochlorate of neurine have the same effect as the base. Supino¹⁹ repeated Marino Zucco's experiments with a negative result as regards neurine.

What the active principle of the extract of the suprarenal bodies may be is at present not established. Bodies such as leucin (Virchow), lecithin,²⁰ taurocholic and hippuric acid (Vulpian and Closz), and benzoic acid have been extracted from the suprarenal capsules, but there is nothing to show that the effects of injection of suprarenal juice are due to any of them, or that they have been picked out of the circulation, and are in process of being removed by the instrumentality of the suprarenal bodies.

Mr. Moore²¹ has found that the active principle of suprarenal extract is not a proteid or a carbohydrate. It is not affected by acids or by boiling for some minutes, but is destroyed by alkalies, reducing agents, and by continued boiling. It dialyses and it has a powerful reducing action. It has not been isolated; its properties resemble those of a reducing agent found in 1856 by Vulpian in the medulla of the suprarenal bodies.

As leucin is a product of downward metabolism of proteids, its occurrence in extracts of the suprarenal bodies is probably explained as the result of decomposition taking place. Leucin is not poisonous. Subcutaneous injections of increasing quantities of leucin into animals have been described as giving rise to nephritis²² and albuminuria. These results do not follow removal of the suprarenal bodies or the injection of suprarenal extract, and since leucin is normally transformed by the liver into urea, there is no reason to believe that leucin has anything to do with the suprarenal bodies.

Lecithin is found in most parts of the body; in itself it has no toxic effects, but it may be changed into choline,²³ which has poisonous properties like those of neurine. The effects of neurine and of extract of suprarenal capsules have been shown by Schäfer and Oliver to be different; hence as the properties of neurine and choline are alike,²⁴ it may be concluded that the presence of choline or lecithin cannot explain the activity of suprarenal extract, or an accumulation of these bodies in the blood account for the toxic symptoms resulting after removal of the suprarenal capsules.

In the same way benzoic, hippuric, and taurocholic acids cannot be held to be responsible for the active properties of

suprarenal extract, or, on the hypothesis that they accumulate in the body on removal of the capsules, for a toxic condition of the blood.

Tizzoni,²⁵ in experimental removal of the suprarenal capsules in rabbits, obtained remarkable results, which are the same whether one or both organs are removed or whether one is first removed and later the other. It makes no difference if the crushed suprarenal capsule is left to be absorbed in the body. Leaving the crushed suprarenal capsule in the body does not lead to any symptoms of auto-intoxication, as might have been expected if the suprarenal capsules excreted any poison from the body.

Death occurs either shortly after the operation or after a long interval—130 to 997 days—the symptoms being much alike in either case, but after the prolonged interval the symptoms resembled those of Addison's disease more than in the former case. It is interesting to compare these results with the acute and chronic myxedema²⁶ produced by experimental thyroidectomy in monkeys. Pigmentation came on slowly, first around the mouth and nostrils, then on the oral mucous membrane and on the tongue.

Pigmentation occurred in 13 out of 30 rabbits dying at a period remote from the operation, whereas Nothnagel found it in only 3 out of 153 cases in which the suprarenal bodies were crushed. Death was ushered in by diminution of motor power and blunting of sensation, coma, convulsions, and opisthotonos.

The changes in the nervous system were occasionally visible to the naked eye, but though microscopic changes were present in the majority of cases they were by no means universal.

In cases which died soon after operation, disturbance of the circulation, congestion, and hæmorrhages were seen in the grey matter of the cord, especially around the central canal and also in the medulla, where hæmorrhage about the vagus nucleus accounted for death. The change was more intense in the cervical and upper dorsal regions than in the lumbar part of the cord. The pia mater was inflamed, and the grey matter of the cerebrum and the lining of the lateral ventricles underwent a similar, though more diffuse, change to that in the grey matter of the cord. In animals dying long after the operation the parts of the cord affected were the same, and showed inflammatory exudation with atrophic changes of the nerve elements, while in addition a systemic degeneration may be seen in Goll's columns. Degenerative changes occur irregularly in the peripheral nerves. In connection with the situation of these changes which tend to descend towards the suprarenal bodies, it should be noted that Arnaud and Alexais²⁷ have observed, after removal of the suprarenal bodies, an ascending degeneration, starting from the region of the suprarenal bodies, through the semilunar ganglia to the lateral region of the cord.

CONNECTION OF REMOVAL OF THE SUPRARENAL BODIES WITH THE OBSERVED CHANGES IN THE NERVOUS SYSTEM.

Tizzoni argues that as the same result follows removal whether of one or of both organs the cause cannot be a toxic agent, and sees nothing to support the theory that it is due to changes or any trophic influences exerted by the adrenal bodies on the central nervous system. He considers that the nervous lesions are due to alterations in the circulation through the blood vessels, due to influences travelling in the sympathetic, and primarily due to the destruction of the suprarenal bodies. However, he finds that changes in the solar plexus and semilunar ganglia are not always present. He suggests that in cases of some standing, where no change is found, degenerative changes did occur but have now passed away. He, however, leaves the connection between removal of the suprarenal bodies and the nervous lesions open. The fact that death sometimes occurs soon, at other times after a prolonged interval from the operation, he believes is due to the varying amount of damage done in the process of ablation. He concludes by considering the suprarenal bodies of importance from their close relation to the sympathetic, and does not regard them as functional glands.

Stilling²⁸ thinks that Tizzoni's plan of removing the suprarenal bodies from the back may cause the changes in the central nervous system by a direct extension of the inflammatory process from the wound to the cord. Stilling reached

the suprarenal bodies by laparotomy, and though he examined for changes in the central nervous system, never found any. After removal of the suprarenal bodies from dogs, Berdach²⁹ noticed an abnormally low temperature, and attributes this to the influence of the sympathetic. Abelous and Langlois,³⁰ in a series of papers, have come to conclusions of a very different nature from those of Tizzoni.

Removal of one suprarenal body from frogs and guinea-pigs leads to no bad results, while removal of both rapidly causes death by toxæmia. The toxic substance is produced by general metabolism of the body, especially of the muscles, it has some resemblance to toxic bodies in blood of tetanised animals, and acts like curare on the motor nerve endings, and in addition on the muscles themselves. Injections of suprarenal extract postpones this toxæmia, and a piece of suprarenal capsule, if introduced into the dorsal lymph sac of a frog whose suprarenal bodies have been removed, acts in the same way.

Repeated injections of the blood from an animal whose suprarenal bodies have been removed into a normal animal bring on symptoms like those produced by removal of the suprarenal bodies, which are, however, transient: if injected into an animal deprived of its suprarenal bodies death is hastened. Therefore the suprarenal capsules are active glands which normally produce an internal secretion to antagonise toxic bodies formed during metabolism, and thus diminish the toxic properties of the blood. On destruction of the suprarenal capsules the poisonous bodies accumulate in the blood and give rise to symptoms resembling those of curare poisoning.

Supino,³¹ from experimental research, believes that rabbits can survive the removal of one or both suprarenal bodies, but finds that their blood, when injected into frogs, produces a toxic effect like curare. This toxic property of the blood lasts for years.

Langlois and Chassevent³² find that the blood in the suprarenal vein contains less oxygen than arterial, though much more than ordinary venous, blood. The suprarenal bodies thus receive an excess of arterial blood like other important glands—as, for example, the submaxillary gland.

According to Boinet,³³ ligature of the pedicles, including the veins, of the suprarenal capsules is more fatal than removal of the glands themselves. This has an important bearing on the question whether removal of the suprarenal bodies produces ill effects by suppression of their function or from damage done to the neighbouring sympathetic. Ligature of the pedicle of the gland abolishes the functional activity, while it gives rise to much less injury than the ablation of the glands. From this observation it follows that ill effects are due to interference with the function of these bodies rather than to irritation of the sympathetic set up by their removal. Boinet found that after ligature of the pedicle of one adrenal body and removal of the other, which was then engrafted into the peritoneal cavity, life was prolonged for a very considerable time.

In addition to Boinet's work the observations of Thierloix³⁴ show that the results of ablations are to be explained by interference with the functional activity of the suprarenal bodies, and not by the mere traumatic effect of their removal. Removal of one suprarenal body in dogs was followed by hypertrophy of the other and by no symptoms; subsequent removal of the remaining organ led to coma and death. It is very improbable that this was due to injury to the sympathetic, because if the remaining organ was separated from all its nervous connections and left *in situ* no symptoms resulted. The last procedure would entail fully as much, if not more, damage to the sympathetic as removal of the organ.

In the history of all important ablation experiments, for example, the thyroid, pancreas, and kidney, the typical symptoms and physiological changes have been explained by some observers as due rather to secondary effects on the surrounding nerves than to the specific effect of removal of the gland.

G. Oliver and Schäfer,³⁵ working with suprarenal extracts (watery, glycerinic, or alcoholic) of man, calves, sheep, and dogs, and injecting them into dogs, cats, rabbits, and frogs, have found:

1. A rise of blood pressure due to arterial constriction.

This is best seen after section of the vagi, which prevents the concomitant inhibition of the heart. The blood pressure may rise to double or even quadruple the normal and is not affected by stimulation of the depressor nerve. In a limb the constriction of the vessels may be shown by the diminution in bulk, as measured by the plethysmograph, or in the kidney, by Roy's oncometer. As this effect remains after section of the cord or of the nerves going to the limb it is due to peripheral and not to central influences.

2. On the heart suprarenal extract exerts a marked inhibitory effect through the vagus; the beats become feeble and slow. On cutting the vagi the heart beats much more quickly than normally, and its force is much augmented.

3. After a hypodermic injection of extract (equal to 1 or 2 grains of the gland) a frog shows absence of knee-jerks, and appears paralysed. The muscles react to direct stimulation or to stimulation of their nerves, but the contractions are modified, the relaxation period being greatly prolonged, as in veratrum poisoning. The effect is not at all comparable to that produced by curare. The effects come on thirty seconds after intravenous injection, and do not pass off so rapidly as the cardio-vascular phenomena; hence it appears that the extract becomes stored up in the muscles.

4. The active principle of the extract is present only in the medulla and not at all in the cortex.

Suprarenal extract acts on the arteries in exactly the opposite way to thyroid extract. Schäfer³⁶ does not commit himself as to whether the extract contains a useful substance, secreted by the suprarenal bodies, to be subsequently used in the economy, or whether the extract contains a poison which is formed by the tissues during their activity and is carried by the blood to be rendered innocuous by the adrenal bodies. But from the encouraging results he obtained in the treatment of Addison's disease it appears that Dr Oliver³⁷ probably regards it as a useful internal secretion.

Three deductions are possible from these researches into the physiology of the suprarenal bodies:

1. That they have no proper function, and are important only from their close relation to the sympathetic.

2. That they are excretory glands, removing pigment and toxins from the circulation.

3. That they are secretory glands, providing an internal secretion which is of use in the economy.

With the exception of Tizzoni's results, all modern work points strongly to the conclusion that the suprarenal capsules are functional, and that their importance does not depend on their anatomical relation to the sympathetic. The presence of accessory adrenal bodies or incomplete removal have been shown to be possible explanations of the negative results obtained by some of the earlier investigators.

The evidence is sufficiently strong to warrant the conclusion that the adrenal bodies are functional glands. It is, however, more convenient to postpone any discussion as to whether that function is of the nature of an excretion or a secretion until the explanation of Addison's disease is dealt with, since the physiology and pathology of these organs are so inextricably blended.

CONDITION OF SUPRARENAL CAPSULES IN ADDISON'S DISEASE.

In Addison's original paper (published in 1854) 11 cases are recorded; 5 of these cases had caseous tubercle in both suprarenals, and in 1 case tubercle was present in one suprarenal. One case (No. 4) appears to have been an example of cirrhosis and atrophy. In 3 cases there were secondary carcinomatous growths in the suprarenals, bilateral in 1 case, and unilateral in the other 2. In 1 additional case there was a secondary nodule of carcinoma blocking the right suprarenal vein associated with hæmorrhage into the corresponding capsule, but without any growths in either.

While the discovery was Addison's, the general recognition of this disease is, perhaps, chiefly due to the vigorous and loyal efforts of Dr. Wilks.

After the publication of his original memoir, Addison appears to have been inclined to modify his views as to a multiplicity of morbid conditions of the suprarenal capsules giving rise to the same series of symptoms, and to have wished to have removed from among the cases in his monograph those of carcinoma of the suprarenal capsules. While, with regard to the cause of the symptoms, he conjectured that the

intimate connection of the suprarenal bodies with the sympathetic had a large share in the production of the symptoms, thus in some degree throwing over his expressed opinion that the interruption of some special function of the suprarenal capsules was the explanation of the characteristic symptoms.

According to Dr. Wilks all genuine cases of Addison's are due to one and the same lesion of the suprarenal capsules. This view might be called the unity of Addison's disease. This lesion could now be considered to be tuberculous, but Dr. Wilks considered it to be a primary inflammation³⁸ comparable to hepatic cirrhosis, and regarded the atrophied cirrhotic condition of adrenal bodies sometimes seen as the last stage of the fibro-caseous change.

Dr. Greenhow³⁹ was a follower of the view of the unity of Addison's disease, and therefore criticised severely all the recorded cases in which the morbid condition of the suprarenal bodies was other than the fibro-caseous change, and concluded either that the symptoms (especially the pigmentation) were not characteristic of Addison's disease, or that the lesion found was incorrectly described.

The fibro-caseous change begins first in the medulla, and spreads gradually throughout the whole of the organ, and after destroying the cortex may set up inflammation in the adjacent tissues and adhesions to neighbouring organs. The semilunar ganglia and solar plexus are often described as being invaded by the inflammatory process, and again have been found quite free from any morbid change. Typically this lesion is bilateral, but cases of well marked Addison's disease occur with a unilateral lesion.⁴⁰

The caseous change has very frequently been shown to contain bacilli, though in others repeated examinations have failed to demonstrate their presence. I am indebted to Professor Delépine's kindness for leave to mention such a case of Addison's disease with caseous suprarenal bodies in which no tubercle bacilli could be found. Subcutaneous inoculation of caseous material into guinea-pigs after Villemin's method⁴¹ did not lead to tuberculosis. So that although the lesion is generally tuberculous, it is not necessarily so in all cases. This condition is certainly the one more commonly found in association with Addison's disease. In 285 cases (collected by Lewin) of the disease this lesion was present in 211. Tuberculous inflammation of the suprarenal bodies, like that of the lungs, is much commoner than any other form of chronic inflammation. It is interesting to contrast the liability of the suprarenal bodies to tubercle with the marked immunity of the thyroid gland.

The late Dr. Habershon⁴² first showed that as the result of inflammation spreading from the suprarenal bodies the semilunar ganglia and their branches may become surrounded by dense fibrous tissue. Sclerosis of the abdominal sympathetic has been confirmed in cases of Addison's disease by many observers.

Dr. Greenhow⁴³ described two stages in the process: (1) a stage of irritation of the semilunar ganglia and the nerves connecting them with the suprarenal capsules, as shown by redness and swelling; and (2) a further stage of atrophy and fatty degeneration.

On the other hand, the absence of any alteration of these same structures has been repeatedly recorded. The extremely careful examinations made by Dr. Robinson for Dr. Mann⁴⁴ on two cases of Addison's disease serve as a model for such investigations, since a control examination was made at the same time of the same structures from a patient of the same age where there was no reason to suspect anything abnormal.

Von Kahlen⁴⁵ criticises the published observations as to the condition of the semilunar ganglia and sympathetic in cases of Addison's disease, and does not consider either the positive or negative results of much value.

He examined two cases of Addison's disease, and found⁴⁶ the following changes in the semilunar ganglia: Hyaline degeneration and thickening of the vessel walls, small cell infiltration, and hæmorrhages in connection with their adventitia, and pigmentary atrophy of the ganglion cells and thickening of their capsules. He considers that these changes have a direct causal relation to the symptoms of Addison's disease. He found the splanchnic nerves in the two cases quite healthy. Jurgens, however, has described degeneration of the splanchnics in Addison's disease. The bearing of these

observations must be considered in the light of Hale White's⁴⁷ description of the normal histology of the semilunar ganglia in adults. The cells are pigmented and atrophied, the degree of atrophy increasing with age; the fibrous tissue was often very much increased in amount, and in a few instances the section was crowded with leucocytes without any apparent reason. No constant arrangement in small blood vessels could be discovered. These changes occurring normally have such a close resemblance to those to which von Kahlden attaches importance as being responsible for the symptoms of Addison's disease that it seems very doubtful whether the changes described by this observer had anything to do with the production of the symptoms of Addison's disease.

Malignant disease of the suprarenal capsules occasionally gives rise to some of the symptoms of Addison's disease, such as gastric disturbance, extreme debility, and pigmentation. Typical cases of Addison's disease are naturally those in which there is no other organ affected, and in which the disease runs its own course without any complications. When growths develop secondarily in the suprarenal bodies the primary growth may give rise to symptoms which throw into the shade or obscure any that may be due to interference with the suprarenal bodies. The comparatively rapid progress of the primary malignant disease may kill the patient before the secondary affection of the suprarenal bodies has had time to lead to any distinct symptoms.

Again, in many cases the presence of malignant disease, if ascertained, would be quite sufficient to explain any symptoms which otherwise might be due to suprarenal disease.

It is undoubtedly true that the suprarenal bodies may be apparently almost completely destroyed by carcinoma, and yet no special symptoms result. The same, however, is true of tubercle, and especially where there is extensive tuberculous disease elsewhere. Perhaps in both cases death has occurred before symptoms characteristic of Addison's disease have had time to develop.

Well-established examples of simple atrophy⁴⁸ of the suprarenal capsules, without any fibrous increase in the substance of the organ, or of any fibrous adhesions around them, have often been described as giving rise to the typical clinical picture of Addison's disease. The atrophy in some of the cases was extreme, the organs in many cases requiring very careful and minute dissection. In some instances they are described as being of the size of peas. It cannot be wondered at that in some cases, as in Dr. Spender's, they are described as being absent. These cases are of great importance, as will be seen later, in supporting the view that the symptoms of the disease are due to the absence of the functional activity of the organs, and not to irritation of the neighbouring important sympathetic nerves. In these cases of atrophy the sympathetic plexuses and semilunar ganglia were in most instances carefully examined, and stated to be normal. The subject of atrophy of the suprarenal bodies has already been referred to.

Chronic interstitial inflammation⁴⁹ of the suprarenal bodies, leading to atrophy, and homologous with atrophic cirrhosis of the liver, has given rise to typical Addison's disease. The chronic fibrosis is quite unconnected with the production of any caseous material, and does not show any evidence of tubercle, such as bacilli. The late Dr. Haddon compared this change in the suprarenal bodies to those met with in the thyroid gland in myxœdema, and expressed his opinion that the essential factor in Addison's disease is, as in myxœdema, a destructive change, the anatomical condition being of no consequence as long as it is destructive.

A few cases⁵⁰ showing an apparent connection between hæmorrhages into the suprarenals and blood cysts occupying them, on the one hand, and the symptoms of Addison's disease, on the other, have been recorded. Apart from disease of the suprarenals of the various kinds already mentioned, there are some cases recorded of symptoms like those met with in Addison's disease being associated only with alteration of the semilunar ganglia or abdominal sympathetic.

Guay⁵¹ records two such cases: (1) Under the care of M. Raymond, of lymphadenoma, with some of the symptoms of Addison's disease the semilunar ganglia and solar plexus were found enclosed in masses of growth, but the suprarenal capsules were intact. (2) Under the care of Dr. Brault, a man with advanced phthisis, who was in the last stage of debility and markedly pigmented. The suprarenal bodies appeared normal to the naked eye, though microscopically there was a little

chronic inflammation in the right one. In the right semilunar ganglion there was a small caseous nodule.

Dr. J. K. Fowler⁵² has recorded a case under the care of the late Sir George Paget, in which the suprarenal capsules were healthy, but the semilunar ganglia and solar plexus were buried in a mass of lymphadenomatous growth. Clinically the case had marked pigmentation.

Von Kahlden⁵³ quotes a similar case recorded by Nieszkowski in the *Gazette des Hôpitaux*, 1887.

To summarise the conditions of the suprarenal bodies recorded in cases of Addison's disease, there are the following:

1. The fibro-caseous lesion due to tuberculosis—far the commonest condition found.
2. Simple atrophy.
3. Chronic interstitial inflammation leading to atrophy.
4. Malignant disease invading the capsules, including Addison's case of a malignant nodule compressing the suprarenal vein.
5. Blood extravasated into the suprarenal bodies.
6. No lesion of the suprarenal bodies themselves, but pressure or inflammation involving the semilunar ganglia.

The first is the only common cause of Addison's disease. The others with the exception of simple atrophy may be considered as very rare.

ANATOMICAL DISTRIBUTION OF CUTANEOUS PIGMENT IN ADDISON'S DISEASE.

The pigmentation is an exaggeration of the normal, and is met with therefore on the face, neck, hands, anterior folds of axilla, nipples, perineum, and genitals. The occurrence of small pigmented spots on the skin is, according to Dr. Greenhow, characteristic. Any cause of irritation, such as pressure, the application of blisters, or inflammation of the skin, is followed by marked pigmentation. During the progress of the disease the hair has been noticed to become darker. Microscopically the pigment is found in the cells of the stratum Malpighii, the more superficial layers of the epidermis being quite or almost free from any pigment.

The dermis shows a few pigmented cells, "carrier cells," which it is thought convey the pigment from the blood vessels of the dermis to the stratum Malpighii. These wandering cells are found around the vessels in the superficial parts of the dermis, where they absorb pigment from the blood vessels,⁵⁴ the method of absorption being doubtful. That hæmoglobin is not absorbed directly is shown by the absence of iron from melanin, so that if the melanin in normal and abnormal pigmentation of the skin is eventually derived from the blood considerable metabolism must intervene.

Demiéville and Riehl⁵⁵ have found that the vessels of the cutis in the pigmented areas show small cell-infiltration and small hæmorrhages in their adventitia, and conclude that the extravasated blood pigment passes up to the cells of the stratum Malpighii, not in a soluble form as a chromogen, but as pigment particles, and thus accounts for the pigmentation of the skin.

Von Kahlden believes that the pigment of the stratum Malpighii is derived by means of carrier cells from the blood, but does not consider that disease of changes in the vessel wall or hæmorrhages around the vessels have any causal connection with pigmentation.

Nothnagel regards the exaggeration of the normal pigmentation met with in Addison's disease as due to functional, not organic, change in the vessel wall allowing increased transference of pigment to the stratum Malpighii.⁵⁶

The general consensus of opinion is that the melanin of the stratum Malpighii is ultimately derived from the hæmoglobin, and that in abnormal pigmentation this process is exaggerated. Delépine,⁵⁷ however, has put forward the view that by the activity of the cell protoplasm of the stratum mucosum the melanin is manufactured, and passing out of the cells into the lymphatics of the corium, is carried away and transformed into hæmoglobin. On the view that melanin is an antecedent and not a derivative of hæmoglobin, the carrier cells might be regarded as transferring the melanin from the epidermis to the lymphatics and vessels of the dermis. Auerbeck and Burger⁵⁸ believe that the pigment in Addison's disease is due to very active metabolism in the cells of the stratum Malpighii.

PIGMENTATION OF MUCOUS MEMBRANE.

Pigmentation of mucous surfaces is rarer, occurs in more

advanced cases, and is usually regarded as being a sign of more value than cutaneous pigmentation. It may be found along the line of contact of the lips, on the cheeks, gums, or tongue, especially if there be any cause of irritation, such as a carious tooth. It is said to occur in the vagina⁵⁹. The conjunctivæ⁶⁰ may in some cases, though very rarely, be pigmented.

Situation of the Pigment on the Mucous Membrane.—According to Dr. Greenhow⁶¹ the pigment in the tongue is found in the same layer as in the skin, namely, the stratum Malpighii or mucosum. Haddon⁶² found the pigment quite as plentiful in the corium as in the stratum mucosum of the buccal mucous membrane.

Tizzoni⁶³ in the pigmentation produced experimentally in the buccal mucosa of rabbits, found pigmented carrier cells in the corium, and pigment in the deeper layers of the stratum mucosum.

Dixon Mann⁶⁴ draws a sharp distinction between pigmentation of the mucous membrane and that of the skin. Pigmentation of mucous membrane is not general; it requires certain local conditions (friction, local hyperæmia) for its development, and the pigment has a different histological site. The corium contains pigmented carrier cells, as is the case in the skin, but the stratum mucosum contains no pigment, possibly because the cells composing it do not have the finger-like processes⁶⁵ which in the skin are thought to receive the pigment from the carrier cells. When, exceptionally, pigment was found in the stratum mucosum it was seen to be not in, but between, the cells.

Pigmentation of the Serous Membranes.—Addison⁶⁶ described discrete pigmentation of the peritoneum in one of his cases, and a similar case is mentioned by Dr. Wilks.⁶⁷ Dixon Mann⁶⁸ has described the same appearance; the intestines are described as being otherwise normal, and no mention is made of any old peritonitis or tuberculosis.

Dr. Greenhow⁶⁹ records a case of Addison's disease with pigmented tubercle of the peritoneum, accompanied by signs of past peritonitis. The same writer also quotes⁷⁰ a case recorded by Van Andel of pigmentation of the peritoneum, but no mention is made of the presence or absence of tubercle or of past peritonitis. As its occurrence is so rare, it is probable that when present pigmentation is due to past inflammation, and probably of a tuberculous character of the peritoneum. No instance of similar pigmentation in the pericardium or in synovial membranes has been recorded. The marked pigmentation of the pia mater observed by the late Dr. Carrington⁷¹ seems to be unique, and might possibly have been due to the melanæmia of ague.

OTHER ANATOMICAL LESIONS MET WITH IN ADDISON'S DISEASE.

In some of Addison's cases a hypertrophied condition of the lymphoid follicles in the stomach and intestines, as well as some enlargement and softening of the spleen, were noted. The exaggeration of the lymphoid tissue has been frequently noted since, and Dr. Greenhow⁷² considered it as one of "the characteristic, though perhaps not quite invariable, lesions" of the disease. There does not appear to have been any diarrhoea in the cases in which this condition was marked. It might, perhaps, be considered that this condition of the lymphatic follicles is to some extent in favour of the view that when the suprarenal bodies are functionless, whether from destruction or atrophy, some toxin is circulating in the body. The occurrence of leucocytosis after the injection of bacterial poisons or even the injection of albumen⁷³ is presumably accompanied by increased activity of the lymphoid tissue of the organism. In some cases persistence of the thymus gland has been recorded.

A softened condition of the brain with an increased amount of cerebro-spinal fluid has been recorded in some cases⁷⁴ of Addison's disease, and was probably accidental, but its occurrence is of interest from the marked inflammatory changes resulting from removal of the suprarenal bodies in animals in Tizzoni's hands.

Tizzoni⁷⁵ quotes two cases of Addison's disease in which lesions of the central nervous system were found: 1. Bourredi's case: Caseous change in the suprarenal bodies associated with hyperæmia of the cord, perivascular inflammation, degeneration of nerve fibres, and changes of varying

degree in the ganglion cells. 2. Semmola's case: A normal condition of the suprarenal capsules accompanied by mucoid degeneration of the stroma of the abdominal ganglia of the sympathetic and small cell infiltration around the central canal of the spinal cord.

In connection with the view that Addison's disease is of the nature of a toxæmia, it would be natural to expect to find changes corresponding to those described by Bowman⁷⁶ in the spinal cord in pernicious anæmia.

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THE PATHOLOGY OF OEDEMA.¹

By WALTER S. LAZARUS-BARLOW, M.D., M.R.C.P.

[From the Pathological Laboratory, University of Cambridge.]

(Concluded from page 637.)

WE come now to the consideration of the œdema which accompanies inflammation. This œdema has long been regarded as the result of an injury to the blood vessel walls, whereby they allow fluids to exude with more ease than normally. That exudation from the blood vessels occurs as the result of a stimulus which is sufficiently powerful to impair the vitality of the tissues, though stopping short at actually destroying them, there is no doubt. The question we have here to consider is the reason for that exudation. Now the explanation of the œdema of inflammatory origin as dependent upon damage to the vessel wall really depends upon the fact that injury to the tissues is known to occur, and it is assumed that the blood vessels are injured as well. No doubt this is true, but if the exudation occur from damaged blood vessels it is necessary to prove that this exudation takes place in the actual region of damage. This, however, is not the case; the blood vessels which exude the fluid, namely, those which are actively congested, are at

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