THE FUNCTIONS OF THE SUPRARENAL CORTEX, WITH ESPECIAL REFERENCE TO ITS ROLE IN HYPERTHYROIDISM.

INTRODUCTION:

A Doctor in general practice is faced with many problems in many diseases. Amongst his difficulties is the class of patient who complains of the syndrome of symptoms produced by varying degrees of Hyperthyroidism. The condition is comparatively common, and the immediate concern of these patients is that they should recover their health and return to their work. At the present time it is generally accepted that the best way of treating hyperthyroidism is by thyroidectomy, with the preliminary administration of iodine. Operation, however, is not free from risk, and is, at the best inconvenient, and is not absolutely certain to cure the condition. It would, therefore, be a great boon to be able to find some effective method of medical treatment whereby, for example, the treatment of Pernicious Anaemia with Liver Extract, could be paralleled. In this hope, therefore, the investigations contained in this thesis were instituted.

(1) H.S. Plummer's definition of Exophthalmic Goitre is, that it is "A constitutional disease dependent on an unknown stimulus on the Thyroid glands". There are many theories as to the nature of this stimulus, and the whole subject of Endocrinology is still in its infancy, but it seems to be established that the various Endocrine organs react one with another, and it seems not unreasonable to think, that some may have a restraining action on others. As an example of this antagonism, that of the medullary adrenal secretion and Insulin, might be quoted. It was with these thoughts in mind that I read Sir E. Sharpey Shaw's book "The Endocrine Organs" 1924, the following passage -

"According to Marine and Baumann, the cortex of the suprarenals exercises an inhibiting affect over the thyroid".

Is there then, any possibility of controlling the course of Hyperthyroidism, in which there is this unknown stimulus to the thyroid gland, by means of the suprarenal cortex. The following thesis is an attempt to investigate this possibility.

It is hoped that we may arrive at some conclusions by a study of the normal functions of the suprarenal cortex, and of its relationship to the thyroid.
HISTORICAL:

The Adrenals were first described by Eustachius in 1563. No great interest was taken in the suprarenals until 1849, when Addison published his historic paper (77), on what is now known as Addison's Disease. These observations were confirmed by contemporary physicians. Trosseau (78), was the first to name the condition Addison's Disease.

In 1856 Brown Segurad (14) showed that removal of the Adrenal cortices is fatal.

Balfour, in 1878, was the first to differentiate the cortical elements from the medullary elements - reference (a monograph on the development of elasmobranch fishes, London 1878).

In 1894, Oliver and Shafer published the results of their experiments on Adrenalin.
The Suprarenal Glands are divided into the Cortex and the Medulla. Although, in man these are anatomically interwoven, they are morphologically distinct, and their development is different, the Cortex being developed from Mesoderm while the medulla is developed from the same neuroblast masses as give rise to the nerve cells of the sympathetic ganglia, i.e. ectoderm. The histology is well known and description would be mere repetition. A point of interest is that the arterial system of the cortex and medulla are different. The function, however, of the suprarenal cortex as opposed to the medulla is not entirely known, and description of the known facts which have any bearing on it's function might help us to form an opinion as to whether there is any connection between it and the normal or abnormal thyroid. The development throughout life of the cortex is of interest.

Ludwig Ashoff (Reference - Lectures on Pathology (2) Lane lecture, San Francisco 1924) discusses it's development and possible function. The development of the Suprarenal Cortex reaches it's maximum just before the birth of the child. At this time it approximates to one third of the kidney in weight while in an adult it is only about 1/28 of the weight of the kidney. There then occurs a process of absorption of the cortex (first described by Thoma, and confirmed by Kern, Elliott, Pappenheimer and Lewis). As the result of this process of absorption, the suprarenal becomes very reduced in size. This is due to the fact that there occurs during birth, or immediately afterwards a tremendous hyperaemia of the cortex. This hyperaemia affects especially the middle and internal layers of the cortex. In the next few weeks there occurs an increasing fatty change in the cortex, with the result that there is a more or less widespread disappearance of the inner layer of the cortex so that only the glomerular layer remains as a so-called layer of growth from which there occurs a regeneration of the suprarenal cortex.

This period of regeneration is complete at two years. At the beginning of perpuberty there is a new and more marked period of growth, in which there is an obvious differentiation of the cortex, and a peculiar storing of fat in this part. The cortex now shows an outer glomerular zone, a resting germinal layer while the outer two zones would be conceived as the functioning layers. The glomerular zone is poor in fat and lipoids, the functional zones are rich in fat and lipoids, fat being especially prominent in the reticular zone. Also there occurs in the reticular layer a peculiar deposition of pigment.

At the stage of life there is, at least in the male sex a sharp division of the cortex into three parts:

1. The glomerular layer poor in lipoids and with fine droplets of fat.
2. The fascicular layer rich in lipoids and with both large and small fat droplets.
3. The reticular layer containing pigment and fine droplets of fat.

In women the glomerular layer is, in the average, more markedly developed, especially in women who have had
During each menstruation especially, and at each pregnancy, the suprarenal cortex enlarges (Gayesse), and swells, and during this stage becomes a layer very rich in lipoids (contrasting with the male). After the end of pregnancy there occurs a puerperal involution of the suprarenal cortex. This never leads to complete regression of the newly formed cortical parts. The entire cortex, especially glomerular layer, remains wider than before. The entire weight is greater in woman than in man. The glomerular layer is richer in fat in woman than in man.

The final stage is a stage of senile involution, and begins between the 40th and 50th year of life.

From this it will be seen that -

(1) There are differences between male and female.

(2) The periods of change occur at critical changes of life, where firstly there are changes in metabolism as at birth, and also at periods of sexual stress, such as prepuberty, and during menstruation and pregnancy in the female.

A point of interest in connection with the development of the cortex is that in the anencephalus foetus the boundary zone is absent and the suprarenal resembles that of other foetal mammals (Shafer (3) The Endocrine Organs, Page 29, quoting Elliott.

Ceni (quoted by Ashoff) claims to have observed after exterpation of parts of the Cerebral Hemispheres a hypertrophy of the suprarenals and indeed of the medulla and cortex which increased with the sign of the defect. With that went atrophy of the testes.

In a consideration of the function of the suprarenal cortex, we find in the literature very little that is definite, and many conflicting views. It may be well to examine some points from the literature in order to arrive at the truth so far as we are able.

Brown-Bsquard (Ref.14) found that removal of adrenal cortices leads to fatal results. Many other authors such as Wislocki and Low (Ref.13), Beidl, Stewart and Rogoff found the same results, Stewart and Rogoff, however, with an improved technique kept the animals alive much longer. Some animals survived, but were found to have large accessory cortical tissue.

J. Harley (Ref.15) kept white rats alive after adrenalectomy but these animals have accessory cortical tissue.

Beidl quoted by Goldzieher (Ref.5) claims to have kept dogs and rabbits alive after complete destruction of their adrenal medulla if enough cortical substance was preserved.

A number of cats that were operated on by Kellaway and Cowell (Ref.19) died of adrenal insufficiency though a good deal of the cortex has been left intact.

Britton (Ref.17) says that it has amply been shown that the cortex is indispensable to life, and discusses experiments to prove that the medulla is not absolutely essential to life.
Zevemer (12) states that the cortex is essential to life and its absence is responsible for most of the symptoms of adrenal insufficiency. Both dogs and cats show that the medulla is not essential though the medulla has an important function as a strengthenner of the Sympathetic Nervous System. Even the blood needs the presence of cortex. For suprarenal ectomised cats the Basal Metabolic Rate is lowered. In regard to the last sentence a comment would be that the medulla also is absent.

Functions of Cortex.

Aschoff (2), says that Landau supported by others thinks that the suprarenal cortex represents essentially a storage organ for Cholesterin and fats. Aschoff seems to agree with this, but has come to no very definite conclusion. E.E. Glynn (4) is of opinion that there is a connection between the development of the Sexual organs and that of the suprarenal cortex. The experimental evidence discussed by Shafer (3) is very conflicting. He states that there is no clear evidence that any kind of active antitocoid substance is produced by the cortical cells and it is probable that their function is associated with the building up of Metabolic products which are to find employment in other parts of the organism. The lipoid substances which occur in the cortex vary considerably in amount. Corresponding with the excess or deficit of cholesterol in the suprarenals, there is an increase or diminution of the same substance in the blood, a fact which appears to support the opinion that the cortex not only serves as a storehouse for these lipoid substances, but that it is a factory for them. Shafer concludes that the suggestion that the suprarenal cortex may be a seat of manufacture of lipoids of the body, and may especially be related to the formation and development of the myelin of nerves fibres is attractive. He however, at that time (1924) does not seem to regard it as proven. Max. A. Goldzieher (5) enters into much detail on the subject of the Adrenals. He considers that Cholin is the product of Metabolic processes in the living cortical cells. Other authors such as Seidl do not consider this proved.

Sir Edward Sharpay Shafer (3) points out that Cholin is not specific to the suprarenal capsules but occurs to a variable extent in most tissues and organs. Goldzieher describes an experiment which he says seems to prove satisfactorily that cholin is liberated from the adrenals like adrenalin with the outflowing venous blood, and furthermore, this secretion can be increased by adequate stimulation such as the administration of Pilocupin.

He discusses the pharmacology of cholin, and comes to the conclusion that it is antagonistic to Adrenalin that it is liberated under the influence of the parasympathetic Nervous System. He says that an excess of cholin stimulates the sympathetic antagonist.
and leads to the prevalence of the latter. Goldzieher believes that Cholin is not the only active substance produced by the cortex. He extracted, by the same methods used in the production of Insulin a substance he calls "Inter-renin". In describing the effects of this when injected he found that it depressed the blood pressure, thus contrasting with the effect of Adrenalin. It had no effect on the blood sugar. It increased basophil polymorphs. It decreases the blood cholesterol. He found that, when injected into adrenalectomised rats, the rats shortly after the injection seemed as lively and vigorous as normal rats. He does not, however, give details of this in his book and the reader has to take a good deal of it on trust. Quoting Golyakowski, Marine, Baumann and Gaydn he says that removal of the adrenal and particularly of its cortex is followed by a considerable rise of temperature. This rise of temperature, however, depends upon the integrity of the thyroid. He agrees with Marine that the cortex is antagonistic to thyroid activities in fat metabolism. He says that removal or impairment of the cortex only has a marked effect on Oxygen consumption and heat production, which shows that the cortex is very efficient in balancing the stimulating effect of the thyroid and its synergists on protein consumption, Basal Metabolism and production of Nitrogen Waste. In discussing the relationship with the thyroid, Goldzieher goes on to say that there is no definite relationship between the size and weight of the adrenals and thyroid. Marked hypertrophy of the adrenal cortex occurs, however, in cases of Thyroid atrophy. Thyroidectomy leads to increased lipid storage in the fasciculata of the cortex (Gray, Beidl) though the glomerular shows signs of involution. This is in keeping with findings in increased thyroid activity or in experimental thyroid feeding, which decreases the cortical lipoids (Kraus). Thus the antagonism of the thyroid and cortex as to certain functions seems to be definitely established. This antagonism also includes various features of metabolism. In contradistinction to the thyroid, the activity of which, increases Basal Metabolism, and administration of which reduces body weight, the adrenal cortex seems to regulate the assimilation of fat and cholesterol. Goldzieher says that he has shown that cortical insufficiency in diabetic acidooris leads to fat mobilisation lipoaemia and fat metastasis. This antagonism, he says, is in contrast to the synergism of thyroid and medulla. There are certain observations which cannot be adjusted so easily. Rogers showed that feeding with adrenal cortex increases the Iodine content of the Thyroid. (This was corroborated by Tokumitsu). This observation is not so paradoxical after all. We have seen before in the case of adrenalin-insulin balance that the mechanism of hormone equilibrium requires the irritability of the antagonistic endocrine organ by its counterpart. If a certain
limit of hormonal concentration has been reached, the inhibitory effect of inter-renal hormone upon the sympathetic thyroid apparatus revokes compensation which yields the increased storage of iodine in the thyroid.

Finally Goldzieher says that Grave's Disease is a disease in which we may expect, at least theoretically, that the rise of inter-renin will be beneficial to the thyroid.

R. Rivoire (7) gives a summary of the present position with regard to the suprarenal cortex. He considers that the cortex has an antitoxic effect, some connection with lipoids, and has a heat reducing action. He states that Hastings and Cowper have noted a progressive augmentation of Blood Potassium in suprarenalectomised dogs. This augmentation would give depressing effects and would form an explanation of the accidents of insufficient cortex. However, these observations are not confirmed. He also comments on the sexual effects of tumours of the Cortex, and considers that it has some effect on Sulphur Metabolism.

S.W. Britton (8) discusses the state of knowledge concerning the adrenals. He considers that it has amply shown that the Cortex is essential to life, and that there are many indications that the cortex is concerned with the storage and utilisation of carbohydrates and possibly with some phases of protein and metabolism.

Britton mentions some of Goldzieher's conclusions, and considers that many considerations point to the immaturity of this work. He also is rather scornful of Cramer's views. He quotes Wyman and Walker (9) (1929 Amer. J. of Physiol. LXXXIX, 3 (2)) who found a fall in blood sugar in adrenalectomised animals. In rats which possessed gross accessory cortical tissue, or in which successful cortical transplants had been made, the blood sugar remained within normal limits. Swingle (10) has also discussed at length the serious diminutions in blood sugar which he observed in adrenalectomised cats. A small amount of cortical tissue, he emphasises, will suffice to keep animals alive with a normal blood sugar percentage. Britton in conclusion considers that the Cortex and Medulla have separate functions.

In connection with this point of the blood sugar, Levy Simpson (11) reported that 10 c.c. of Cortical extract given intramuscularly or intravenously produced no appreciable change in blood sugar during a period of observation of 3 ½ hours in normal individuals, (ii) in Addison's Disease, (iii) in Diabetes Mellitus, but as will be seen later, this matter is disputed.
Hadfield and Garrod (26) suggest that the adrenal cortex is concerned in or even controls cholesterol metabolism. Goldzieher reports many experiments on this point, and himself supports it. He also considers that the cortex has a function in sulphur metabolism, and possibly in fat metabolism. Goldzieher (5) considers also that the cortex has some function in depressing excessive heat production, and also that the adrenals, especially the cortex has a defensive action in toxic diseases. He also considers that the cortex has a detoxicating effect, quoting among other things the fact that organisms in an infection are found in specially large numbers in the cortex. Perl and Marmonston-Goltesman (18) quote experiments to show that the cortical extract of Hartman raises the resistance of suprarenalectomised rats. Goldzieher considers that the cortex depresses cellular combustion, that it is very efficient in balancing the stimulating effect of the thyroid in protein consumption, Basal Metabolism and production of Nitrogen waste (this conclusion will be discussed later). He also considers that it has an effect on growth and sexual characteristics.

In connection with the inter-action of the cortex and Sexual glands, it has been noticed by several observers that pregnant animals survive adrenalectomy longer than non-pregnant animals. W. Cramer (20) and (22) working with histo-chemical methods, describes what he considers to be adrenalin and its precursors are to be found in the cortex spreading towards the medulla. This process being specially marked and can be stimulated by injection of B. Tetrahydronaphthylamine or by exposure to cold.

He considers therefore, that the cortex is essential to the formation of adrenalin. He considers that the cortex may conceivably work independently of the medulla, but that the medulla cannot work independently of the cortex. Further referring to what he terms self control and inhibition of the adrenals gland, he states that the adrenal gland possesses the power to control it's functional activity in such a way as to prevent the gland from stimulating itself to complete exhaustion. In addition, there is a mechanism which affects an inhibition of the functional activity of the gland. This mechanism is situated in the cortex and manifests itself as a disappearance of the cortical lipoid. The phenomenon of inhibition, in which there is an adrenalin free zone interposed between the cells of the Zona Reticularis of the cortex and the adrenalin containing cells of the medulla, has also been observed after thyroid feeding over a prolonged period. There also occurs in thyroid feeding a change in the distribution of the lipoid globules, which he considers is a mechanism situated in the cortex to control excessive output of adrenalin. Since this mechanism of self control comes into action with thyroid feeding, i.e. in experimental
hyperthyroidism, it is likely that this condition may play an important part in clinical Hyperthyroidism. (Here, in parenthesis, we may note Mason's (21) interesting observation that healthy people fed on thyroid show no symptoms of exophthalmic goitre, but neurotic people do). Insufficiency of this mechanism may be an etiological factor in Grave's Disease as the degree of hyperfunction of the thyroid. A degree of thyroid hyperactivity which in a normal organism may produce a condition remaining within physiological limits, owing to the efficiency of the mechanism of self control in the adrenal, will produce a greatly exaggerated effect if this mechanism is not efficient. From this point of view, the functional condition in the suprarenal may be an important factor in the etiology of Graves Disease. Cramer also instances amongst others the effects of experimental infection in mice with B. Welchii where there is congestion of the adrenals, and disappearance of lipoid from the cortex. Other infections are also described. He quotes T.R. Elliott to say that the load of lipoid is not directly related to that of adrenalin. Cramer's observations agree with this statement in the sense that a medulla may be depleted of adrenalin, while the cortex may either be filled with lipoid or empty of it. But there is this important functional relationship, that so long as the cortex is full of lipoid a depleted medulla may fill itself rapidly with adrenalin. In the absence of lipoid the new formation of adrenalin is impaired and the condition of such a gland may be described as being in a state of exhaustion. He says that in the bacterial infections which have been studied experimentally by him, those that lead to the death of the animal in a state of collapse with a greatly subnormal temperature, show a depletion of adrenalin from the medulla, which is always accompanied by a disappearance of lipoid from the cortex. Cramer, therefore, considers that the adrenal cortex is an organ which is essential to the formation of adrenalin in the medulla, which exercise also a controlling and inhibitory effect on the output of adrenalin. With the thyroid and Sympathetic Nervous System it controls the heat regulation of the body. This conception of Cramer's does not seem to be universally accepted. Goldzieher (The Adrenals) commenting on his views says that the rise of temperature is due only to the medulla and cortical function works on the opposite side of the balance. Britton (17) rather scornfully rejects his conclusions. He considers that the cortex is essential to life and discusses experiments to prove that the medulla is not absolutely essential to life. He quotes Banting and Cairns who have found that when the cortex is shaved off in two or within two minutes
after the arrest of the blood flow through the gland no adrenalin can be detected in the tissues. Two hours, however, after the death of the animal, adrenalin could be demonstrated even in the outer layers of the cortex. I think, however, that if one reads Cramers work carefully, one would see that this objection does not really hold. He finds such variations in differing conditions, and seems to be perfectly alive to technical difficulties. Lutz and Weyman (23) say that extract of the inter-renal of elasmobranch fishes do not give the usual tests for adrenalin. Certainly the fact that in elasmobranch fishes the cortex and medulla are separate is a point to be considered against Cramer. Cramer, himself, does not consider it, and points out that the heat regulation is of small importance in cold blooded fishes. The truth here would seem to be in the fact that while the cortex may have the functions ascribed to it by Cramer in warm blood animals, it also has other functions too. In those other functions close proximity to the medulla is not essential. Hartman and Aaron (Endocrinology 16, 1932, p.44) say that in a quoted case the presence of well stained normal medulla coupled with almost complete absence of Cortex, indicated that the cortex was not necessary for the formation of adrenalin. This, they say, seems to disprove Cramers theory. Goldzieher (5) refers to the morphological changes in the adrenal cortex which have been observed after injection of adrenalin, and which would suggest an enhanced cortical function. No other evidence maintains the possibility of such cortical responses to Sympathetic Nervous stimulation and, he says, the morphological findings alone do not carry sufficient weight to decide the question. In spite of all these objections, however, Cramer's work seems to me of great value, and not lightly to be dismissed. Mazer and Goldstein (24) consider that the cortical hormone stimulates the generative organs of the young, but through some mechanism at present unknown, an excess of this hormone in the adult female produces a reversal of sex characters. They also consider that pregnancy seems to increase the demand for cortin. They further consider that the adrenal cortex stimulates sex functions, brings about pigmentation and obesity of pregnancy, that hyperfunction of the gland leads to virilism, obesity and precocious menstruation, that hypofunction leads to Addison's Disease. Korenchevsky (25) finds in castrated rats that the adrenals are enlarged on the average by 23 per cent. and that on the average the weight of the thyroids of castrated rats was 30 per cent. less than that of the controls.
PATHOLOGY OF ADRENAL CORTEX:

It might be well to examine some of the records of disease in the suprarenal cortex, in the hope that they may give us some help in our problem. It is well to know that tumours of the adrenal cortex first described by Sequira (27), lead to striking results. There is abnormal growth with obesity, precocious sexual maturity, and an excessive growth of hair, and also virilism.

According to Langdon Brown (28), defect of the adrenal cortex in children, has been associated with the rare condition termed Progeria by Hastings Gilford, in which the child runs its life cycle in a few years, and shows signs of infantilism.

In his original description of Progeria (29), Hastings Gilford does not consider that the cause of Progeria is necessarily in the suprarenal cortex. Cases have been described where such a disorder can arise from a disordered pituitary. Very few cases seem to have been described, consequently, one feels that it would be unwise to draw any conclusions from Progeria, other than that it is a disorder of Endocrine function, in which the suprarenal cortex is involved.

Langdon Brown (28), considers that in childhood, the normal function of the adrenal cortex is that of a retarding agent, while playing a more active part at puberty and later.

Layton, Otto, Turnbull, Hubert M, and Bratton (30) quote two cases of interest. In these two cases, Carcinoma of the thymus appears to have been associated with pluriglandular disturbance.

In both cases at necropsy a carcinoma of the thymus was associated with great hypertrophy of the suprarenal cortices, functional hypertrophy of the thyroid gland, infiltration of the medulla of the suprarenal bodies with lymphocytes and plasma cells, and fatty infiltration of the centres of the hepatic

Duguid and Kennedy (31), also describe a case of Carcinoma of the thymus, in which there was enlargement of the suprarenal bodies and a colloid goitre.

These cases are of great interest. I think it can be said that there is no doubt that the various glands of the endocrine system react one with another, and though it would be foolish to draw conclusions from the facts of these cases alone, there is a hypertrophy of the suprarenal cortex, and with it there is a functional hypertrophy of the thyroid.

Of course, there is also the tumour of the thymus, which is thought by many to have a connection with the thyroid (Sir E. Sharpey Shafer).

It is interesting to note in this connection, that Langdon Brown (32), says that the condition of Progeria has been seen in cases where the Adrenal Cortex has failed to develop, and also, it has been known to occur in an infant affecting the Anterior lobe of the pituitary in childhood.
Pathology of Adrenal Cortex (Contd.)

Sir Edward Sharpey Shafer (3), says that various attempts have been made to produce a chronic condition of adrenal insufficiency, but it has not been possible to reproduce the symptoms of Addison's Disease experimentally, and bronzing of the skin has never been obtained in animals.

A consideration of —

ADDISON'S DISEASE—might give us some help. The signs and symptoms of Addison's Disease are well known, and do not need detailed description. It is, however, not certain whether the essential lesion is in the cortex or the medulla. Therefore, as we are considering the cortex, any case in which the medulla also is affected, might be misleading. Furthermore, many cases of Addison's Disease are due to Tuberculosis and the symptoms of some of these cases might have the symptoms of tuberculosis superimposed.

A single case of Addison's Disease reported by I.M. Nears and W.G. Millar (33), is of much interest. It apparently was a case of pure atrophy of the cortex with no signs of tuberculosis. The symptoms here were scantly menstruation, rather defective sexual development, loss of weight, Temperature 100, on admission, some acetones in urine, low blood pressure, and some anaemia of the Secondary type. On postmortem examination, the suprarenal glands were markedly diminished in size, and there was almost complete absence of the cortex. No signs of tuberculosis. The thyroid gland was small, but otherwise healthy. On histological examination, what remained of the cortex was thought to show signs of regeneration. This then was a pathological case in which there was almost complete destruction of the cortex. If Marine's theory that the essential lesion in hyperthyroidism is a loss of the cortical restraint, one would expect some signs of Hyperthyroidism. As it is, we have loss of weight, and tachycardia, both of which are found in hyperthyroidism but also in many other conditions.

The Basal Metabolism is not noted. Goldzieher (5), says that loss of weight in Addison's Disease is a sign of a more rapid burning up of tissue elements, but surely, it might equally be due to faulty absorption and nutrition. As for the tachycardia, it is only likely that it should be found in anaemia, and it would seem far fetched to ascribe it to excessive thyroid action. This case then does not seem to favour Marine's theory, nor does it seem to give us a great deal of help in estimating the functions of the cortex. Other similar cases have been recorded where the medulla of each adrenal seems unchanged while the cortex is severely affected.
Addison's Disease. MacCallum (Textbook of Pathology) describes two such. In both cases there was distinct enlargement of the thymus. One fears, however, that Addison's Disease gives us little definite help in the consideration of the Functions of the Cortex. It is possible that some of the symptoms should be referred to defective functioning of the medulla, even when it seems that the cortex alone has disappeared.

Levy Simpson (34), in discussing Addison's Disease, says that in his experience, low blood sugars are of common occurrence in Addison's Disease. He considers that the low blood sugar is due to diminished or absent secretion of Adrenalin. He also contends that there is no direct action of Cortical Extract on Carbohydrate metabolism. There is also a rise in blood pressure in treatment of Addison's Disease with Eucortone (35). He considers that both this, and the rise of blood sugar even in some cases, is due more to a readjustment of metabolism, than to a direct action of Cortical Extract. In a case of pituitary tumour, he found no rise in Basal Metabolism following treatment by Cortical Extract. In the treatment of Addison's Disease, however, Basal Metabolism tends to rise to normal on the injection of Cortical Extract.

As previously shown, Marine, Goldzieher, Stewart and Rogoff had produced extracts of Suprarenal Cortex. Hartman and his colleagues also (36), also produced a Cortical Extract which they say keeps suprarenal-ectomised cats alive indefinitely. Later, they have elaborated it. Hartman (37) states that the potent extract of Suprarenal Cortex which they have isolated, lowers the blood pressure when it is high, increased the resistance to infection and to cold, and accelerates repair to injury.

Swingle and Pfiffner (38), prepared an extract from the suprarenal cortex, which seems to be a potent extract, although at present, it seems not to be sufficiently concentrated, at least, very large quantities are needed for adequate treatment. It keeps suprarenal-ectomised cats alive indefinitely. It's action in the treatment of Addison's Disease is well known, and in many cases it acts as a specific. In Addison's Disease, however, we must bear in mind that the usual cause being Tuberculosis, an Extract of suprarenal cortex can hardly be expected to cure Tuberculosis and, therefore, it seems that we must expect disappointments.

Experiments with this Extract are still proceeding. It causes a rise of blood pressure in some cases, but not in all, and it effect on blood pressure is still uncertain. It causes a rise in Basal Metabolism in Addison's Disease. The question of it's effect on Blood Sugar is doubtful, some authors saying it causes a raising of blood sugar, but most authors agree that it has no effect, for instance Levy Simpson (34), who considers that any effect on the
blood sugar is due to the Adrenalin content of the extract.

Hartman, Brownell and Lockwood (67), in studies indicating the functions of the cortex, conclude that loss of cortex leads to muscular fatigue which is restored by injection of Cortin. They consider that the cortex exercises this action through the nervous system. With deficiency of cortex early fatigue of the reflexes occurs.

Loss of cortex leads to increased susceptibility to heat. Cortin is necessary for Gonadal Function. The Basal Metabolic Rate is lowered by loss of Cortex and brought back to normal by cortin. The cortical hormone is essential to growth. Cortin increases the resistance of Adrenalectomised animals. Toxin increases the demand for Cortin. Cortical extract lowers the high non-protein nitrogen of the blood in both adrenal insufficiency of animals and in Addisons Disease.

Cortical Extract also increases the water intake and urinary output. In the later stages of cortical insufficiency there may be dehydration. Lowered blood sugar in cortical insufficiency can be raised to normal by administration of Cortin. Finally they suggest that Cortin is a general tissue hormone.

Swingle and Pfifner (66), in a long and important article on the Adrenal Cortex Hormone, discuss our knowledge of the suprarenal cortex. Using their extract, Cortin, they found that no phenomena are produced by overdosage of normal individuals.

In normal animals they were unable to detect characteristic changes in the blood constituents they followed. Carbon Dioxide content and capacity, Oxygen capacity, non-protein and Urea Nitrogen, Creatinine, Sugar, Calcium, Potassium, Magnesium, Cholesterol, Lactic Acid, Plasma, Chlorides, Haematocrit and plasma proteins examined in arterial blood samples are not altered in any definite or quantitative manner. They found no changes in Basal Metabolic Rate.

In respect of overdosage, they consider that the cortical hormone differs from adrenalin, insulin, parathyroid and thyroxin, but falls into the same class as the anterior pituitary and gonad hormones, which also does not have toxic effects in normal animals.

Their experiments in Basal Metabolism with adrenalectomised and also thyroidectomised cats (previously quoted) indicated that the changes in respiratory exchange following bilateral adrenalectomy in cats, are essentially the same whether the thyroid is intact or totally removed, and the results indicate that the Adrenal Cortical Hormone has a direct action upon respiratory metabolism. It was a constant finding that in adrenalectomised
dogs, the first significant change observed was a rise in blood non-protein nitrogen and urea. Changes in blood creatinine do not occur until the animal is very ill. Potassium concentration rises steadily during the period of insufficiency. The secretion of urine diminishes rapidly and there may be anuria. There is suppression of urinary nitrogen and urea. There is also defective excretion of Chlorides and phosphates and later creatinine. Injection of Cortical Hormone is followed by Diuresis and increased excretion of Nitrogen and Urea and Chlorides. Blood values return to their previous levels. No lesions are found in the kidney and the lesion is therefore, a functional one. They conclude that their extracts contain the possible sexual principle of the gland. Finally, they conclude that it is impossible to draw any definite conclusions regarding function. All the changes reported as occurring in the organism following bilateral adrenalectomy, they regard as secondary to some at present unknown underlying derangement of the animal. In their treatment of Addisons Disease with the extract, they found that resistance to infection was increased.
DISCUSSION: Functions of the Cortex.
Our knowledge of the functions of the suprarenal Cortex is ill-defined. Writers on the subject differ widely, their conclusions are often at variance, and there is much research yet to be accomplished. Perhaps by a survey of the Experimental, Physiological, and experimental evidence, we may be able to arrive at some conclusions which will be of value.
Firstly - Has the suprarenal cortex any function at all? It has been abundantly proved that the organ is essential to life. Swingle and Pfiffner have succeeded in preparing an extract which enables suprarenalectomised animals to survive indefinitely. This extract has been prepared from the Cortex. Many other authors have demonstrated that life without the cortex is impossible. We may, therefore, definitely conclude that it is essential to life. What then are it's functions? It is intimately associated with the medulla. Is this close association accidental, or are the two organs synergists, one depending on the presence of the other? Cramer's experiments are of great interest. He considers that the cortex exercises both an exciting and inhibitory influence over the output of the Medulla, that the cortex is a mechanism for controlling the support of adrenalin, and for preventing it's exhaustion. It is not easy to prove a case on merely experimental grounds, possibilities of error of technique and individual observation are easily understood. Anatomically, the cortex and medulla are closely connected, but the fact that these are separate in elasmobranch fishes suggests that this close connection does not necessarily imply similar functions.
As previously noted, Cramer does not consider that this fact invalidates his theory. Cramer's theory, I consider, fits the facts of Addison's Disease. In this disease, while similar symptoms are produced, yet one finds Postmortem that in some cases there is destruction mostly in the medulla, and in other cases there is destruction of cortex. Furthermore, many cases have been published in which there is atrophy of the cortex and the medulla is still present. In these cases, the symptoms of low blood pressure, asthenia, and the other symptoms of Addison's Disease are still present. It, as has been suggested, the cortex was purely antagonistic to the medulla, one would expect a very different series of wants in the cases of Atrophy of the cortex. While, therefore, one is willing to conclude that Cramer's views contain much truth, one cannot, in view of much other evidence, conclude that they represent the whole truth.
Recent observations on the pituitary gland, have taught us that the functions of this gland are much more complex than was first thought. In the same way, it is not impossible for the suprarenal cortex to have diverse functions.
15.

Turning our attention to the changes which occur throughout life in the suprarenal cortex, we see that it is an active organ which goes through many phases. These changes take the part of increased size and evidences of activity at critical times of life, such as birth, puberty, and the menopause, and also in pregnancy and menstruation. We see also that there are differences between the male and female, and that in the female especially, there appears to be a connection between the cortex and the sexual apparatus. The connection between the suprarenal cortex and sexual characters is shown in many other instances. Tumours of the adrenal cortex with supposed overgrowth of the gland, first described by Sequira (27), lead to abnormal growth with obesity, precocious sexual maturity, excessive growth of hair, and virilism in women. According to Hadfield and Garrod (26), these effects may be due to simple hypertrophy or to neoplasms. There are now on record several cases in which the removal of such a tumour has been followed by the reversion to normal sex characters. A series of cases described by Aschard and Thiers (61), and known as the Diabetes of bronzed women, is of interest in this connection. In these cases are found hirsutes on face, masculine in type, Obesity, and disturbed genital functions. Necropsies, when obtained, generally showed adrenal or pituitary tumours. One such case seen by Langdon Brown (32) had an Adenoma of the Anterior Pituitary, and another had Bilateral hypertrophy of the adrenal cortex. Goldzieher observed (5) that sexual development in adrenalectomised rats, is late and inadequate in both male and female. Ceni (62) (quoted by Ashoff Lane lecture) claims to have observed after extirpation of parts of the cerebral hemispheres, a hypertrophy of the suprarenal. With this went atrophy of the testis. Britton (8) found that adrenalectomised rats live longer if pregnant. Levy Simpson's observation that in Addisons Disease, injection of Cortical Extract leads to a return of Sexual function, is a further point to be considered. Furthermore, Levy Simpson (63) found that in a patient with a pituitary tumour, a loss of secondary sexual characteristics, injection of cortical extract caused a return of sexual manifestations, which had been completely absent in the previous twelve months. This was not associated with any improvement in the general condition. We, therefore, have a great deal of evidence to lead us to conclude that there is a definite connection between the suprarenal cortex and sexual characteristics. The exact nature of the connection is not absolutely clear, probably as Landon Brown says, the cortex influences the developments of puberty and sexual maturity, but always in the direction of virilism.
The rare disease of Progeria, first described by Hastings Gilford (64), in which the child runs its life cycle in a few years and often shows infantilism, has been considered to be due to the defect of the suprarenal cortex. In reading Hastings Gilford's book, one sees also that other endocrine organs are often affected. In view of this, and in view of the great rarity of the disease, I feel it would not be wise to draw any conclusions from Progeria. There is a great similarity in the appearance of the Corpus Luteum, and of the suprarenal cortex. Experimental work is proceeding on this point at present and the results obtained will be of great interest.

There is a great deal of evidence to show that the cortex has an antitoxic effect, and that loss of Cortex leads to an increased susceptibility to toxins. The effect is seen after experimental extirpation of the glands and in Addison's Disease. It is found also that injection of Cortical Extract increases the powers of resistance to Carcinoma. For example, Rowntree and his colleagues (65) observed that cases of Addison's Diseases treated with Cortical Extract show a much greater resistance to infection than is found in untreated cases. This effect of cortical extract has also been noted by many other observers.

We may now consider what is to be learnt of the functions of the cortex, by the consideration of the effects of Cortical Extracts. Goldzieher bases a good many of his conclusions as to the functions of the cortex on the effects of Inter-renin - Inter-renin he isolated from the suprarenal cortex. He says:

1. That Inter-renin depresses the blood pressure in contradistinction to Adrenalin.
2. That it has no effect on Blood sugar.
3. That it causes a marked drop in blood cholesterol.

I am, however, unable to find a definite statement that Inter-renin keeps adrenalectomised animals alive indefinitely.

Swingle and Pfiffner in a detailed paper (66), on the results of experiments with injection of their cortical hormone, arrive at different conclusions. They find no phenomena on overdosage of normal animals. They say:

1. That the effect on blood pressure is slight, and is, they believe, rather secondary in nature.
2. That it has no direct effect on Blood Sugar.
3. That it has no effect on Blood cholesterol.
4. They conclude that the adrenal cortex hormone has a different effect on the respiratory metabolism of animals.
5. Furthermore, they found that the first significant change observed in adrenalectomised animals was a rise in blood non-protein nitrogen and urea. This was remedied by injection of cortical extract.

6. They conclude that their extracts contain the possible sexual principle of the gland.

7. In cortical insufficiency the secretion of urine diminishes rapidly, and there may be anuria. There is suppression of urinary nitrogen and urea. There is also defective secretion of chlorides and phosphates, and later injection of cortical extract is followed by diuresis and increased excretion of Nitrogen and urea and chlorides. Blood values return to their previous level. Finally, they conclude that it is impossible to draw any definite conclusions regarding function.

Hartman, Brownell and Lockwood (67) working with Swingle and Pfiffners Extract state :-
1. That cortical extract is necessary for gonadal function.
2. That the cortical hormone is essential to growth.
3. That cortin increases the resistance of adrenalectomised animals, and that toxin increases the demand for Cortin.
4. That cortical extract lowers the high non-protein nitrogen of the blood in both adrenal insufficiency of animals, and in Addisons Disease.
5. Cortical Extract also increases the water intake and urinary output.
6. Loss of cortex leads to muscular fatigue which is restored by injection of cortin.
7. Finally, they suggest that Cortin is a general tissue hormone. The exact meaning of a general tissue hormone is not very clear.

Britton and Silvette (68), consider that liver and muscle storage of glycogen is greatly increased after injection of cortical extract in normal animals, and that this represents a highly important function of the Cortico-adrenal hormone. Most observers find the suprarenalectomy is followed by a fall in blood sugar, and also that the blood sugar is low in Addisons Disease. Rowntree and Snell (65) regard hypoglycaemia as a terminal phenomenon. It must also be remembered that in Addisons Disease, the suprarenal medulla is often affected.

Levy Simpson concludes that the cortex has no direct effect on blood sugar. We are faced, therefore, with conflicting observations. Goldzieher produced his extract of Inter-remin, and with it found different results to those of Swingle and Pfiffners Extract.
and Pfiffner. Other extracts such as Hartman, of Marine and Stewart and Rogoff have also been made. At the present time, the only extract which may be said to have scientific proof behind it, is that of Swingle and Pfiffner. These two observers are very conservative in their views, and hesitate to draw conclusions without absolute proof. Goldzieher appears to be more venturesome. We must assume, therefore, that the conclusions of Swingle and Pfiffner are to be greatly respected. We are not, however, forced to assume that their extract is the final one. It is quite possible that there are several internal secretions in the suprarenal cortex, as there are in the Pituitary gland. Some of these internal secretions may be absent in Swingle and Pfiffner's extract. We look to the future to produce other extracts which may help in the elucidation of the functions of the cortex.

The suprarenal cortex has long been associated with the question of cholesterol and fat metabolism. Ashoff considered that the cortex forms the most essential regulatory organ for cholesterol and fat metabolism. Landau (69), supported by others, thinks that the suprarenal cortex represents essentially a storage organ for cholesterol and fat. Goldzieher (5) basing his conclusions on the loss of weight following adrenalectomy, and also on the effects of injection of Inter-renin, considers that the cortex decreases the fat content of the blood and elicits increased storage of fat in the tissues. Swingle and Pfiffner (66) found no changes in blood cholesterol after injection of cortical extract. They studied the cholesterol and blood lipoids in a few cases of Addison's Disease, and found no great changes.

Sir Edward Sharpey Shafer (3), discusses this question and concludes that the suggestion that the suprarenal cortex may be a seat of manufacture of lipoids of the body, is, and may be especially related to the formation and development of the myelin of nerve fibres, is attractive. Much work, and many writings are concerned with this subject. One of the chief characteristics of Addison's Disease is wasting, and experimental destruction of the cortex is followed by defective nutrition. It is the recovery of weight and improvement in general nutrition associated with the treatment of Addison's Disease with cortical extract, is very striking. It is surely to be considered that the suprarenal cortex does exercise a profound effect on nutrition. How this is brought about we do not know, nor am I aware of definite experimental proof. Yet I think we...
are justified in concluding that the suprarenal cortex does in some way exercise a profound effect on nutrition in a manner not yet determined. As Sir Edward Sharpey Shafer says, it should be the case that the main function of the suprarenal cortex is the manufacture of lipoids and cholesterol, one can understand why their removal by operation or their destruction by disease should be incompatible with the prolonged maintenance of life.

The fact, that in anencephaly there is an absence of suprarenal cortex, suggests that there may be some connection between the cortex and the development of the brain. It is interesting to note here a connection quoted with the testis. Possibly the cortex is a factor in the production of Myelin in the nervous system. To the cortex must be ascribed some connection with pigmentation. It is to be remembered however, that the pigmentation of Addison's Disease has never been experimentally reproduced. The theory that the cortex is responsible for the pigmentation of pregnancy is an attractive one. Goldzieher associates the cortex with the production of Choline, and accordingly ascribes to the cortex the properties which are possessed by choline. He describes an experiment which he says proves that the cortex does produce Choline. Sharpey Shafer referring to such a possibility in his book on the Endocrine Organs says, "It is perfectly legitimate criticism regarding the employment of extracts of organs, that we are not justified in assuming that because we obtain evidence of the presence of active substances in such extracts, they are necessarily preformed in the organ, and still less that they are passed out of it into the blood.

In the absence, therefore, of further proof, one feels that one would not be justified in ascribing to the cortex results which would be produced by the injection of Choline.

Other functions have been ascribed to the cortex, for example, some connection with sulphur metabolism, and with blood potassium, and with blood urea. These functions remain more in the realm of suggestion, than of proven fact.

Loss of the cortex leads to anuria which is remedied by giving a cortical extract. No kidney lesions have been found to account for this, and the defect is sufficed a functional one. Whether or this is due to direct action of the cortex, or whether to secondary disturbance following the general ill-health of adrenalectomised animals, we do not know. Further evidence will be needed on this point before we can come to any positive conclusion. Levy Simpson (63) considers this failure of renal function similar to that occurring in Diabetes Mellitus and Intestinal Obstruction, and to be due to (1) dehydration, (2) Toxaemia, (3) superadded acute fall of an already low blood pressure.
The effects of the Suprarenal cortex on Hyperthyroidism.

Shapio and Marine (42) reported a case of Exophthalmic Goitre which showed improvement by the parenteral administration of fresh ox suprarenal gland. The case presented several unusual features in addition to the classical ones. The more important were:

1. Period of Pyrexia of unknown origin.
2. Very low systolic Blood pressure.
3. Purpura.
4. A rapid gain in weight, muscular strength, rise in blood pressure, and decrease in bleeding time associated with administration of fresh ox suprarenal gland, but without any noteworthy changes in pulse rate, exophthalmos or thyroid gland.

Unfortunately in this case they were unable to make estimations of the Basal Metabolic rate during the period, though in another institution rates of plus 68 per cent. and plus 49 per cent. were obtained.

There was a gradual rise in blood pressure (which they did not ascribe to the suprarenal extract). Other striking evidences of improvement were the return of the menstrual function, lessening of tremor, and new growth of hair, disappearing of abnormal sweating, though the thyroid gland, as regards size, consistency, and expansile pulsation remained unchanged, as did pulse rate and exophthalmos.

They summarise the case and say that very striking improvement was obtained by the administration of suprarenal gland, and state that the observation contains an additional suggestion from the clinical viewpoint of a possible relative functional insufficiency of the suprarenal cortex as one of the underlying factors in Exophthalmic Goitre. This experience suggests that fresh suprarenal cortex may be administered in 5 gram doses daily by mouth, without ill effect. Large doses of whole gland suprarenal caused nausea and vomiting.

They say that evidence both experimental and clinical is now rapidly accumulating, that the suprarenal gland, and particularly its cortical portion, plays an essential and fundamental role in the etiology of Exophthalmic Goitre.

On reading this case, a few criticisms come to mind. The diagnosis of Exophthalmic Goitre is no doubt correct, but it is hard to be convinced that it is not complicated by some other condition. From the scientific, but not the patient's point of view, it is a pity that we do not know the exact state of things which would be found on pathological examination.

There is also the fact that the classical signs of Graves Disease, with the exception of tremor and
sweating, were the signs which did not improve. And lastly, of course, is the eternal question one asks oneself in assaying the effects of treatment—would this case have improved in similar fashion without the Suprarenal Extract?

For all these criticisms, the case is of interest. Marine and Baumann (43)(44) report experiments in 53 rabbits showing that partial, but sufficient destruction of the suprarenal cortex in rabbits with intact thyroids, usually leads to an increased heat production lasting from a few days to several months, depending on the degree of injury produced and the rapidity of compensation. They also point out that lethal destruction of the inter-renal function causes a fall in heat production. These observations were confirmed by Scott in the same laboratory, using cats (43).

On the basis of these findings, the hypothesis is advanced that the suprarenal glands normally exercise an inhibitory or regulatory influence over the activity of the thyroid gland. Additional evidence of effect of the suprarenal cortex on heat production was obtained in 10 normal babies (45).

As was pointed out above, there occurs during the second week of extra-uterine life in babies, a remarkable natural destruction of the two inner layers of the cortex. Marine and his colleagues thought that if experimental destruction of the suprarenal cortices in cats could cause an increase in heat production, perhaps the same reaction occurs during the natural or normal destruction of this gland in babies. Marine Baumann and Cipra (47) undertook experiments to determine whether heat production in the normal animal could be lowered by administration of Suprarenal Cortex Extract. They refer to the fact that they had been able to obtain a definite reduction in the heat production of rabbits by the oral administration of Glycerol extracts of fresh or inter-renal glands (48)(49).

Their present experiments of feeding emulsions of inter-renal gland to rabbits suggest that the metabolism depressing substance acts directly or indirectly through the visceral nervous system on the thyroid cells either to inhibit the formation of the thyroid hormone or to prevent its excretion rather to neutralise any secretion. In all cases the heat production increased again after stopping the emulsion. In most cases this occurred between the 4th and 8th day, but in one instance it was delayed over a month. Dried preparations both commercial and those prepared by themselves in their hands have been without definite effects, and also have a large number of extracts prepared during their attempt to concentrate this substance for subcutaneous or intra-peritoneal injection. Most of these extracts have contained more
or less adrenalin and had a tendency to raise metabolism when injected.

Marine, Baumann and Bruce Webster (50) in a paper on the value of Hexuronic Acid in the treatment of Grave's Disease with Suprarenal Cortex describe, how they during the past six years have treated 50 addition cases by the administration of Glycerol Extract of Fresh Ox Suprarenal Cortex, with the same general results, i.e. very striking improvement in 12 to 15 days in the following particulars, i.e. of (1) a gain in body weight, (2) a gain in muscle strength, (3) disappearance of Diarrhoea, (4) control of excessive menstrual flow, (5) a marked decrease in the Basal Metabolic Rate, approaching normal after two to four months.

In 1928, Szent - Gyorgyi (51) isolated a Hexuronic acid from suprarenal cortex, which is easily destroyed with exposure to air. In the preparation of an extract of Suprarenal Cortex, this would probably be destroyed.

Case 1 - female. During a preliminary rest period of 2 months, there was a decrease of Basal Metabolic Rate from plus 62 to plus 41 per cent. Between January and May, 12 to 24 c.c. of Cortex was given daily by the mouth. The B.M.R. decreased from plus 41 per cent to plus 15 per cent. Between May and October 1930, there was no further medication. The B.M.R. was than 0. The pulse had dropped from 112 to 68 and the weight increased. A further six cases improved on administration of Suprarenal Cortex, but no affects were obtained by hexuronic acid. This evidence, they say, strongly supports the conclusions reported in their previous papers, that -

1. A symptom complex essentially identical with Grave's Disease in the physiological and pathological aspects, can be produced by the sublethal injury of the suprarenal cortex of rabbits and cats.
2. A glycerol extract of suprarenal cortex consistently causes strikingly beneficial affects in Grave's Disease.
3. This suprarenal cortical extract as shown in 1926 lowers the metabolism in rabbits when thyroids are intact.
4. No results were obtained by the administration of Hexuronic Acid.

They state that they are firmly convinced that the primary etiological factor in Grave's Disease, is the deficiency of the inter-renal secretion of the suprarenal cortex.

Marine (52) discussing the etiology of Grave's Disease, states that one of the most prominent features of Graves Disease is the hyperplasin of the thymus, spleen, and regional lymph glands. Experimentally he says, removal of thyroid hastens atrophy of the thymus gland, while the removal of the
suprarenals in animals causes regeneration of the thymus - a clinical pathological condition resembling status lymphaticus. He believes that Addison's Disease, Graves Disease, and Status Lymphaticus are closely related states, and that all three are intimately associated with the insufficiency of some secretion of the suprarenal cortex and gonads. He discusses his experiments on rabbits, and on the basal metabolism of infants, quoted before in this thesis, and his favourable results in treatment with fresh Ox Suprarenal Cortex.

In conclusion he says that while the view that Graves disease is essentially a thyroid disease, is still the prevailing one, and while therapy should be based on this assumption, he is convinced that a much more fundamental disturbance lies in a deficiency of some function of the suprarenal cortex and sex glands, which either provides another means of promoting tissue oxidations, or has to do with the regulatory control of these oxidations.

Langmead (53) discusses the role of the cortex in the etiology of Graves Disease. He says that Obregia had treated Graves Disease with glycerin Extract of whole suprarenal glands of sheep, pigs, or calves. He records rapid amelioration of the conditions, and states that all the patients have recovered. With Adrenalin also, by the mouth, he obtained improvement, but this was less pronounced than with the whole gland. Langmead concludes by suggesting that the suprarenals play an important part in the etiology and clinical manifestation of Graves Disease, and by saying that there is a good deal of evidence to show that suprarenal cortex exerts a controlling influence on thyroid activity, and that its failure to control is an important factor.

Swingle, Pfiiffner and Bruce Webster (39) reported that, experimenting with cats, after excision of both adrenals, there was a progressive fall of Metabolic Rate till a level 50 per cent. below normal was reached. On administration of the cortical hormone the Basal Metabolic Rate rose again to normal. The same authors (54) find no affects on Basal Metabolic Rate when cortex is injected into normal cats, and that with cats having had thyroidectomy, injection of Cortical Hormone caused the lowered Basal Metabolic Rate to rise 15 per cent. to 30 per cent. in 80 per cent. of experiments. The same results were obtained when the cats had had both suprarenals removed.

These results were in some contradiction to Marine and Baumann (55), who reported an increase in metabolism in 50 per cent. of their rabbits when the adrenals were removed or injured by freezing. They noted no change in 33 per cent. and a fall in 14 per cent.
Aub. (56), also using cats, found a drop of 28 per cent. in their metabolism following total removal of the adrenals. Intravenous injection of the cortical extract produced no effect on the metabolism of these animals.

One cannot think that the above experiments lead us very far in considering the function of the cortex. They are contradictory, and there would seem to be a possible large margin of error in them. It is also hard to be assured of the potency of the Cortical Extracts in use at that time.

It is certainly true that pathological findings, as in cases of Addison's Disease lend support to the theory that with destruction of the suprarenal cortex, there is a fall in Basal Metabolism. This is a fact which would seem to contradict Marine's results.

Rowntree, Greene, Ball, Swingle and Pfiffner (57), treated three cases of exophthalmic Goitre with cortical extract. Subjectively, two out of the three felt considerably better. Objectively, they showed evidence of less stimulation, and some increase in strength, with slowing of the pulse and decrease in Basal Metabolic Rate from plus 50 to plus 30 per cent. in one case, and from plus 55 to plus 28 per cent. in the other.

Practically, the results could not be considered of consequence since both patients had been given Iodine and had been operated on. Scientifically, they say, the results are of interest, and make them feel that the suggestion of Marine as to the participation of the suprarenal gland in Exophthalmic Goitre should be thoroughly investigated.

Harrop, Weinstein and Marlow, Swingle and Pfiffner (58), state that in a certain number of cases of Hyperthyroidism, a significant drop in the Oxygen consumption occurred after injection of 10 to 30 c.c. of Cortical Extract. No significant change in pulse rate or clinical condition occurred in these short experiments. One well controlled case showed an effect - the others were quite negative. They concluded that an influence of this material on the course of Hyperthyroidism cannot be shown, although the possibility still remains -

(a) either that the dose is insufficient,
(b) that due to differing etiology, it may be effective in certain cases and not in others.

They believe that the suprarenal cortex has an effect on kidney function, especially in the excretion of fluid, chlorides, and urea nitrogen.

Oppenheimer, in the discussions following, said that he found the effect of cortical extract in Graves Disease disappointing. He quotes two cases of interest to support Marine's theory.

One, a case of tremor who received massive doses of X-Ray to the suprarenal region in 1923 and 1924, and in 1926 he developed typical symptoms of Graves Disease, confirmed at operation.
The second case was a doctor to whom the same thing happened. The doctor, who knew nothing of the theory, thought that the cause of the Hyperthyroidism was the damage to the cortex by X-Rays. Barrop in the same discussion said that he found that several cases of Graves Disease treated with Cortical Extract, expressed themselves as feeling better, but no objective proof was obtained. Brasser (59) in a review of Addison's Disease, states that the thyroid is often diseased in Addison's Disease; in most cases there is some infiltration and fibrosis. In some cases there are signs of Graves Disease, and in some, signs of Myxoedema. He says that it seems probable that the changes in the thyroid are due to the same cause as the suprarenal lesion, and not to loss of suprarenal functions.

Rowntree, Greene, Ball, Swingle and Pfiffner (60) discussing the treatment of Addison's Disease with Cortical Extract, stated that they treated in collaboration with others, four cases of Exophthalmic Goitre, and one of Myxoedema with Cortical Extract, with some improvement, in two cases mostly subjective, and no change in the other two. There was no change in the case of Myxoedema.
CASES.

Although the grounds for thinking that the suprarenal cortex will restrain excessive action of the thyroid gland, can hardly be taken as established, there yet remained sufficient evidence in Marine's experiments to try the clinical use of Extract of Suprarenal Cortex in cases of hyperthyroidism. With this in mind in 1929 and 1930, I tried the effect of tablets of Suprarenal Cortex (Carnich) Gr.2 three times daily in cases of Hyperthyroidism. There was at that time no extract available for injection, and there was no guarantee that the tablets could be absorbed from the alimentary tract, nor was there any certainty that the extract contained in them was active. The cases chosen were of various types; early exophthalmic goitres as well as severe ones, and also two or three cases of toxic goitre, and also one case of toxic goitre in which partial thyroidectomy had been performed without appreciable benefit. The first case January 1930, was a woman age 38, who was an almost typical case of exophthalmic goitre. She had exophthalmus, tachycardia, but no enlarged thyroid, and slight tremor. When first seen she had a pulse rate of 132. Blood pressure Systolic 140, Diastolic 90. Weight 7 st. 4½ lbs. No other signs of disease were found. She took the tablets of cortical extract for 6 months. At the end of that time her weight was 7 St. 7½-lbs. Pulse averaged about 90. The exophthalmus was improved and only slight tremor remained. The tablets were then stopped and she was given Calcium. The slight improvement continued and in November she had a pulse rate of 76 and a weight of 8 St. 2½-lbs. She continued to be fairly well, though apt to have exacerbations of pulse rate on the slightest excuse till November 1931, when she worsened. X-Ray treatment was given and on the last occasion seen she had a pulse rate of 84. Weight 7 st. 7-lbs and felt a lot better. Exophthalmus and tremor gone. No estimations of Basal Metabolism were made.

In this case then there certainly was improvement on taking Suprarenal cortex, but the improvement was equally maintained on Calcium, and finally in 2½-years the patient is almost completely well. There is, I fear, no reason to think that she would not have done equally well on rest alone. In view, however, of that fact that she certainly did improve when taking Suprarenal Cortex I felt justified in trying the Cortical Tablets on other patients. In all, eleven patients were thus treated. I do not propose to consider the cases in detail, some seemed to improve, some did not. In no case could one find that improvement occurred when taking tablets, and retrogressed when the tablets were stopped.
NOTES OF CASE.

Name: [Handwritten name]
Age: [Handwritten age]
Diet: [Handwritten diet]

Case Book No.: [Handwritten number]

Urine:
Sp. Grav.: 10.20
Reaction: Acid
Abnormalities:

Urine Test:

Sp. Grav.: 10.20
Reaction: Acid
Sugar: [Handwritten sugar]

DATE OF ADMISSION: 1.10.52

Result: [Handwritten result]
NOTES OF CASE.

Name: Elizabeth Brindle

Age: 44.4

Diet: 

Case Book No.: 1.38

DATE OF ADMISSION: 1.10.32.

Result: 

PULSE

RESP.

DATE

DAY OF DISEASE
One case was seen early on in the course of the disease, and tablets were given for eight months, but the disease still at the end of two years is in statu quo.

As far as I could see, the tablets had no affect whatever, beyond the efforts which might be ascribed to faith on the part of the patient.

It would seem, however, that in view of the grave doubt about absorption and activity of the tablets, that one would not be justified in considering the possibility of Supra-Cortex being of value if only one could find an extract, which one knew to be active.

It was about this time that Swingle and his co-workers produces his extract of suprarenal cortex which he proved to be active. And, therefore, I then decided to try the effect of this known extract in cases of Hyperthyroidism.

The results of this method of treatment will now be described.


History: For the past year the patient has been losing weight, has had gradually increasing dyspnoea on exertion attacks of palpitation. She felt extremely nervous and irritable. She kept at work until six months ago and then consulted a doctor. Her friends noticed about that time that her eyes were becoming prominent. She sweated easily, and developed a marked trembling of the hands. Menopause 4 years ago. There was nothing of importance in the previous history or the family history.

On examination: Colour good. Exitable. Exophalmos. Skin moist, pigmented with alternative whitish and brownish areas.

Mouth: Tongue clean. Teeth - some pyorrhoea. Tonsils healthy.

No abnormal alimentary symptoms or signs.

Exophalmos both eyes. Marked tremor of both hands.

No palpable enlargement of the thyroid.

Heart: Pulse 120 regular. S.P. 140/60. Slight enlargement of heart to left. Softening of first sound in the mitral area.

Lungs: Some scattered at bases. Otherwise there were no abnormalities found.

Weight 7 st. 7-lbs.

Soon after admission the Basal Metabolic Rate was plus 40 per cent. Three months before it had been taken and found to be plus 23 per cent. and 13 lbs. of weight had been lost since then.

After a preliminary rest in bed of 10 days, the pulse rate fell to about 100. 2 c.c. of Suprarenal Cortex were given daily and the pulse rate gradually increased. The dose was increased to 5 c.c. and stopped. The pulse rate was then almost 120. After cessation of treatment for 4 days Cortical Extract was restarted.
**NOTES OF CASE.**

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**Case Book No.**

- **Urine Test:** 2.9.82
- Spec. Gram: 1022
- Read: Acid
- Abnormal: + ic.

**DATE OF ADMISSION.**

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and the pulse rate increased again. Treatment was stopped for 3 days and then restarted with 2 c.c. daily, increased to 5 c.c. The Basal Metabolic Rate was taken again and found to be plus 24 per cent. Weight was 7 st. 4 lbs. and pulse rate about 100. Three days rest was then given and then 5 c.c. of Cortex was given daily. At this period the pulse rate was noted as being reduced. Actually this was a false reading, as on consultation it was found that many extrasystoles were re-imposed, and all the beats were not getting through to the wrist. On this account treatment was stopped, and the extrasystoles disappeared. After a further fortnight of rest, the patient was sent home. Her weight was 7 st. 3 lbs. Basal Metabolic Rate plus 64 per cent. She expressed herself as feeling better, but as is shown her objective signs were not better. No change in exophalmo or tremor.

It will be seen that in this patient no appreciable benefit resulted from treatment. The extrasystoles were a feature which occurred only when 5 c.c. of Cortex were given, and ceased when it was stopped, and must be attributed to the cortical extract.

Observations were made on her blood pressure and blood sugar, and no appreciable effect was found on administration of Cortex.

Alice B. Age 58. Married. Weaver. Toxic Goitre.

History: Since an accident two years ago the patient has been nervous, "felt trembly" in her hands and legs on attempting movement. Has had palpitation, worse on exertion. Was easily tired. Occasional sickness. Constant headaches. Menopause 9 years ago. Losing weight.


Weight 6 st. 5 lbs. Basal Metabolism not then taken. She was advised to rest. Operation was considered not advisable. She was treated with Tabs. Suprarenal Cortex (Carnick) gr.2. One t.d.s. with no result. She was also given Calcium afterwards. Her pulse rate and symptoms varied, but on the whole she improved slightly. Her pulse rate keeping between 120 and 150.

In September 1932, she was kept under strict observation. Her condition was rather better. Her resting pulse in bed being 100 or 80. The tremor had improved, and she could go out and do some household work. There was no apparent enlargement of the thyroid. Her weight was 6 st. 5 lbs. She was kept at rest for a week, and then her Basal Metabolism was taken and found to be plus 98 per cent. For the next week she was treated with injections of Evans Suprarenal Cortex subcutaneously, starting with 2 c.c. and working up to 5 c.c. At the end of the
time her pulse rate was much as before. Weight 6 st. 6 lbs. and her pulse 106 down to 92. She stated that she felt no affects from the injections.

It will be seen from the accompanying chart that 5 c.c. of Cortical Extract caused at first a slight rise of temperature, and a slight increase in pulse rate. The last two injections did not give so marked a reaction. In view of the expense and the absence of improvement, the injections were stopped, and tabs. of Suprarenal Cortex again given.

On 13th October, her pulse when walking about was 120, weight 7 st. Her tremor and general condition were appreciably better. One found, however, that she had taken very few tablets, and she thought they made her pant for breath a little.

This was at the start a moderately severe case of Hyperthyroidism, most likely a toxic goitre. Under conditions of rest, advice as to diet and so on, she did improve slowly. The injections of cortical extract, in this case Evan's Extract, had no marked effect. The only one we observed was a slight rise of pulse rate. Unfortunately, we were again unable to estimate her Basal Metabolism when treatment was stopped.

Mary B. Age 19, Single. Hat trimmer. Diagnosis - Exophalamic Goitre.
Complains of a large swelling in the neck, tiredness, dyspnoea, palpitation and fatigue, also of general nervousness, sweating, and on two occasions at the onset of the disease she vomitted.

Previous illnesses: Chorea and Diphtheria - latter two year's ago.
Four years ago the patient states she became unwell, and from then till now has been getting worse. She says the Diphtheria aggravated the condition considerably. She has a good appetite and sleeps fairly well. A tendency to diarrhoea. She says she has gained weight just lately.

Menstruation: No abnormalities except some irregularity.

On examination: Patient moderately well nourished, somewhat anaemic. Skin very moist and clammy. Tongue clean. Teeth fair. Patient very excitable. Thyroid gland: Bilateral enlargement mainly of lobes through isthmus is palpable, extends from level to sub-sternal notch, and posteriorly to mastoid muscles. The skin is not attached. Superficial veins seen in the skin. The gland moves in the vertical meridian with degentition, and moves freely in the deep structures. Fairly solid consistency. Venous and Eyes: Some slight exophalmas. Joffroy's sign plus. Van Grafe - Moebins -. Stellwag -.
**NOTES OF CASE.**

**Name:** B.O. T. D. W.  
**Age:** 5 years  
**Diet:**  
**Case Book No.:**  

**DATE OF ADMISSION.**  
**Result:**  
**DATE**  
**B. D. S.**  
**Pulse**  
**Resp.**  

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**Date:** 4.  
**Result:**
NOTES OF CASE.

Name: Actoron

Age: 19 years

Diet:...

Case Book No:...

DATE OF ADMISSION: 16.4.32

Result:...

DATE OF DISEASE: 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
Hypermetropic. Accommodation and reflexes normal. No inflammation.
Heart: Apex 5th space, external to nipple line.
Action quick and forcible. Mitral systolic murmur conducted towards axilla, 2nd pulmonary sound reduplicated. Rough presystolic element down border of sternum.
Lungs, abdomen, and urinary system - nothing abnormal.
Weight 7 st. 8 lbs.
Wassermann's Reaction negative.
Blood Count, slight Secondary Anaemia.
On admission Pulse 128.
Was treated with rest in bed, Calcium and T.Iodine, and with X-Rays. An electrocardiogram taken later showed intense serratic tremor and an inverted T.

Baseline Metabolic Rate after two months was plus 25 per cent.
Pulse then about 140. Blood pressure 120/50.
Weight 7 st. 13 lbs.
Treatment with subcutaneous injections of Evan's Extract of Suprarenal Cortex was then instituted. She was admitted to a surgical ward in the Preston Infirmary on 16/4/32, but was not considered a suitable case for operation, and was transferred to a medical ward after a fortnight. Her pulse then averaged about 130. Her Basal Metabolic Rate was found to be plus 25 per cent. This was thought to be a low reading, as the patient maintained very low respirations throughout. In the medical ward she was treated with Iodine and X-Rays.
At the beginning of July the pulse averaged about 135.
Weight was 7 st. 13 lbs. Basal Metabolic Rate plus 25 per cent. Blood pressure 120/50.
She was then treated with injections of Suprarenal Cortex Extract (Evans) starting with 2 c.c. subcutaneously daily and increasing up to 5 c.c. daily.
As will be seen by the accompanying chart, the pulse rate slightly increased and 5 c.c. of the Extract caused a rise of temperature, in one case to 101.
She became very nervous, with much palpitation and dyspnoea, and after 8 days the treatment was stopped.
Her weight then was 7 st. 13 lbs. and 6 days later was 7 st.11 lbs. 14.0z.
She expressed a wish to go home, and did so. Unfortunately, her Basal Metabolic Rate was not taken before discharge.

It will be seen that in this case, the only effect of injections of Cortical Extract, was to make the patient worse, so much so that they had to be stopped.
I think it probable that some of the effects obtained were due to adulteration of the extract used with some Adrenalin, and furthermore, I am inclined to think that the treatment coincided with a period of remission of the disease.
NOTES OF CASE.

Name: Wade
Age: 31 yrs.
Diet:...

Case Book No: 122

Min test: 15-9-32
S.G: 1020
Reachin - Acid

U. A. discovered

DATE OF ADMISSION: 14-9-32

Result:...

PULSE
RESP.
DATE
DAY OF DISEASE
### NOTES OF CASE

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### NOTES OF CASE

**Name:** Charles Wade  
**Age:** 21 years  
**Diet:**  
**Case Book No.:** 122

### DISEASE

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### DATE OF ADMISSION
- **14. Q. 3. 30**

### RESULT

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**PULSE**
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**RESP.**
- 23  
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**DAYS OF DISEASE**
- November
The effect on the blood sugar was not tested in this patient. An injection of Cortex caused a rise both in pulse and blood pressure which subsided in about an hour.

The patient was a typical case of Exophthalmic Goitre.


History: Was at work till about 10 months previously when he had an attack of "poisoned stomach". Since then he has not felt well. He was nervous, had dyspnœa and felt his heart fluttering. About 4 months previously his friends noticed that his eyes were becoming more prominent and a swelling was noticed in his neck. He had 3 weeks X-Ray treatment.

No previous history of note.

On examination: Marked exophthalmos. Excitable and easily bursts into tears. Skin moist and velvety.

Mouth - tongue clean. Dental caries present.

Appetite good. Bowels regular.


Systolic murmur on auscultation over thyroid. Nothing else abnormal found.

He was, in fact, a severe case of Exophthalmic Goitre. On admission he had a pulse of 150 and was put to bed for 10 days and no treatment given.

At the end of that time his Basal Metabolic Rate was estimated and found to be plus 33 per cent. This was thought to be a falsely low reading owing to the patient persisting in shallow incomplete expiration. His urine later showed glycosuria. Blood sugar curves showed this to be non-Diabetic, and it was ascribed to the hyperthyroidism. There was no ketosis. He was then given Encortone subcutaneously. He greatly resented injections, and was very nervous about them. The first dose given was 1 c.c., and daily increased by 1 c.c. till 5 c.c. were given. The small doses did not seem to have much effect except that his evening temperature tended to rise to 99.5. The first dose of 5 c.c. was followed by a rise of temperature of 101.2. Pulse rate was then about 140. Encortone was stopped for 2 days, and then 2 c.c. were given daily for 4 days. There was no marked effect. Owing to expense and lack of improvement, it was stopped and rest only was given for 20 days. During this time he slightly improved. Encortone was again given and the dose increased up to 5 c.c. up to a period of 12 days. No reactions of temperature were noticed, and no particular effects.
The Basal Metabolic Rate was taken again, and was found to be plus 31 per cent. Again his respirations were shallow and rapid. The Encortone was again stopped. He continued to slightly improve, but was still showing signs of marked Hyperthyroidism. He was not considered a suitable case for operation, and on 29/11/32 went home, with a pulse rate of about 120. His weight had varied from 7 st. 2 lbs. to 7 st. 2½ lbs. when last seen. Readings of blood pressure taken every ½-hour after an injection of 5 c.c. Encortone showed that there was a rise of 160 to 180 for ½-hour which in another ½-hour returned to normal. An injection of 5 c.c. Encortone showed no affect on a blood sugar curve.

When discharged, the patient expressed himself as feeling better. He was indeed better, but not markedly so, and no objective signs of marked improvement can be quoted.
### NOTES OF CASE

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#### PULSE

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History. The patient was perfectly well till 18-months ago, when she developed shortness of breath on exertion. She became nervous and developed a tremor of the hands. She sweated a good deal and lost weight.

About 4 months ago a swelling of the neck was observed and her relations noticed that she had prominence of the eyes. She became so nervous and short of breath that she had to leave her work.

On admission she complained of the above symptoms. Her appetite was good. She had no diarrhoea or gastric disturbance. She had no idea why the disease had commenced.

Micturition - nothing abnormal.

Menses regular, but the loss had been excessive during the last few months.

On examination: Weight 7 st. 7 lbs. Fair haired. Well developed. Thyroid uniformly enlarged and prominent. Neck 13" in diameter. Systolic thrill over gland. Exophthalmos was marked. She had a blotchy erythema distributed over the body. Tongue clean. Teeth good. Tonsils slightly congested. Heart rapid and tumultuous. Rate 124. Not enlarged. No murmurs or irregularity.

Lungs: Nothing abnormal was found. She had a fine tremor of the hands. She was in fact, a typical case of Exophthalmic Goitre.

After a preliminary rest in bed of three weeks, the Basal Metabolic Rate was found to be plus 52 per cent. She was then given treatment with Eucortone, working in 4 days up to 5 c.c., and then was given 5 c.c. daily for 10 days.

At the end of that time, her pulse rate was still averaging 120, and no signs of improvement were noticed. Her weight was still 7 st. 7 lbs. Her Basal Metabolic Rate had increased to plus 68 per cent. Treatment with Eucortone was stopped; after a further month of rest, no appreciable improvement was found. She was, therefore, advised to submit to operation, which she did. The operation lead to a great improvement in her condition.

In this case, therefore, the injection of Eucortone did not benefit the patient, nor did it lead to any delayed improvement during the following month.
SUMMARY OF CASES:

It will be seen from the results of cases of Hyperthyroidism that were treated, that no demonstrable improvement can be noted. On the whole, one is inclined to think that treatment with injections of Swingle and Pfiffner's Extract retarded their progress. In some cases after the injection, there was a rise of temperature, and of pulse rate, which subsided after injections were discontinued. Basal Metabolic Rates showed no improvement. What improvement was manifested, is no more than can be ascribed to the rest in bed.

In one case, injections were followed by an irregularity of the heart, which subsided on cessation of injections. I am inclined to think that the reason for some of the bad effects of injections observed were -

1. The fear of the hypodermic needle.
2. The presence in the extracts of a small amount of Adrenalin.

It is true that the doses used were not large, but it will be noticed that in some cases as one approached the maximum dose given of 5 c.c., the increase of pulse rate and temperature became more marked. One felt, therefore, that it was inadvisable to increase the dose beyond 5 c.c.

This latter fact seemed to show that injections of Cortical Extract have a definite detrimental affect on Graves Disease. It may be due to Adrenalin content, or to some degree of protein shock from the animal extract.

Experiments were made in three cases to see if injections had any effect on -

1. The blood pressure.
2. The blood sugar.

In neither case were the results sufficiently marked to draw any conclusions that Cortical Extract exercises any affect on either the blood pressure or the blood sugar.

We, therefore, come to the definite conclusion that the injection of Cortical Extract is of no value in Graves Disease, and indeed, may lead to harmful results.
DISCUSSION: Effect on Thyroid.

Now let us turn to the point which has been in mind throughout this thesis, whether or not there is any foundation for Marine's belief that one of the underlying causes of Graves Disease is defect of the suprarenal cortex. I do not think we can seriously consider that it is the only and essential cause of Graves Disease.

In the term Graves Disease, I include hyperthyroidism or Toxic Goitre, and I do not intend to enter into the controversy which continues to rage as to whether Toxic Goitres and Exophthalmic Goitres are different diseases, or whether they are different stages of the same disease.

One realises that this is perhaps not necessarily the best way to approach the subject. One might have discussed the phenomena which occur in Graves Disease and see if they suggested any link with cortical insufficiency. I have, however, tried to visualise the problem from the other angle, namely, to see if we can discover the functions of the cortex, and from them see if any defect or overaction, or perverted action might give rise to action in the thyroid.

In view of our knowledge of the endocrine system, it is perhaps hardly to be hoped that the problem is to be determined simply. The more we learn of the endocrine system, the more we realise the complexity of the system.

Now let us examine any point which would seem to favour an interaction of the thyroid and cortex. This mostly rests on experimental evidence. Marine's experiments, if correct, are striking. They are, however, in contradistinction to other observers.

1. He finds that partial destruction of the cortex leads to an increased Basal metabolism, is brought back to normal by injections of fresh Glycerol extract of the cortex. If so, this is a potent argument in favour of their theory.

Other observers such as Swingle and Pfiffner and their colleagues find the opposite result, namely, that with destruction of the cortex, the basal metabolic rate is lowered and is to be heightened again by injection of Eucotone. Here, therefore, we have two absolutely different conclusions, which it is hard to reconcile. There is a difference in their methods, in that Marine's extract was probably prepared in a different way to that of Swingle and Pfiffner. Marine points out that he has found that only the extract prepared in his own way was found to be of any use in his experiments. Does his preparation then contain a hormone which is destroyed by other methods of preparation? It may be so, yet the extract of Swingle and Pfiffner is at present the only one which definitely produces therapeutic effects in Addison's Disease, and we must conclude that it is a potent extract.
2. Again Marine finds that in babies at a period when there is natural destruction of cortex, heat production is increased. This point is one which certainly lends support to his theory. It would, however, be difficult to disprove that the other glands could not be concerned. The thyroid, may be, is stimulated in the early critical weeks.

3. He finds that in treatment with his extract a definite improvement in cases of Graves Disease. It is of interest to note that the improvement seems to be most marked on the sexual side, which is in accordance with the apparent functional connection of the cortex and the sexual glands. The cases he quoted in the papers referred to show that there was a definite decrease in Basal Metabolic Rate. This, however, was slow, and as is well known, many cases of Graves Disease, if treated by rest alone, will show a similar fall. One would be more convinced of the action of cortex in diminishing Basal Metabolic Rate if the fall occurred rapidly after administration of Cortical Extract. On the whole, therefore, we cannot consider that Marine has proved his case. There are a few other points which tend to lend support to his theory.

The cases quoted by Oppenheimer where X-Rays to the suprarenal region were followed by Graves Disease, are of great interest. It is a pity that one does not know the microscopic appearance of the Cortex in them. One could not otherwise be sure whether the effect was due to the inhibition of medulla.

Goldzieher definitely agrees that the cortex has an antagonistic effect to the thyroid. He supports this firstly, with the effects on an extract which he prepared from the cortex, which he called Inter-renin, which he finds experimentally opposes the action of the thyroid.

2. He quotes the observation that removal of the cortex is followed by a considerable rise of temperature, if the thyroid is intact, thus suggesting that a restraining factor to the thyroid has been removed.

3. He states that in thyroid atrophy, marked hypertrophy of the cortex is found, and that after thyroidectomy, the cortex shows signs of decrease of cortical lipoids.

4. He considers that Choline which is in many ways antagonistic to the thyroid, is produced by the cortex.

Sharpey Shafer, however, as previously noted, does not consider this point proved. Goldzieher definitely comes to the conclusion that the cortex is antagonistic to the thyroid. It is difficult to disagree with Goldzieher's findings if all the experimental work is correct, and certainly there seem to be many facts which lead to his conclusion. One feels, however, in reading his work, that he is inclined to prove what he wishes to prove, and to come to conclusions on rather insufficient evidence. Furthermore, the results obtained
with Swingle and Pfiffners extract do not add support.

Cramer considers that defect of the cortex may lead to hyperthyroidism in a different way, not by any direct interaction of the cortex and thyroid, but by an indirect action through adrenalin.

It is generally admitted that in hyperthyroidism there are signs of excessive secretion of adrenalin, and the classical picture of exophthalmic goitre is one of fright, in which there is said to occur an outpouring of adrenalin (70). Bason’s observation (21) that to give large doses of thyroid to a normal person does not produce symptoms of hyperthyroidism, but given to a neurotic person, symptoms are produced, is an extremely interesting one. It would be interesting to know if a neurotic person had an easily excited adrenal medulla, and if so, following up Cramer’s theory of the nervous action, which presumably leads to the action of the cortex is restraining excessive output of adrenalin, was inhibited in a neurotic.

This is admittedly theorising, but it is an attractive theory, and seems to fit together.

It occurred to me that one of the signs in Addison’s Disease is gastro-intestinal upset, and that similar gastro-intestinal disturbances are sometimes ascribed to deficiency of Vitamin B.

McCarrison (71), points out that goitre results from Vitamin deficiency (amongst other things), though he does not consider that it is fully proved that Vitamin B. is concerned.

It is an interesting speculation to consider if there is any relationship between the suprarenal cortex and vitamins. Goldzieher states that in experimental deficiency of Vitamin B. there is an enormous hypertrophy of the adrenal cortex, the size of which may be 2 to 2½ times the size of the controls.

Unfortunately, I am unable to bring forward any further observations on this point. Perhaps the future might lead to some developments along these lines.

McCarrison and many others, also consider that goitre may follow toxæmia. It has previously been shown that the cortex seems to have a special affinity for toxins. I do not try to draw any conclusions from these observations. Both glands, after all, are part of the human organism. The only point I would consider relevant is, that while Toxaemia may lead to Graves Disease, yet it is not impossible that it may not only do so directly, but also indirectly by a toxic interference with the suprarenal cortex. Conversely the cortex raises resistance to toxæmia, less of this power of resistance may lead to increased susceptibility of the thyroid.

However, this is all theorising, and perhaps not particularly helpful. Let us see if a study of the postmortem findings of Exophthalmic Goitre help us. It does not seem to me that they do except in one particular.

That is that in Exophthalmic
Goitre, an enlargement of the thymus is often found. Many writers consider that occurs sufficiently frequently to be more than coincidence. It is not unknown for exophthalmic goitre to develop before puberty when the thymus is still active, but it is extremely rare. Jaffe (72), says that the thymus regenerates after suprarenaleectomy, and believes that the persistence of the thymus which occurs in Addisons and Graves Disease, are brought about by the same disturbances in glandular inter-relations, which bring about regeneration of the thymus after suprarenaleectomy.

Some other points referring to a possible relationship of the suprarenal cortex with the thymus, have been previously quoted in this thesis. Eason (21) shows that in 70-95 per cent. of cases of Graves Disease, the thymus is persistent and enlarged except in those cases where the onset occurred after the 35th year. On the other hand, when the onset of the disease is late and the thymus is not persistent, the adrenals are then large. But whether the adrenal enlargement is in the cortex or the medulla, he does not say. He goes on to say that the findings, therefore, do not furnish evidence of increased suprarenal function, and thymic hypertrophy, as characteristic features.

Joll (73) says that there is no constant relationship between enlargement of the Thymus, Status Lymphaticus, and Exophthalmic Goitre, for when the latter develops after the age of 30, enlargement of the thymus and lymphatic glands are usually lacking.

Langdon Brown (Physiological Principles in Treatment) says that whereas there is an association between the cortex and sexual development, there appears to be an equally definite antagonism between the thymus and the sexual organs, and raises the suggestion that only those who are the subjects of persistent thymus can suffer from Graves Disease.

McCallum (Textbook of Pathology) says that the hyperplasia of the thymus in Addison's Disease has been frequently observed, and it has been experimentally proved that the involution of the thymus is greatly delayed after castration at an early age. The latter observation is of interest, as it has been found that the suprarenal cortex enlarges after castration.

Maranon (74) also found at necropsy of cases of Addison's Disease, enlargement of the thymus. There does, however, seem to be plenty of evidence that while the thymus is an active gland, it enlarges in hyperthyroidism. After the age of 30 it has presumably ceased to be an active gland.

There also seems to be a good deal of evidence that there is some relationship between the suprarenal cortex and the thymus. Therefore, we may postulate a relationship possibly indirect between the suprarenal cortex and the thyroid. Otherwise the pathological findings in Exophthalmic Goitre are against the theory.
of suprarenal cortex thyroid relationship. There are no constant changes in the suprarenal cortex in Exophthalmic Goitre. This fact is a very strong argument against Marine's theory, and is not easily explained away. Goldzieher states that marked hypertrophy of the adrenal cortex occurs in cases of thyroid atrophy. Schafer also finds that after thyroidectomy, the cortex of the suprarenal is somewhat enlarged.

Now let us consider the postmortem findings in Addison's Disease. As many of these cases are tuberculous, it would be as well to consider the cases in which suprarenal atrophy is found. At present the cause of this atrophy is unknown, and it appears mainly to affect the cortex. W. Susman (76) finds that of the published cases 18.5 per cent. are atrophies. In the cases he quotes, there is in the thyroid a state of fibrosis with glandular atrophy and signs of lymphocytosis. Such an experience is typical. At first sight, if Marine's theory is correct, one would expect in cases of cortical atrophy that there would be signs of excessive thyroid function. One cannot, however, be satisfied on this point unless one could imagine the thyroids in the early stages of the disease. It cannot be considered impossible that when a case comes to postmortem examination, any early stimulation of the thyroid which might have occurred has led to an exhaustion and atrophy of the gland.

An interesting observation of Kowntree and Green (75) might be mentioned here, that in a case of Addison's Disease, 9 grains of Thyroid Extract given in 4 days caused a set back. It would appear as if the thyroid used up the Cortical Extract. We must, however, conclude that postmortem finding in both Exophthalmic Goitre and in Addison's Disease is against Marine's theory that the essential lesion in Hyperthyroidism is a defect of the suprarenal cortex.

In the same way one cannot find much encouragement from a study of the symptomatology of these two diseases. Dressner in a review of cases of Addison's Disease found that in some cases there were symptoms of Graves Disease and in some there were signs of myxoedema. This is rather perplexing. It is not, however, impossible for a thyroid gland which has been overactive or perverted to become exhausted and give rise to myxoedema. On the other hand the disease of Graves and Myxoedema may have been present before the onset of the Addison's Disease.

An examination of the effects of thyroidectomy in normal animals does not show any symptoms which would lead us to infer an antagonism between the suprarenal cortex and the thyroid.
The results of thyroidectomy in experimental animals may be found in Sir Edward Sharpay Shafer's book on the Endocrine Organs. We see that there is retardation of growth, immaturity of the sexual organs, delay in involution of the thymus, diminution of metabolism, anaemia and poor muscular tone. Many of these symptoms are also found in cases of defect of the suprarenal cortex. In Addison's Disease where postmortem examination shows atrophy of the suprarenal cortex, we also find diminution of metabolism, anaemia and poor muscular tone. In experimental absence of the cortex we find retardation of growth and sexual immaturity. The effects of thyroidectomy on other glands show us that the pituitary is enlarged, involution of the thymus is delayed, and the suprarenal cortex is somewhat enlarged. On the whole, therefore, there is no direct evidence in favour of Marine's theory. The enlargement of the suprarenal cortex with that of the pituitary and thymus suggest that there is an attempt on the part of these glands to take over the functions of the thyroid. If the suprarenal cortex was an inhibiting agent to the thyroid, a diminution in size rather than an enlargement would surely be expected.
CONCLUSIONS

The Functions of the Cortex.

It is to be confessed that our exact knowledge of the functions of the Cortex is still in its infancy. The help given to us by Swingle and Hiffners extract has been disappointing, and has not lead to the increase of knowledge which we had hoped.

I would conclude that,

1. The cortex is essential to life.
2. That the cortex is not wholly independent of the medulla. Cramers experiments seem to me to be supported by the evidence of Addisons Disease, and while we cannot at present consider that all his points are fully proved, I yet feel that there is sufficient evidence to justify us in believing that the cortex and medulla work in harmony.
3. The cortex has a stimulating effect on growth and sexual development in youth. In maturity it is still essential to normal sexual function.
4. That it has an antoxic effect, or rather that lack of cortex leads to increased susceptibility to toxaemia.
5. That lack of cortex leads to a lowering of Basal Metabolic Rate, and that giving of sufficient extract bring a return to normal. This occurs in thyroidectomised animals. We may conclude that the adrenal cortex contains a stimulant to tissue oxidation.
6. That other functions which has been ascribed to the cortex, for example, the production of choline, and the production of lipoids, have not been proved.
7. That it is likely Cortex like the pituitary has several functions, and that at present our knowledge of these, and of their extraction is in its infancy.
CONCLUSIONS - as to the relationship of the Suprarenal cortex to the production of Exophthalmic goitre.

Our study of the literature, and of the pathological, clinical and experimental evidence leads us to conclude,

1. That Marine does not show sufficient proof to render his theory tenable. His results have not been repeated by others. Swingle and Pfiffner's work has been in contradistinction to that of Marine. We must conclude that the effect of the suprarenal cortex is to raise Basal Metabolism, rather than to lower it.

2. That pathological findings do not support the view that defect of the suprarenal cortex leads to hyperthyroidism.

3. That the results of treatment of hyperthyroidism by means of cortical extract are negative.

4. That the suprarenal cortex and the thymus have some synergistic interaction, and there is some evidence to show that the thymus is antagonistic to the thyroid. As, however, the inter-relationship of the Endocrine organs is so complicated, and as yet much of their relationship is obscure, we cannot consider this fact of sufficient weight to allow us to draw any conclusion as to the antagonism of the suprarenal cortex and the thyroid.

5. Our conclusions as to the function of the thyroid do not give us any indication of antagonism between the thyroid and the suprarenal cortex. While, therefore, it is possible that the future may show us that the suprarenal cortex is involved in the production of hyperthyroidism in some indirect measure, yet at present we can only conclude that the evidence which we at present have, is against any direct action of the suprarenal cortex in the production of hyperthyroidism.
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