Thesis for the Degree of M.D.

On Addison's Disease.

With notes on two cases; and also notes upon a case of Phthisiasis, complicated by Tubercular Pyo-nephrosis, which presented the Symptoms of Disease of the Suprarenal Capsules.

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Since the publication by Thomas Addison, in 1855, of his monograph on "The constitutional and local effects of Disease of the Supra-renal Capsules," the condition was known as Addison's Disease has attracted much attention, and the smallest addition to the literature on the subject is of interest especially if in any carefully recorded case the nature of the pathological lesion found post mortem is not such as might have been expected from the clinical features observed during the patient's life.

Addison himself gives in his monograph a complete clinical picture of this condition when he says that the "leading and characteristic features" usually presented are: anaemia, general languor and debility; remarkable feebleness of the heart's action, irritability of the stomach, and a peculiar change of colour in the skin, occurring in connexion with a disarranged condition of the supra-renal capsules; and in the majority of recorded cases these symptoms have been present in a greater or lesser degree, and in combination, without the presence of any other obvious causative lesion, form sufficient grounds on which to
base a diagnosis of the condition.

The suprarenal glands, normally two in number, are situated respectively in front of the upper portions of the right and left kidneys, the right suprarenal is roughly triangular in shape and is packed in between the kidney and right crus of the diaphragm, the left suprarenal is more semilunar in shape and also is in relation with the kidney and crus of the diaphragm of its own side; these bodies are supplied with blood by branches from the aorta and the phrenic and renal arteries, the right suprarenal vein returns its blood into the inferior vena-cava and the left into the left renal vein; the lymphatics communicate with the lumbar glands and the renal supply is from the solar and renal plexuses and also through the phrenic and perineuralic nerves.

Structurally the suprarenal capsules are divided into a cortex of a yellowish-brown colour and glandular in structure, and a medullary portion which is deep chocolate brown in colour and contains very numerous nerve cells, which are almost absent in the cortex which is divided into three zones, the zona reticularis nearest the medulla, the zona fasciculata and the zona glomerulosa which is most external; they are surrounded by a fibrous capsule and each.
organ weighs about a drachm. These glands are ductless.

The physiology of the supra-renal capsule has
given rise to much discussion, and before the publication
of Addison's observations they were considered as having
no special function, a view which was supported by
the experimental evidence of Harley and others, who
stated that in some animals these glands could be
removed without producing any ill effects, and
Tizzani, who was also of opinion that the capsule
were not necessary to life, attributed the death of
animals from which they had been removed as due
to the injury of some other structure.

More recently, however, Olivier and Schäfer have
fully investigated the functions of these bodies and
they state that their removal in sooner or later
invariably followed by death which is preceded by
great muscular prostration. These observers also
found that they could extract from the medulla of
the gland, but not from the cortex, a substance
which, when injected into the general circulation of
an animal, caused a enormous rise of blood-
pressure due to the constriction of the arterioles
throughout the body, and also to its direct effect on
the heart, this action they found to be equally well
marked when the vagi were cut and the spinal cord
destroyed, showing that it was a direct action upon
the muscle tissue itself, they also found that in a
nervous muscle preparation treated with these extracts
and stimulated by a single induction shock the
contraction was greatly prolonged, and from these
results they concluded that the suprarenal glands,
though ductless, are true secreting glands, and that
the matter which they form is a tonic by direct
action to the muscular tissue in general and to
the heart and arterial system in particular, and
this matter they found to be absent in the capsules
of patients suffering from Addison's disease.

With regard to the etiology of this disease there
is little to be said; it is more common in males than
in females in the ratio of about three to one.
Greenhow collected 183 cases of which 119 were males
and 64 females, while Wilks had twenty-five cases, 19 being
in males, and Osler twelve of which 9 were males.

The age at which the symptoms usually show them-
selves is from twenty to sixty years, a fact which
Greenhow emphasized as being the most energetic
period of life, but cases have occurred during the
first decade of existence, and Osler mentions a con-
genital case in which the organs were found cystic;
cases sometimes occur after fifty and Greenhow had
a case in a female whose age was said to be sixty-nine.

The disease is more common in the working classes, sometimes there is a family history of tuberculosis or malignant disease, or the patient may show signs of tuberculous disease of other organs, the symptoms may follow some injury to the back such as a strain, or a blow upon the abdomen, but in the great majority of cases the condition is insidious in its onset and can be referred to no particular cause.

The pathology of Addison's disease has been a matter of much dispute and still presents many difficulties which have not been lessened by the number of spurious cases which have been published under this name.

Addison, in his monograph, collected eleven cases in which the suprarenal lesion was in five definitely tuberculous; in four, including his case caused by the blocking of the left suprarenal vein by a malignant node; the lesion was malignant; in one the capsule was described as being in a fibro-fatty condition with considerable atrophy, while the remaining one is indefinite though probably tuberculous. Greenhow, however, considered that there was only one change in the suprarenal capsules which was the cause of true Addison's disease and that this change, though in different stages was identical in them all, an
opinion in which he was supported by Wilks and later by Faiger; the former however considered that the lesion was of a simple inflammatory nature whereas Greenhow favoured its tubercular origin, without definitely committing himself in either direction, and these authorities considered that the cases recorded by Addison himself, and others, in which the lesion was other than the fibrous capsule, were not to be regarded as examples of Addison's disease but as cases which merely bore a superficial resemblance to this condition and in which the symptoms were not pathognomonic. Greenhow also observed that in some cases the supra-sural capsule might be entirely destroyed by malignant growths without any of the symptoms of Addison's disease being produced and this fact led him to search for some agent other than the implication of these glands, which might be regarded as the main factor in producing the symptoms characteristic of the condition: he found that in many cases the nerves of the solar and sural nerves showed under the microscope marked evidence of increase in their fibrous coverings and that the nerve fibres themselves, though usually healthy, sometimes also showed inflammatory changes. Habershon and Tuckwell had found the cells of the
Solar plexus and semi-lunar ganglion in a state of fatty degeneration, and showing marked pigmentation in cases where the capillary lesion was typically fibrinous, and Greenhow states that Addison himself drew attention to the fact that Mr. Quinsey had found on microscopical examination of a portion of the semi-lunar ganglion and solar plexus in one of his cases, that they had undergone some form of fatty degeneration: this however was a misconception on Greenhow's part as the specimen referred to are from a case of Pernicious Anaemia, of which Addison gives a beautifully concise description in the early part of his monograph on "Diseases of the suprarenal capsules." These observations however led him to conclude that Addison's disease was in reality caused by implication of the abdominal sympathetic nerves and ganglia, secondary to the lesion in the glands themselves, and that the symptoms were due at first to the irritation and later to the consequent atrophy of these nervous structures; and he strengthened this theory by the fact that both glands might be entirely destroyed by malignant disease without causing symptoms of Addison's disease which appeared to prove that it did not depend upon abolition of their
function, and furthermore that symptoms might be present though only one gland was affected, (a statement which was doubted by Fagge).

More recently however Hale White has shown that fatty and pigmentary deposits occur in the cells of the abdominal and sympathetic ganglia in many conditions, and are practically normal in advanced age, and hence the theory of nervous causation of Addison's disease gains no support from the occurrence of these changes; further Fowler and others have recorded cases in which the abdominal sympathetic has been involved in masses of lymphadenomatous tissue or exposed to continued irritation from spinal disease without causing any of the classic symptoms, excepting perhaps a little pigmentation, and this theory of nervous implication will not account for the cases in which the brown was a simple atrophy of the glands.

Rollston has shown that accessory supra-

venals are by no means rare, and that they may hypertrophy and carry on the functions of the main gland, which offers an explanation of the cases in which the glands were destroyed and symptoms were wanting; and the patient may have died before the more prominent symptoms set in.
In cases where only one gland is found affected, Rollerton thinks that the vessels, nerves, and lymphatics are probably implicated in inflammatory masses, or else that the single remaining gland is unable to cope with the increased strain thrown upon it.

These facts seem enough to prove that implication of the Solar Plexus symphonic ganglia and nerves is not enough to cause Addison's disease, and the researches of Oliver and Schäfer, before mentioned, support very strongly the theory that the condition is due to suppression of function of the Supra-rennal Capsules: cases in which the glands have been found healthy, but the sympathetic involved in those masses of old standing adhesions are also explained by Rollerton by the implication of the pia of the gland containing its vessels and nerves; though if this be so, it is difficult to understand why the capsules have not atrophied unless a collateral circulation has been established in which case their function would probably not be in abeyance.

Most recent authorities however agree that Addison's Disease may be produced by any destructive lesion of the Supra-rennal glands and Rollerton gives the following classification of these lesions:
in order of relative frequency:

(i) Fibro-caseous tuberculosis.
(ii) Simple atrophy.
(iii) Chronic interstitial inflammation causing atrophy.
(iv) Malignant disease.
(v) Haemorrhage into or around the capsule.
(vi) Pressure or inflammation involving the semilunar ganglia.

The symptoms from which Addison concluded that disease of the supra-renal capsules might be diagnosed are, as stated in his monograph, anemia.

2. General languor and weakness, or asthenia.

3. Feebleness of the heart's action.

4. Irritability of the stomach.

5. Pigmentation of the skin; and he pointed out that the disease was not to be diagnosed upon any one symptom but rather from the combination of them all: and these symptoms may now be considered individually.

Anemia, the first of Addison's symptoms, is one upon which he laid much stress; he alludes to the condition while speaking of the discoloration of the skin as "this form of anemia." He also speaks of the "anemicated eye" of one of his cases; he does not, however, appear to have enumerated the red corpuscles
or leucocytes in any of his cases, though this had been done by Vicini in 1852, neither did he estimate the haemoglobin; but he states that the blood of one patient showed a "considerable excess of white corpuscles." 38. Greenhow, on the other hand, did not find the blood abnormal in his series of cases, except in one, who had lost blood from a wound, in whom the red-corpuscles were deficient and many "small, highly refractive nuclei" were found, possibly haemoglobinemia, which Muller 39 noted to be increased in one case of Addison's disease. Anemia however, though frequently present, is not as a rule profound; it may however exist in a very advanced degree, so much so that Oster saw a case in which the diagnosis was not at first clear between Addison's disease and primiparous anemia. 30 Da Costa 31 states that in advanced cases erythrocyte counts of between two and three million may be seen while the haemoglobin percentage falls between twenty and forty; in these cases, poikilocytes and microcytes are numerous and small numbers of normoblasts occur, but megalocytes and megaloblasts are not met with; high erythrocyte counts, such as one of 5,800,000 per cmm recorded by Stockman 32; are attributable to blood inspiration from continued vomiting or diarrhea.
The leucocytes are usually normal or decreased in number sometimes even to extreme leucopenia, a relative lymphocytosis is usual according to Da Costa, and in some instances a few myelocytes and basophil leucocytes are to be found. The blood condition is therefore usually little below normal, but all degrees of secondary anaemia may occur depending probably upon the nature of the primary lesion.

As anaemia, the second of Addison's cardinal symptoms, is extremely characteristic of this condition, the onset of this languor may be very gradual but it reaches a profound degree, in uncomplicated cases, before death. In some cases however this debility may have been noticed a few weeks or even only a few days before the fatal event, and though frequently the first symptom to appear it may follow the pigmentation of the skin by some months or even by as much as five years, as was the case in a patient seen by Drs. Comill and Vast in Greenhow's collection.

The anaemia may be accompanied by little wasting of the muscles and emaciation is slight as a rule if present at all, and not infrequently the subcutaneous and intra-abdominal fat is even more abundant than usual; there seems
to be a mental and physical inability for any sustained effort, and the patient frequently lies for some days as if paralysed and finally dies of exhaustion, and this debility might well be produced by the absence of a normal muscular stimulant such as Schäfer and Oliver have shown to exist in the medulla of the suprarenal glands.

**Weakness of the Heart's action**, the third symptom, is always marked; the heart is not usually much enlarged and is frequently smaller than normal, and this weakness is shown by the small and feeble pulse which increases greatly in rate upon the slightest exertion or excitement. The volume of the pulse is as a rule very small, but it may be large and soft but extremely compressible, resembling that seen in some cases of pernicious anaemia.

The depressed condition of the circulation also shows itself by the frequent presence of faintness and palpitation, and by the syncope which so often proves fatal. This cardiac condition was supposed by Greenlaw to be due to the irritation of the abdominal sympathetic nerves, but it is probably in great measure caused by absence of the suprarenal secretion and consequent want of tone in
the heart and arteries, as in the other muscles of the body. On auscultation a faint blowing systolic murmur may often be heard over the base and great vessels; and the heart is commonly found post mortem to be in a condition of brown atrophy with some fatty or interstitial change. Effusion into the pericardial sac has been frequently noted.

Irritability of the stomach, the fourth cardial symptom, may be extremely prominent, and Adison has recorded one case in which the vomiting and pain to a suspicion that some "acid poison" might have been administered. The nausea and vomiting are usually late in their onset during the course of the disease but they may occur spasmodically for many months before the death of the patient: the vomited matters have no distinctive features and the tongue is usually clean. The bowels are most frequently constipated but this condition may alternate with intractable diarrhea which often proves fatal.

The post-mortem appearances of the stomach are not characteristic except that an increase of lymphoid tissue giving a laminated appearance to the organ was noted by Adison and has since been confirmed.
by other observers, and in this connexion it is of interest that the spleen has been frequently described as enlarged. Minute haemorrhages may often be seen in the gastric mucosa, and sometimes small ulcers formed by the breaking down of the summit of the lymphoid follicles; possibly the alimentary disturbance may be due to an atomic condition of the muscular structure of the stomach and bowel, and possibly in some part also to nervous irritation when this factor is also present.

**Pigmentation of the Skin**, the fifth and last classic symptom, is, when present, most striking and peculiar. Addison himself says that “the great distinctive mark of this form of anaemia is the singular dusky or dark discoloration of the skin”, and he infers that it is usually present, though it may be to only a slight extent, when the pathological change in the suprarenal capsules is in an early stage.

The typical discoloration is of an olive brown or smoky tint, sometimes approaching to greenness; it affects the whole of the body but is not of a uniform depth of colour, but is deepest in tint upon the face, neck and hands and upon the normally more deeply pigmented parts, the nipples, areolae,
The external aspects of the limbs are usually of a deeper colour being more subject to irritation, and the axillae and navel; those parts of the skin also, which are subjected to continued pressure or friction, as by garters or petticoat strings, are deeply pigmented, a fact which was well shown in a case recorded by Nicholson, where a baker's boy suffering from this disease exhibited broad dark bands from the friction of his braces and the basket which he habitually carried strapped to his back.

There may be, scattered over the body, numerous small intensely deeply coloured moles, and these were considered by Spencer to be of much diagnostic importance, and are, when present, of great assistance in differentiating the pigmentation of this disease from that caused by other agencies in which they do not, as a rule, occur. The dissemination may be blotchy and not general, and this is especially so in lesions of the capsule other than the fibro-casous tubercular change, and it may be interspersed with patches of sharply-defined leucoderma: the superficial scars left by blisters usually show increased depth of tone but...
in the typical discoloration of the skin the darker and lighter areas merge gradually into each other and are not clearly circumscribed, though at first sight this may appear to be the case. In well marked cases the appearance of the skin resembles that of a mulatto or one of the darker races of mankind, and, a point of much importance, the exposed parts of the skin are those in which the discoloration is most marked. The palms of the hands, the soles of the feet and the matrices of the nails are usually free from pigment.

The pigmented change is not however limited to the skin but is often in addition present in the mucous membrane of the mouth where slaty or brownish patches occur on the gums, lips, tongue and buccal mucosa, these areas on the tongue and lining of the mouth usually correspond to the sites where pressure is made by the teeth, they may however occur upon the hard palate where the pressure could hardly be operative, and discoloured stains have also been recorded upon the conjunctivae and vaginal mucous membrane: this change closely resembles that frequently seen in Lascars and Negroes and is considered by some authorities to be of more value than the cutaneous pigment-
...ation as a diagnostic sign, Schultz has observed similar mucous pigmentation in chronic stomach trouble and Thilings has recorded pigmentation of the buccal mucosa and glans penis in cases of pediculosis vestimenti. This localized deposit of pigment was not apparently noticed by Addison as he makes no mention of it in any of his cases. Darkened areas have been noted upon the serous membranes, and Yarger quotes a case of Carrington's in which the pleura of the lung was more deeply pigmented than normal. Addison also found in one of his cases numerous small deposits of black pigment beneath the peritoneum of the gut.

The pigmentation, though subject like the rest of the symptoms to acute exacerbations and remissions, is, like them, progressive; it may be the first symptom noticed by the patient and may precede the asthma by many months or years; on the other hand, it may be late in its onset and many well-marked cases are recorded in which pigmentation was almost or completely absent, and in these cases it is probable that the patient died before the pigment had time to appear.

The cause of the pigmentation is not at
present known: Greenlaw regarded it as due to 'reflex irritation through the cerebro spinal nervous system' and Wilks also took this view, it has also been attributed to vasomotor nerve irritation, trophic disturbance, some peculiar change in the blood, and want of excretion of some toxic material by the suprarenal glands though the latter theory is not supported by the fact that some cases of Addison's disease improve under treatment with extracts from these capsules.

In this relation it is interesting to find that Tizzoni noted pigmentation of the lips, tongue and oral mucosa in rabbits in which the capsules had been crushed in situ, and that these animals finally died with symptoms resembling those of Addison's disease in man.\(^\text{88}\).

Pigmentation of the peritoneum may be caused by former peritonitis and is of little value, and Greenlaw thought that in non-tuberculous cases the cutaneous discoloration was not characteristic but was such as is sometimes seen in other morbid states, Fagge was also of this opinion and called attention to the bronzing of the skin in chronic phthisis, paracolosis, malaria and other conditions.\(^\text{49}\) and mentions a case of leucoderma which was diagnosed as one of bronzed skin; the change of color...
seen in some cases of Graves' disease and of diabetes mellitus might give rise to diagnostic difficulty while chronic heart disease, uterine ehdoema, argyria, and pityriasis versicolor have each caused errors.

The pigment in Addison's Disease is found in the form of small brown or blackish granules situated in chief part, in the cells of the deeper layers of the sere mucosa; it is not however entirely intracellular and a certain amount is frequently found in the superficial layers of the epidermis; the greater part is however confined to the deeper layers of prickle-cells, as is the case in the dark skinned races. 51.

The skin itself is usually soft and moist but in some well marked cases there is a slight localized branny desquamation, and the general surface may be harsh and dry.

Symptoms referable to other systems have been recorded but are not of the same diagnostic value as those which have just been considered.

The nervous system shares in the general asthenia and while the muscles may not appear atrophied the patient may be quite unable to stand without support and almost unable to make any movement; cramps in the legs are not unusual and pains in the back and abdomen are of frequent occurrence.
Death may be preceded by coma, and convulsions were marked in one of Greenland's patients whenever he was touched. Dullness of sight and disturbances of sensation have also been recorded in the later stages, but the intellect is usually clear to the end.

In connexion with these nervous symptoms, the fact emphasized by Benda, that congenital atrophy of these glands is always associated with mal-development of the cerebro-spinal system is of great interest, and this observer considers that the suprarenal gland and nervous system are mutually necessary to each other's perfection; and Rehn states that in decapsulated rabbits, where death is rapid, the spinal cord and medulla show congestion and haemorrhages, while if death is more delayed sub-membranous extravasation is seen.

The urine shows no peculiar characters, though a pigment resembling melanin was described by one observer, indican may also be present, as in many other conditions. The thyroid may be somewhat enlarged and the thymus persistent, while the spleen is often enlarged, dark and soft. The other systems present as a rule no features directly referable to the condition of the suprarenal glands.
The diagnosis of Addison's disease is not difficult if the pigmentation be well marked and is accompanied by increasing asthenia and gastric irritability for which there is no discoverable cause. The profound debility of diabetes mellitus and pernicious anaemia, which bear some resemblance to this asthenia, must be severally excluded by the examination of the urine and blood, and in the former condition also by the polyuria and smaciation.

The characteristic discolouration of the skin and mucous membranes may be closely imitated by that produced by the presence of parasites, but this change of colour is not most deeply marked on the exposed parts or in those areas subjected to pressure and friction, and the presence of the deeply pigmented moles is of differential value: in Addison's disease also the typical distribution is general, though it apparently may be definitely localised especially in non-tuberculous lesions.

No single symptom is pathognomonic but the occurrence of asthenia without as a rule evacuation, pigmentation of the skin, irritability of the stomach and feeble circulatory functions, all of which are subject to acute exacerbations and remissions, a feature which is extremely characteristic, and for
which no other cause can be made out, from suffi-
cient ground for the diagnosis of some pathological
lesion affecting the function of the Supra-renal Capsules.
When however pigmentation is absent or only
present in very slight degree, diagnosis is rendered
much less easy, and the occurrence of a sudden
paroxysm of vomiting associated with collapse may
suggest irritant poisoning or acute abdominal ob-
struction or, as in one of the following cases, influ-
enza of the gastro-enteric type, whilst the discoulour-
ation of the skin is frequently attributed to sunburn
which, except that it is usually general, it closely
resembles; or to jaundice from which it may be
distinguished by the fact that the conjunctivae are
not stained yellow.

On the other hand though many cases of Addison's
disease escape early diagnosis, cases in which this
condition was suspected to exist but which proved to
be examples of other diseases in which some discoulour-
ation of the skin was present are equally numerous,
and Greenhow collected eleven cases in which pigment-
ation was more or less marked and the capsular tie
from disease, but in only one of these (case No.5)
were the symptoms comparable to those of the
supra-renal lesion, and in the remainder there were
physical signs sufficient to account for all the symptoms present.

There are still many who agree with Semmow's views upon the pathology of this disease, and it seems to be an established fact that the fibro-caseous tubercular change in the capsules produces a more typical clinical picture of this condition than does any other morbid change, with perhaps the single exception of the simple atrophy of these bodies.

The Prognosis is extremely unfavourable, the large majority of cases dying within eighteen months of the appearance of the first symptoms, and but a few even apparent recoveries taking place: the occurrence of periods of intermission, extending sometimes over several months, may give rise to a hope that the disease has been checked, but the symptoms are practically invariably progressive and death ensues in from five or six days to as many years.

Treatment must be for the main part on general lines; the debility when pronounced necessitates the patient being confined to bed; sudden movements and disturbances both mental and physical must be avoided in the fear of producing fatal syncope; the gastric and intestinal symptoms are usually not influenced
by diuretic measures and are best combated by the
use of bismuth and opium; purging must be very
carefully approached as diarrhoea if produced may
be rapidly fatal. Iron and strychnia appear in
some cases to do good, while the administration of
preparations of the suprarenal gland, either in dried
or fresh form, has in others been followed by
considerable and even lasting improvement; in
these cases under its influence flesh is gained,
energy increased, and even the pigmentation may
to a great extent disappear, and Lauder Brunton states
that perhaps occasionally complete recovery may
occur. Osler quotes Kinnicutt as saying that
out of 46 cases treated in this manner 6 were
cured and 22 improved, a proportion far above that
obtained by most observers whose cases have been
under prolonged supervision, and Rolleston is most
probably correct when he states that the lesion
in patients who have shown improvement to any
marked extent, under treatment with the gland-
substance, is most likely a simple atrophic change
whilst unfortunately the chronic interstitial
tubercular lesion is the typical, and by far the
most common, pathological change found in the
suprarenal substance in cases of Addison's Disease.
The following three cases form a series of cases which, I think, are of great interest, which is the greater since although the first two were typical examples of the condition under consideration, the third was proved at the post-mortem examination to be suffering from an entirely different disease; and although the clinical features presented by this patient during his illness, and the history of the onset of his symptoms, were, with the exception of the length of time during which the skin had been discoloured, identical with those which have been described as characteristic of Addison's Disease, the suprarenal capsules and their nervous and vascular connexions were found to be absolutely healthy.

Cases No. 1 and 2 show between them almost every point of interest in connection with this disease; in both there was a family history of tuberculosis: in Case 1 an uncle and aunt had died of phthisis, and in Case 2 a sister had died of phthisis and a brother of hip-joint disease; in neither case however was there a history of injury preceding the symptoms. Both patients were of the lower class, their ages were respectively 25 and 23 years; the onset was gradual in Case 1, extending over several months, whilst in Case 2 it was more sudden; in Case 1 browning of the skin...
was the first symptom noted, but in Case 2 the gastric symptoms preceded pigmentation by some weeks. In both the pigmentation was very typical and the buccal, and in Case 2 the vaginal, mucosae also were discoloured, and both showed numerous pigmented moles. Anaemia, fairly marked in Case 1, was slight in Case 2; the gastric and cardiac weakness were marked in both and both showed progressive atrophies: in Case 2 remissions were marked, but slight in Case 1; the temperature it may be mentioned was usually subnormal in each case; in Case 1, the duration from the onset of the first symptom till death was ten months, in Case 2 it was 20 months: the supra-renal capsules in both cases were both the seat of chronic tuberculous disease of an advanced degree; the spleen in both was congested and diffusely and the heart showed brown atrophy and some fatty change; the stomach in Case 2 was markedly mummilated but in Case 1 it was healthy, and in neither case the sympathetic plexus involved; in Case one there was old standing tubercle of the cervical glands, and in Case two the bronchial glands were affected. Both patients died of heart failure, preceded in Case 2 by unusual excitement. In Case one the discoulour-
ation was at first attributed to jaundice, and in case two to sunburn. Case 1 showed consider-
able emaciation through the abdominal fat was of anything increased, while case 2 showed no emaciation at all.

The history in regard to the pigmentation given in case 1 is very unusual; she stated that from some weeks before the time at which she was admitted into hospital the discolouration had been improving, although the asthenia and gastric symptoms had got steadily worse. Improvement in regard to the pigmentation is not unusually seen to accompany the periods of remission of the other major symptoms, but I have been unable to find a published record of any case in which the cutaneous discoloration lessened while vomiting and weakness progressed, and it is fair to suppose that this is a very unusual feature of the condition. The pigmentation in Case 2 seemed to improve under treatment with supra-

-ventral gland but this may have been merely a coincidence. The supra-ventral capsules in both cases consisted of firm connective tissue with many caseous and purulent foci and a few deposits of lime salts, showing lesions of very long

standing.
Case No. 1.

Kate Chalmers, aged 25, single, dressmaker, of 10 South Street, Perth. Admitted March 5th, 1898, under the care of Dr. Gikson, into the Royal Infirmary, Edinburgh.

Complaint: "Change of colour, vomiting and a feeling of fatigue with pains in the back and sides and between the shoulders."

Family history: Father dead cause unknown; mother alive and well, no mention is made of any brothers or sisters. A maternal uncle and aunt and two cousins had died of phthisis, and there was no history of other hereditary tendencies.

Home surroundings comfortable, and diet good in quality and quantity: her hours of work were sometimes very long and the workroom small and ill ventilated.

Previous illnesses: the patient had had measles, scarlet fever, diptheria, and smallpox as a child, and suffered from cough and anaemia three years previous to the illness for which she was now admitted.

The condition which she now complained of began in May 1897 when the patient noticed that her hands and face were getting dark, this she thought...
to be caused by sunburn. At this time there was no pigmenta-
tion of the body or legs and at this time no other symptoms were present. Two months later she felt breathless on exer-
tion, and she soon began to retch and vomit and felt extremely tired and weak; the vomitting was unconnected with meals and the vomited matters were bloody. At the end of July she had to leave her work and was at home for six weeks, and the jaundice symptoms improved. The vomitting recurred spasmodically and for six weeks before admission she was practically confined to bed by the weakness.

The pigmentation of the skin became general and gradually darkened until at the end of the year it was "almost black" on the face and hands; then a few weeks before admission she noticed that her face was getting lighter in colour, and this steadily improved though the vomitting and exhaustion continued to get worse until a fortnight before admission when she saw Dr. Norvell who gave her medicine which stopped the vomitting, and recommended her to the Royal Infirmary.

On Admission, the patient was thin but not emaciated, slightly anaemic with black hair and deep brown eyes; the skin was of a light bronze colour all over and scattered over the body and face were many small black spots. Weight 58 lbs. Temperature 98° F. She was exhausted but not collapsed.
and appeared to be cheerful.

**Alimentary System** : Lips show patches of pigmentation.

Gums also pigmented especially between the teeth.

Tongue indented at the edges by the teeth and these indentations are pigmented. There is a white central fur and the tip is red.

Fauces and pharynx are normal; appetite very poor and thirst excessive.

There is a feeling of oppression after food and vomiting is very frequent. She has attacks of pain in the epigastrium and between the shoulders, of a dull aching kind. Bowels constipated, but the vomiting is sometimes accompanied by diarrhoea.

The abdomen is of a general light bronze colour which is deeper at the umbilicus. The scar of a blister on the epigastrium is deeply pigmented; the walls are flaccid, at a point half an inch below and one inch to the right of the umbilicus there is some resistance and deep palpation here causes pain. Liver and stomach not enlarged.

**Haemopoietic System** : The glands behind the sterno-mastoids have been slightly enlarged since childhood; in both axillae are a few slightly enlarged tender glands. Spleen and thyroid normal.

**Blood** : Red corpuscles 4,000,000; haemoglobin 80% (the leucocytes were not counted).
Circulatory System: Patient is breathless on exertion and feels faint at times but has never lost consciousness. There is faint pulsation in the fourth and fifth left intercostal spaces and in the episternal notch and vessels of the neck: apex beat 3 inches from mid-sternum in the fifth interspace, is very feeble in character.

On percussion the upper border of the heart is at the level of the third rib: right border 1½ inches, and left border 4 inches from mid-sternum. The heart sounds are faint but closed in all areas except for an occasional faint mitral systolic murmur.

Pulse rate 84 per minute, pulse small and weak, tension low. The rate varied much on exertion.

Respiratory System showed nothing abnormal.

Integumentary System: The whole surface of the body is of a light bronze colour especially well seen on the backs of the hands, face, axillae and back. There are many small black spots on the face and abdomen; the skin on the forehead, round the mouth and over the knees and elbows is rough and brawny and there is a dry seborrhoea on the scalp: the legs are not so deeply pigmented and the matrices of the nails are free from pigment.

The urine is normal in characters and quantity. Catarrhia absent for six months; patient has been cured.
Nervous System: Patient's sight has been weak since this illness began but has improved lately, reflexes normal; she sleeps constantly and heavily. Perspiration free.

Further Notes: The patient was put on to suprarenal tablets (edis V.) t. i. d. and seemed to improve until March 18th, when the temperature suddenly ran up to 101.2°F and the pulse to 100 per minute and respirations to 40 per minute; she became collapsed, vomiting set in again, and she died from heart failure early in the morning of March 20th, 1898.

A post-mortem examination was made by Dr. Hume on March 22nd, and he reported as follows:

Kate Chalmers, aged 25, Addison's Disease.

Body markedly emaciated, post mortem rigidity and lividity slight. Body is deeply pigmented, especially in the genitals, axillae, knees, umbilicus and nipples, and the mucous membranes of cheeks and tongue in parts are similarly deeply coloured or bronzed. Face is more uniformly bronzed and there are numerous small black "moles" varying in size from a pea's head to a pea, most marked on the face, also seen on the legs and back.

Abdomen: Large amount of yellow fat notwithstanding
Skin of Kate Chalmers: showing enormous deposit of pigment in deepest cells of reticulosaum. Section stained piericarmine; drawn under ¼ inch objective.

Micro-photograph of above showing masses of pigment.

Opposite page 34.
the emaciation. Liver, 17th. 13 oz., shows marked cloudy swelling. Spleen, 4 oz., soft and diffusely, slightly congested, several small hemorrhages apparently in Malpighian tufts. Liver and spleen both adherent to diaphragm.

Kidneys: right 4 oz., left 4½ oz., seem distinctly atrophied.

Suprarenals: Right very adherent to kidney and displaced downwards to hilus; it consists of two caseous nodules, hard and cartilaginous at periphery, soft and caseous within, deposit of lime salts has occurred in parts.

Left suprarenal also markedly adherent and displaced downwards, consists of one marble-like nodule similar in appearance to right but more caseous on section, no deposit of lime salts. No supernumerary capsules were found; the Semilunar Ganglia appeared normal.

Heart: marked hemorrhage under epicardium, muscle shows fatty degeneration and slight brown atrophy of aorta slightly atheromatous at its origin. Pleurae were adherent and lungs show patches of collapse and early fibroid change at apices; no evidence of tubercle.

Microscopically: Both suprarenals showed marked caseous areas and little healthy tissue, several large marked giant cells in both. Skin showed enormous increase of pigment in cells ofrete Malpighii especially in the "moles". Semilunar Ganglia are healthy.
Case No. 2.


Admitted to the Royal Infirmary, August 27th, 1898 under the care of Dr. Gibson.

Complaint: "Sickness, pain across the bowels, weakness and dark colouration of the skin."

Family history: Patient's father died aged 50 of heart disease; her mother died of stoppage of the bowels; one brother died of hip joint disease, and one sister of consumption; one brother and one sister are alive and well.

Patient's surroundings in her situation were excellent, food good and plenty and she takes neither tea nor alcohol. There is no history of previous disease except measles in childhood.

The present illness began at Christmas 1897 when she was confined to bed with "a biliousness" for a fortnight, after that she was troubled with retching in the mornings and she brought up a yellow fluid. About this time she noticed that her hands were getting dark and she consulted Dr. Spence of Burntisland who diagnosed influenza and jaundice.

Since that time the attacks of sickness have returned about every three months and the face
has become discoloured. In June she consulted Dr. Jamieson of Edinburgh who attributed the colour of the skin to sunburn; in August she had another attack of the vertigo and felt very weak and from the 20th till 23rd she had violent pain in the abdomen and as this did not improve she was admitted to the Royal Infirmary on August 27th 1898; between the attacks of vomiting she felt fairly well but the skin continued to get darker.

On Admission: the patient is well nourished and appears cheerful. no emaciation, jaundice or dropsy. The skin generally is of a yellowish brown colour, darkest on the face and hands; the hair is dark and there is a dark pigmented mole on the left cheek. Weight 8 stone. Temperature 93°F.

Alimentary System: Lips slightly brown at the corners, teeth not good, on the gum there are dark spots between the teeth. Tongue shows brown dis-colouration where the teeth touch it. Appetite good between the attacks (of gastric irritability) and while the attack is present she has excessive thirst. There are no particular symptoms connected with the stomach except the recurrent attacks, and at these times the vomiting is only in the mornings. The bowels are constipated.
The abdomen is of a general brown colouration, most deeply marked at the linea nigra and umbilicus, and there is also a deeply pigmented band round the waist. Nothing further abnormal, the liver and stomach are not enlarged.

**Hæmopoietic System:** Spleen and lymphatic glands normal. Blood—red corpuscles 4,290,000 per cubic millimeter; leucocytes 20,000 per c.m.m. (the haemoglobin was not estimated).

**Circulatory System:** Since Christmas patient has suffered from palpitation and faintness on exertion, and slight dyspnoea. Apex beat not visible but palpable in the fifth left intercostal space 3½ inches from midline; it is very weak.

**Percussion of the Heart:** Upper border is at the 3rd rib. Right border is 2 inches from midline (the left border is not given).

The pulse rate is 82 per minute, regular, volume small and pressure very low.

The Respiratory system was normal; the urine is acid, of specific gravity 1020 and shows no abnormal constituents. The Cataract has been absent for four months, previously there was some Dysmenorrhoea during the flow.
Cutaneous System: the skin is of a general yellowish-brown colour all over the body and most deeply marked on the face and hands, abdomen, axillae, elbows, knees and toes and also over the spines of the lumbar vertebrae. There is a deeply pigmented band round the waist and also round the legs where the garters are worn, and over the body are scattered numerous intensely pigmented spots resembling black moles.

Nervous System: during the attacks of sickness patient suffers from severe headaches and there is great prostration during the attacks; she has felt chilly since the present illness began. The skin reflexes are normal and the knee jerks somewhat exaggerated; she sleeps very well; Vomiting and nutritive functions are normal except that patient sweats excessively on exertion.

Joints and muscles normal.

Further Notes:

October 27th: patient was put upon tabloid suprarenal gas. She improved and the skin got lighter, but about a week ago the vomiting returned and has continued, and as her friends thought she was dying she left hospital today.
December 16th Patient reported great improvement, no sickness, pigmentation less, still taking tablets
January 5th Improvement maintained
March 20th Patient returned to hospital today with the following history. She returned to her situation in the middle of February and felt well for a fortnight when she began to feel sick in the morning again and soon felt extremely exhausted, and then got so much worse that she went home on March 31st and as she did not improve she returned to the Infirmary.

The condition is much the same as before, the pigmentation has deepened and the nipples are very dark in colour and the skin dry.

Further Notes: The patient improved until April 21st but was very weak and had attacks of faintness, on this date she had an attack of acute tonsillitis but made a good recovery; the pigmentation is increasing.

June 5th Patient improved steadily until today when she has begun another attack of tonsillitis, temperature 103°F.

June 7th Patient yesterday felt very weak and became excitable, her heart grew weaker and she died of heart failure at 1 a.m. today.

Dr Fleming made a post-mortem examination on the day of the patient's death with the following result:
Emma Horner am 23. : Addison's Disease.

Body fairly well nourished; post mortem rigidity slight in legs, absent in arms; body somewhat pigmented all over especially on face, nipples, umbilicus, labia and back; mucous membranes of mouth and vagina are pigmented the latter deeply; there are several pigmented moles on trunk.

Heart : boy, small and flabby. Aortic valve slightly pitted and shows a few fine fibrous vegetations. Microscopically heart showed fatty degeneration and brown atrophy. Lungs showed slight congestion and edema, some cavernous glands at their roots, otherwise healthy.

Liver : 2 to 3 oz. shows early fatty infiltration and cloudy swelling. Spleen : boy, soft and sullen, marked acute congestion. Kidneys : right 5 oz, left 5½ oz, showed remains of fetal lobulation.

Suprarenals : left much larger than right, firmly adherent to pancreas which was otherwise healthy.

It was about the size of a pigeon's egg. On section it consisted of dense fibrous tissue, almost cartilaginous, containing large cavernous sacs in some of which urine salts were deposited. Weight about 1½ oz.

Right suprarenal, about normal in size, on section showed several cavernous sacs and little if any evidence of normal suprarenal tissue. The pancreas was
healthy, but was adherent to the stomach and left suprarenal. Stomach showed marked chronic gastric catarrh and its capacity was about 40 oz; it was markedly "mammillated". Semilunar ganglia appeared healthy and were not involved in adhesions.
Case No. 3.

Thomas Moses, at 37 yrs. a congenital imbecile of no occupation. Address 23 West Port, Edinburgh Admitted to the Royal Infirmary, Edinburgh, under the care of Dr. Gibson, on May 4th 1903.

Complaint "Vomiting".

Family History: There is no history of hereditary tendencies, the patient's father is a medium-fair Scotchman, and his mother, who died of bronchitis and heart disease, was said to have been a very fair complexioned Scotch woman. Patient has one sister and five brothers alive and well, all reported to be fair. Three sisters died in infancy of unknown diseases. The patient has always been neglected and ill treated and apparently badly fed: he is not addicted to alcohol or tobacco, his surroundings at home were very bad and he has not been kept clean since this illness began: he has always been dirty in his habits and his skin has been very yellow since birth, but the colour has deepened very much during the last two months.

This history was obtained from patients sister who was fair complexioned with a slightly Jewish cast of features. She could give no explanation of their surname, Moses, but stated that both parents were Highland.
Our patient had suffered from bronchitis since childhood but otherwise had been healthy except for his mental condition.

The present illness began in the end of February; the patient was in his usual health until then and one morning went out apparently well; in the middle of the day he returned complaining of headache which he attributed to some beer which he had been given and which he was not used to; he went to bed and on the following day had a good deal of nausea and vomited once or twice, he did not get up and became gradually weaker until the date of his admission. The vomiting began again on May 3rd and as it could not be controlled he was admitted to the infirmary on May 4th, 1903.

On admission the patient was in a state of collapse and unable to sit up in the chair in which he was brought to the ward. His features are mongoloid in type and his skin is of a general olive brown color resembling that of a Hindu; the hair and beard are black and coarse and the eyes dark brown. Encephalitis and anemia both being marked; the body is filthy and dirty and is swarming with parasites; no Tonsillic or droopy. Over the left trochanter is the scar of a large ulcer which is deeply pigmented at its periphery.
but not in the centre. He is markedly very deficient, and has a marked scoliosis, the convexity being to the left. Expression anxious and he lies with his feet drawn up and toes pointed. Temperature 96.4° F.

Alimentary System: the lips, like the other mucous membranes are very anaemic; they are moist and show many clearly defined pale slate coloured areas which are level with the surrounding tissue and correspond chiefly to points where there is pressure from the teeth. The buccal mucosa shows similar dis-coloured areas and slaty patches are also present on the tongue in its anterior third and at its edges.

The tongue is very anaemic but not furred or fissured except anaemic and shows a few small pigmented areas. Teeth very dirty and many carious; deglutition normal.

Appetite very poor but thirst is excessive and the patient cries continually for "a drink of water."

Vomiting is frequent and seems irrespective of food. The total acidity of the vomit is 0.14 per cent; hydrochloric acid is present, but no organic acids; the vomit was not large in amount and showed no splenium.

Patient has a tendency to diarrhoea and passes his stools under his

The abdomen is much retracted in its upper half
but is fuller below the umbilicus and moves freely with inspiration. In palpation the walls are atrophied and somewhat resistant and deep palpation over the kidneys causes considerable pain, especially over the left kidney. Stomach and liver not enlarged.

Circulatory System: patient does not complain of any subjective symptoms; the visible cardiac impulse is diffuse over the precordia into the sixth interspace just external to the nipple, the veins in the neck are pulsating but not engorged, the abdominal aorta is pulsating forcibly. A left beat is best felt in the fourth left intercostal space 3½ inches from mid sternum, it is sharp and fairly localised but not sustained.

The right border of the heart is 2 inches from mid sternum in the third interspace, and the left border 4 inches from mid sternum in the fifth interspace.

On auscultation: in the aortic area both sounds are faint and the first sound is impure; in the mitral area first sound is loud, sharp and closed, the second sound is accompanied by a loud harsh bruit, best heard half an inch above the left nipple and conducted into the axilla; in pulmonary and tricuspid areas both sounds are closed but weak.

The pulse is regular, in time and force, the volume and pressure small and the tension low; the vessels
Cells from Blood of Thomas Moses:

1. Spherocyte showing deficient haemoglobin.
2. Normoblast.
3. Poikilocyte.
5. Ditto, containing pigment granules?

From a blood film stained with Jenner's Stain.

Microphotograph from blood film of Thomas Moses, showing poikilocytes and one normoblast in the centre of the field. Opposite page 46.
are not thickened. The heart seems irritable and weak and the pulse rate varies much being greatly increased by the least exertion or emotion.

The Respiratory System shows nothing abnormal, but the exact condition is not easy to make out owing to the deformity of the chest. Respiratory rate 24 per minute, the type of the breath sounds is harsh, vesicular all over with prolonged expiration at both apices, patient has no cough.

Haemopoietic System: Spleen, thyroid and lymphatic glands are not enlarged.

**Blood:**

<table>
<thead>
<tr>
<th>Date</th>
<th>Erythrocytes</th>
<th>Leucocytes</th>
<th>Haemoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td>May 4th, 1903</td>
<td>2,000,000</td>
<td>5,000</td>
<td>under 15 percent</td>
</tr>
<tr>
<td>May 5th</td>
<td>1,800,000</td>
<td>6,000</td>
<td>10</td>
</tr>
<tr>
<td>May 11th</td>
<td>1,800,000</td>
<td>6,000</td>
<td>under 10</td>
</tr>
<tr>
<td>May 25th</td>
<td>1,300,000</td>
<td>5,000</td>
<td>10</td>
</tr>
<tr>
<td>May 29th</td>
<td>1,800,000</td>
<td>8,000</td>
<td>12</td>
</tr>
<tr>
<td>June 23rd</td>
<td>2,000,000</td>
<td>10,000</td>
<td>about 15</td>
</tr>
</tbody>
</table>

The blood is extremely pale and watery and does not coagulate well; the stained films show much irregularity in size and shape of red corpuscles but no large forms; a small number of normoblasts are present but no megaloblasts; the red cells do not form rouleaux and do not take the stain well, the
leucocytes are in about normal differential proportions, a few basophil leucocytes are present but no myelocytes are to be found. Many neutrophiles show faint iodine reaction.

The Cutaneous System: The skin is of a general olivé brown or bronze colour which is deepest in tint upon the forehead and sides of the neck, beneath the eyes, upon the upper part of the chest and the abdomen especially on the left side, round the umbilicus and on the penis, scrotum, areolae, nipples and axillae, the knees elbows and ankles of the right side are also darker than the general surface and there is a dark band round the waist which the patient wore his belt. The areolae are deep sandy brown in colour and the scrotum is almost black contrasting strongly with the glans penis which is very white and anaemic: the darker areas are not sharply defined but merge gradually into those less deeply pigmented, the back of the hands are not so dark but are still very markedly discoloured, but the palms and soles and the matrices of the nails show no pigmentation. There is a cicatrix on the left trochanter which is deeply pigmented at its edges but not in the centre, the skin is harsh and dry and there is a slight leonine desquamation in some areas.
The urine shows no abnormal constituents, the amount is about thirty ounces, but is difficult to measure with accuracy as the patient passes it under him: colour pale straw, S. & 1018; reaction strongly acid; urea 13.6 to the fluid ounce, neither blood, bile, albumin, sugar or pus are present but indigio is present in considerable amount and there is a deposit of uric acid crystals. There is no pain or difficulty on miction.

Nervous System: Patient is a congenital idiosyncratic and his information is unreliable, he lies perfectly quiet all day but cries continually for a drink or a penny, he answers any question put to him either rightly or wrongly and occasionally originates a remark himself: his expression is cunning and he keeps his premises under his pillow and is very watchful of them. Sensation and sensibility to stimuli are undisturbed; the knee jerks are more brisk than normal.

The muscles are much wasted but patients is said to have always been emaciated, he cannot sit up but can easily lift a cup and can resist passive movements with some force, sudden movements seem to give him pain. The bones and joints appear to be healthy.
Further Notes: — May 5th. Patient's head face pubis and perineum shaved today and white precipitates ointment rubbed in to the pubis, while the remainder of the body was well scrubbed with carboolic soap. He vomited three times today.

May 12th. Patient now is having tabloid suprarenal gas 5. tor in die.

May 16th. Getting weaker; the pulse ran up from 80 to 130 today; temperature 99.4°; respiration 22 per minute.

May 27th. Patient had cramp in his left foot at 10 a.m. which was found intensely congested and livid; there was no appearance of this condition at 6 a.m. The congestion rapidly spread to the thigh. Mr. Mac Gillivray saw the patient and confirmed the diagnosis of thrombosis high up the femoral vein; the thigh is intensely tender. Temperature 99°. Pulse rate 80 per minute.

June 9th. The foot of patient's bed, which had been tilted for some days, was today put level again as the face and scalp became very edematous although the leg became less swollen.

June 25th. Patient has complained of headache for the last two days and has more tenderness to tapping over the left temporal region, and
there is slight internal strabismus of the left eye, tendon reflexes and muscular irritability much exaggerated and there is slight head retraction.

July 2nd: Temperature which has been sub-normal for the last five days was this morning 97°F; the pulse gradually rose to 120 per minute; the strabismus persisted and he made no attempt to move or reply to any questions, he died at 10 A.M. today apparently from asthenia.

This patient was observed to be getting gradually darker up till his death though the parasites were destroyed and he was scrubbed daily with soap and water. The gastric symptoms improved to some extent towards the end of May when the vomiting recurred and continued spasmodically till death.

The supra-rennal tubuloids through persued with seemed to do no good. Temperature and pulse rate were both extremely irregular and the former was often swinging, with morning remissions.

This patient was shown at a meeting of the Windermere Medical Association during his residence in the Infirmary and was considered by Dr. Gibson, and many others well qualified to judge, to be a particularly well marked case of Addison's disease, with unusually profound anaemia and
Emaciation, but thin bony symptom, or rather condition, had been present since childhood at least, as had also been a certain amount of discoloration of the skin.

A post mortem examination was made by Dr. Beattie on July 3rd 1907, and he has kindly sent me the following extract from his report:

**Thomas Moses, 38, Addison's Disease**

Marked scoliosis and emaciation; left thigh, leg, and foot edematous. Skin shows marked pigmentation, slaty pigmentation on tongue and buccal mucous membrane.

Supra-auricul, no special change to naked eye or microscopically, they appear to be healthy; no obvious change in vessels or ganglia in their neighbourhood.

In the kidneys there are several abscesses in the cortex up to $\frac{1}{4}$ inch in diameter, apparently spreading along the tubules, most marked in the left kidney; pelvis of kidneys healthy as is the remainder of their substance. Liver weighs 2 lbs. 10 oz., brownish in colour, contains a considerable amount of pigment, no iron reaction. Spleen 9 oz., very firm, no obvious naked eye changes.

Stomach, duodenum, intestines, and pancreas all seem healthy. Heart: marked oedema of pericardium...
Skin of Thomas Moses:
Sharply ribbed pigment granules; chiefly in deeper layers of Rote Museum.

From a section stained haemalum and eosin.
Drawn under 1/2 inch objective.

Micro-photograph of another part of same section, also showing great increase of pigment in deep layers.

Opposite page 52.
Arterial valves competent, muscle brownish and shows well marked interstitial myocarditis and brown atrophy. Lungs, slight oedema and bronchitis otherwise healthy. There is a recent thrombus in left femoral vein extending from the iliac to the popliteal. Brain and cord, nothing abnormal except pigmentation of membranes of the cord.

Sections of the skin showed considerable deposit of pigment granules, chiefly in the deepest cells of the Malpighian layer but also to a much less extent in the more superficial cells. The pigment was of a deep reddish brown colour and where present in large quantities appeared almost black.

The accompanying watercolour drawing is from a section of the skin stained with haematoxylin and carmine, and the micro-photograph is from the same section.

The mucous membrane of the mouth, in the uncoloured areas, showed the same pigmentary deposit, but to a very much less marked degree.
The preceding case of the patient Thomas Moses is one which serves to exemplify that the clinical picture characterizing Addison's disease of the supra-renal capsules may be exceedingly closely simulated by other pathological conditions, which may, in combination, reproduce so perfect a facsimile as to cause a doubt, even after a post-mortem examination has been made by a skilled pathologist, whether some lesion may not have been overlooked which was causing suppression of the function of these glands, or whether some theory might not be put forward which would explain the existence of Addison's disease in this case notwithstanding the fact that no morbid change was found to be affecting the capsules or their neighbouring structures.

To review the main points of the case: the patient was of Highland extraction according to his sister's statement, was called Moses, and was a congenital imbecile; he was admitted to the Infirmary with a history of sudden nausea and collapse beginning rather more than two months before he came under treatment, and which had steadily progressed until intractable vomiting had set in two days before admission. He
was found on examination to present the following group of symptoms: "Anæmia, general languour and debility, remarkable feebleness of the heart's action, irritability of the stomach, and a peculiar change of colour in the skin," and patchy discolouration of the oral mucosae and tongue. And this group of symptoms is that by which disease of the suprarenal capsules is to be diagnosed, in the absence of any other factors by which they might be produced.

In addition to these features he was mentally deficient, markedly scoliotic and extremely filthy and verminous. His face and head were those of a mongolian idiot, and he exercised no control over his sphincters, although this seemed to be due more to his apathetic and debilitated condition than to any actual paresis of these muscles. He showed a marked degree of emaciation, but this was said to have been always present and not to have increased materially since the onset of his final illness, and the discolouration of the skin, which was also said to have been present since a very early age if not since birth, was said to have increased much in depth during the progress of the disease, and it undoubtedly
became more marked during his residence in hospital, notwithstanding his improved hygiene surroundings and enforced cleanliness.

There were no deeply pigmented moles on the body; but the pigmentation was otherwise quite typical of Addison's disease being strongly marked on the face and hands and particularly deep on the penis and scrotum, areolae, nipples, axillae, and umbilici, and also round the waist where pressure was made by the belt, and at the margin of the cicatrix upon the left trochanter but not in the centre where presumably the deeper tissues had been injured; furthermore the palms of the hands and soles of the feet and also the matrices of the nails were free from any signs of pigmentation. The discoloration was general, the darker and lighter areas merging gradually into one another except in the before mentioned scar, and sections of the skin showed the pigment granules to be in the deeper layers of the epidermis, which is the position occupied by them in Addison's disease.

The patient got steadily worse, with one slight remission; the vomiting, which at first improved, returned and was accompanied by
Micro-photograph of section of right Supra-renal gland from Case No. 3. showing perfectly normal tissue.

Micro-photograph of section of Supra-renal gland from Case No. 1 showing almost complete destruction of cortex and medulla which are replaced by homogeneous, caseating tubercular material.
Diarrhoea, the asthenia and cardiac debility increased and the patient finally died of asthenia, death being preceded by signs of basal meningitis and greatly increased muscular irritability; and at the necropsy all that was found was the existence of some small suppurating foci in the cortex of either kidney, with a large deposit of pigment in the liver which was iron-free, and increased pigmentation of the spinal membranes; the suprarenal glands and semilunar ganglia appeared healthy; there was no increase of lymphoid tissue in the stomach, and the spleen was not congested and diffusely but firm and somewhat small, and the heart showed advanced brown atrophy and interstitial myocarditis. The renal abscesses were found to be tubercular, but apart from this deposit there were no signs of other tubercular disease either recent or old standing, and the lungs were, except for some terminal oedema, healthy as were the other abdominal organs than the kidneys.

The urine, though carefully examined, was at no time found to contain Purp and this is accounted for by the fact that the abscesses were small and definitely localized to the cortex of the kidneys and the condition was in a very early stage,
indeed the disease had made such slight progress that it seemed hardly possible that it was the sole cause of death or that it could have produced symptoms of such extreme urgency: as, however, no other lesion was discoverable, death was apparently due to tubercular pyo-nephrosis.

The first thing to catch the eye in connection with this patient was the extremely marked pigmentation of the skin which has already been described, and secondly the presence of swarms of parasites; and these two features appeared to be in the relation of effect and cause.

Now cutaneous pigmentation in Phthiriasis has the following characters.

The skin is thick, dry and harsh; discolouration may be general or patchy and in the latter case the margins of the discoloured areas are sharply defined. The colour of the pigmented parts is of a brownish or blackish tint and may be very deep indeed; it is usually most marked upon the back of the neck, chest, upper part of the abdomen and back and frequently also upon the sacrum and the thighs in their outer aspects. The face, hands and feet are but little affected, as are the nipples, areolae,
and genitals, a fact which is of the utmost value, as Dubreuilh points out, in differentiating this condition from the melasma of supra-renal disease which it so closely resembles.

The irritation produced by the pediculi, more especially in those individuals who have more recently acquired them, causes scratching and thus the skin often shows old cicatrices and recent haemorrhages from this cause, and though the essential pigmentation is of an iron-free kind there is thus a combination of haemosiderosis and melanosis which does not occur in Addison's Disease. Again the scratching often causes a pustular eruption to appear which when healed leaves small white cicatrices on the discoloured background: these features may however not be present if the disease is not accompanied by pruritus, although in these cases the pigmentation may be very marked.

Further, in phthiriasis the mucous membranes may show a slaty and patchy pigmentation which is identical with that which Greenhow described as being among the strongest characteristics of Addison's Disease and which was well marked in a case recorded by Chatin of a chiffonier aged 78 who was infested with vermin.
It also appears that in phthisiases pigmented moles may be seen, but Owen has called attention to the fact that in a case of his these moles were all upon the parts of the skin which were not discoloured, in which they differed from those seen in Addison's Disease.

The seat of the pigmentation appears to be the same in both conditions. Owen states that in the parasitic affection the pigment is diffused through the Malpighian layer of the skin but is chiefly in the sub mucous ("Keim Schleim") and Dubreuilh found it in the lower reproductive layers ("veuves génératrices") of the epidermis, and also in the derma, in the neighbourhood of the lymphatics, in loose granules and branching cells. The pigment is in the form of fine brownish or blackish granules, which resemble those of Addison's Disease as closely as to the sites of its distribution in the skin. The discoloration of phthisiases, both cutaneous and mucous, according to Dubreuilh, diminishes in some weeks and disappears in some months when the parasites are destroyed and the patient is well fed.

The skin condition in the Patient Thomas Moses resembled that of phthisiases in the following points.
The skin was harsh and dry. Pigmentation was general but not present in the form of pigmented moles. The backs of the hands were not so deeply discoloured as many other areas. Pigmentation was very marked upon the back of the neck, chest, upper part of abdomen and back. It differed from the pigmentation of phthisis in that it was very well marked on the face, legs and arms, and of a particularly deep shade on the nipples, areolae, penis and scrotum, and that there were no signs of scratching or white, healed cicatrices, and the discolouration was marked round the umbilicus and in a band round the waist, and in these points it was identical with that seen in Addison's disease and also in the fact that there was no improvement under improved conditions and the darker and lighter areas merged gradually into each other and the more superficial parts of the cicatrice over the trochanter were deeply pigmented.

The mucous pigmentation, and the layer of epidermis in which the pigment is chiefly collected are the same in the two conditions, but it appears to me, from the study of sections of the skin, that in the parasitic affection the extra-cellular deposit is greater
than in Addison's disease, where the pigment is chiefly inside the cells massed round the nucleus.

In the patient Moses, the pigment was to a great extent extra-cellular, but this differentiation is not well marked, and in Addison's disease the pigment is in many cells, largely at the periphery. In the whole the pigmentation in this case much more closely resembled that of supra-renal disease than that caused by the pressure of the parasites, to which in all probability it was due at least in some part.

Another very prominent symptom in this patient was the anaemia which was of a high grade. There were none of the characteristics of pernicious anaemia and no large erythrocytes were present and the colour index was about .3; the appearances were those of severe chlorosis but the eosinophiles were not very markedly decreased. It is difficult to find a cause for this profound anaemia as none of the usual etiological factors were present and chlorosis, if it occurs at all, is extremely rare in males; possibly the renal disease, the debility, and the mental condition and want of proper nourishment all combined to produce this impoverished state of the blood. There was, however, little improvement after several weeks of cleanliness and good feeding.
this anaemia, though unusually profound, was not, as has been shown, incompatible with a diagnosis of Addison's Disease, in which it may be so marked as to suggest the "idiopathic" variety. A moderate anaemia is common in the later stages of tubercular pyonulosis, but it must be very rare to find it in such an advanced degree when the renal disease is yet in an early stage.

The marked asthenia shown by this patient may have been due to the blood condition to some extent, and there was also great emaciation; this however had been present since early youth whereas the asthenia set in with extreme sub-
~dveness, such as is seen in some cases of supra-
renal disease; this symptom is also not easy to account for unless it was produced by the effect of the early renal tuberculosis on an already imperfect nervous system. Further the post-mortem appearances of the stomach did not show any signs of any change to account for the nausea and sub-
sequent uncontrollable vomiting, and on the other hand there were none of the changes often seen in Addison's disease, no mammillation or abrasions.

The pathological state of the heart was only what might have been expected in a subject show-
ing such an extreme degree of debility and of emaciation, and will fully account for the feeble excitatory pulse which was another factor in the diagnosis.

The presence of all these symptoms may thus be explained without the supposition of a lesion interfering with the supra-renval function, with the exception of the pigmentation which was very characteristic of capsular disease in that the umbilicus, genitals, areola, and waist-band were especially deeply discoloured. Now the diagnosis of this condition was negative at the post-mortem examination, but is it possible that there may have been some lesion which was not pathologically recognisable?

In hisoulstonian lectures, Rolleston refers to the researches of Alexander, who found that in still-born infants who showed mal-development of the supra-renvals the central nervous system was never perfect, and he believes these two structures to have a mutual developmental influence: if this be the case is it not possible that in the patient Moses both the central nervous system and the adrenals were congenitally deficient, and that these glands produced
an anomalous secretion different, and latterly even perhaps entirely wanting, in physiological properties, thus causing the symptoms of Addison's disease.

It may be urged that this is going far a-field for a cause which is to be found near at hand, but the pigmentation was, in many essentials, other than that of phthisis, and in these particulars it resembled that of the supra-renal condition, though probably the parasitic infection played some part in it also; but this theory of congenital defect may explain the presence of the discoloration since childhood, that is for at least thirty years, which does not easily fit in with the parasitic theory.

A semi-analogous anomaly of secretion may be found in the absence of spermatozoa in the seminal fluid when the testicles are seemingly healthy, and though in putting forward this theory I feel that I am upon ground which is almost non-existent, my justification is that this patient appeared during life, to suffer from, and finally to die of, Addison's Disease of the supra-renal capsules. It is a matter for regret that in this case the semilunar ganglia were thrown away before they could be examined.
microscopically; they were, however, very carefully examined by naked eye, and appeared to be quite healthy, and neither they nor any of the nerves, blood vessels or lymphatics of the supra-renal glands were implicated in masses of inflammatory tissue or in any other pathological lesion.

In conclusion if, as seems probable, the subject of this third case was not in truth an example of Addison's Disease, the simulation was far closer than that shown by any other recorded case which I have seen; not only with regard to the pigmentation but also in the accompanying nervous, gastric, and cardiac symptoms which when co-existent point so strongly to disease of the supra-renal Capsules.

The majority of the books and publications to which I have referred I have got from the Manchester Medical Library, and for the opportunity of consulting the remainder I am indebted to Dr. Brooke of Manchester.
List of Figures

1. Section of Skin of Kate Chalmers (Case 1) showing great deposit of pigment in the lower cells of the Retzi Mucosum. Drawn in water-colour; section stained with Picrocarmine. Page 34.


5. Section of Skin of Thomas Moses (Case 3) showing deposit of pigment in lower cells of Retzi Mucosum. Water-colour, section stained haematoxylin and eosin. Page 52.

7. Micro-photograph of section of Right Supra-renal gland from Case 3. showing normal healthy structure.

8. Micro-photograph of section of Supra-renal gland from Case 1. The normal structure is almost completely replaced by homogeneous caseating tubercular material, with some fibrous tissue.

The appearance of the Supra-renal glands in the patient Emma Horsman (Case 2) was almost identical with that of Case 1.
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