

THE EVOLUTION OF MODERN THERAPY

IN

ADDISON'S DISEASE

AND ITS APPLICATION IN SEVERAL  
ILLUSTRATIVE CASES

An Essay Submitted for  
The Gunning Victoria Jubilee Prize in Therapeutics

by

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From  
The Clinical Laboratory  
Royal Infirmary  
Edinburgh.

31st May, 1938.



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PART I  
THE EVOLUTION OF MODERN THERAPY  
IN  
ADDISON'S DISEASE

ENDOCRINE DISORDERS

PREFACE

Living as we are in a world of peace and good  
scientific advancement it is a little difficult for  
us to appreciate the progress in the science of  
medicine that has been made in the past. Yet, a  
brief review of the evolution of our knowledge  
concerning the endocrine system and the better  
methods of treating the various diseases that  
arise from its dysfunction will be of interest  
to every physician and layman alike.

P A R T I

THE EVOLUTION OF MODERN THERAPY  
IN  
ADDISON'S DISEASE

In a clear and concise manner this book on Addison's  
disease is written for the physician and the layman  
alike. It is a valuable addition to the literature  
of the disease, and it is hoped that it will be  
of interest to all who read it. The author has  
written this book with a view to making it  
interesting and instructive to all who read it.  
The book is written in a simple and direct  
manner, and it is hoped that it will be  
of interest to all who read it. The author  
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HISTORICAL INTRODUCTIONGENERAL

Living as we are in a world of speed and rapid scientific advancement it is a little difficult for us to appreciate that progress in the science of medicine has not always been so speedy. Yet, a historical review of the evolution of our tenets regarding practically any of the better known medical diseases reveals the interesting fact that our knowledge was almost invariably in a state of stasis until some individual concentrated his attention on the condition and presented its features in a clear and logical manner. Such an individual was usually a physician with good clinical acumen; sometimes a pathologist with a keen faculty of observation. Not infrequently he possessed the attributes of both and was thereby in a position to correlate any peculiarities that he noted in both spheres of his studies. Often he was a man who was able to sift from the dust of the ages those particles of knowledge that possessed value, and was capable of adding thereto original observations, and by blending these together he produced eventually a composite picture that is now regarded as the correct presentation of the disease. His work often provided the spark which set alight the desire/

desire for knowledge and promoted a series of researches that in many cases have continued unabated to the present day.

Such tardiness was evident in the development of our knowledge regarding the condition that is now termed Addison's Disease.

#### ANATOMY AND PHYSIOLOGY.

The actual existence of the suprarenal glands was unnoted by the anatomists of the pre-renaissance period. The first known description of them is that of BARTHOLOMAEUS EUSTACHIUS in his book "Opuscula Anatomica" published in 1563 in Venice.

His work was republished by BEMAN in 1724 and by the courtesy of the librarian, Edinburgh University it has been possible to obtain access to this book. Photographs of the title page and of the relevant chapter are reproduced herein (Figures 1 and 2). In view of the historical interest attached to this original description the liberty is taken to quote the relevant section of the text in extenso:-

#### "Concerning the Glands which lie on the Kidneys

Although what I have said about the appearance of the kidneys may seem sufficient, all the same to prevent anyone making with justice the criticism that something has been left out in this treatise, I have thought it proper to write here about some glands of the kidneys/

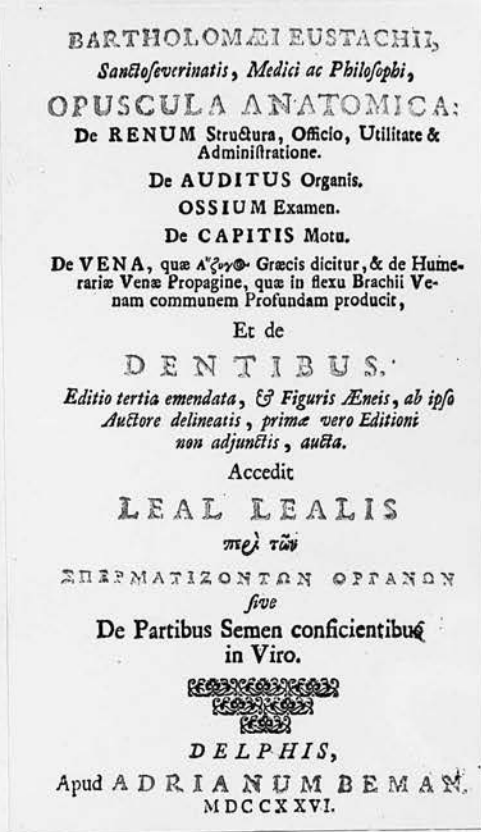


Fig. 1.

Photographic Reproduction  
 of the Title Page of the earliest edition  
 of "Opuscula Anatomica" still in existence.

## C A P. VI.

*De Glandulis quæ Renibus incumbunt.*

Quamquam hæc, quæ de Renum superficie diximus, satis multa videri possint: nihilominus ne aliquid in hac tractatione prætermisissimum esse quispiam mihi jure objiciat: contentaneum esse duxi de quibusdam Renum glandulis ab aliis Anatomicis negligenter prætermisissimum hoc loco scribere. Nam utrique Reni, in eminentiori ipsorum regione, quæ venam cavam spectat, glandula adhæret, hæc autem externæ eorundem membranæ, quæ Peritonæo transversæ septi continua est, adeo adnectitur, ut non raro, nisi quis animum diligenter advertat, evulsis Renibus ipsam septo transverso strenue adhærentem, quasi nulla sit, prætereat. Ejus substantia quemadmodum & figura Renibus fere respondet: licet sæpe depressa quoque ac adeo lata occurrat, ut potius placentæ, quam Renis formam referre videatur: longitudinem habet duorum digitorum: latitudinem unius; crassitudinem mediocrem fortitè est: quæ omnia pro ratione suæ figuræ, quum ea unà semper non sit, non minimum quoque variare cernuntur: magnitudinem præterea utraque harum glandularum nec parem obtinet, nec perpetuo servat: sed vicissim nunc hæc, nunc illa est major altera.

quemadmodum item Renis cui quævis earum insidet, altero major vicissim est: evenit tamen frequentius, ut dextra, sicut etiam Renis, sinistram superet. Hoc glandularum genus desiderassem a prioribus Anatomicis, & ab his, qui hodie hanc artem excolunt, quique admodum prolixam humanarum partium tractationem scripserunt, minime fuisse prætermisissimum; idque quum præsertim, in aliorum ipsi erroribus persequendis adeo se accuratos præbeant, eosque tam minute observent, ut haud ita raro contentiosi potius, quam anatomicæ veritatis studiosi esse videantur.

Fig. 2.

Photographic Reproduction  
of the chapter from "Opuscula Anatomica"  
containing the first known description of the  
Suprarenal Glands.

kidneys that have been disregarded by other anatomists. For a gland sticks to each of the kidneys at the higher part of them, which faces the "vena cava". This, however, sticks so closely to their outside capsule, which is joined to the peritoneum of the diaphragm, that very often, unless one observes carefully, when the kidneys are removed, one passes it by as non-existent, as it is adherent to the diaphragm. Its substance and shape are more or less the same as the kidneys. However, it often is so deep and broad that it seems more like the placenta than the kidneys. It is two fingers long and one broad. It is fairly thick. All of which measurements seem to vary a great deal in correspondence with its shape, since it is not always the same. Besides each of these glands has not always the same size, nor does it keep it continually. But in turn now one, now the other is the bigger, just as, in the same way, one of the kidneys to which either of the glands is attached may in its turn be larger than the other. As a general rule, however, the right is bigger than the left, as with the kidneys".

During the seventeenth century little advance was made. Various authors repeated and to a slight extent elaborated the observations of Eustachius, but many anatomists were apparently in ignorance of the discovery by Eustachius and omitted any reference to the suprarenals in their works.

Many varied and fantastic functions were ascribed to the newly discovered glands. SPIGELIUS (1627) postulated that they merely occupied the space between the kidneys and the diaphragm in order to aid in the support of the stomach. WHARTON (1656), impressed by the/  
the/

the size of the nearby nerve plexuses, suggested that the adrenals received from these some substance, apparently useless in the nerves, which the adrenals absorbed and passed into their veins, where it performed some useful purpose. CASSERIUS, (1627), one of Harvey's teachers at Padua, taught that the adrenals served as an aid in the secretion of urine. MOLINETTI (1675) put forward the view that the adrenals acted as "diverticulae" of the blood, diverting most of it away from the kidneys and thereby preventing the secretion of urine in the foetus. SYLVIUS (1663) considered that the adrenals prevented coagulation of the blood coming from the kidneys after it had been concentrated by the secretion of urine. Molinetti's views were later supported by COXE (1827) of the University of Pennsylvania, who according to SCHUMACKER (1936) was the earliest American writer on the subject. The story of the knowledge about the adrenals during this period is ably summarised by BIEDL (1910) and by SCHUMACKER (1936).

In 1716 the Academy of Sciences at Bordeaux offered a prize for an essay on "Of What Use are the Suprarenal Glands". However, the various competitors presented such conflicting views on the subject that it was apparent that it was inadvisable/

inadvisable to award the prize. Not one of the multiple theories advanced was capable of proof and in consequence the Academy withheld the award on the advice of Montesquieu, the celebrated author of "L'Esprit des Lois", who at that time held the post of secretary to this institute of learning. During the remainder of the eighteenth century many other theories were put forward regarding the function of the adrenals.

SEVERINUS (1645), VALSALVA (1719), MECKEL (1809) each independently considered that the glands were part of the reproductive system. SENAC (1764) put forward the view that the adrenals secreted meconium in the foetus and VAN HELMONT (1644) suggested that they elaborated a juice which prevented the formation of renal calculi. RIEGELS (1790) went so far as to consider that these glands secreted the fat into the abdominal cavity. DUMAS (1800) expressed the view that they functioned in some manner in the nutrition of the foetus. However, despite the fact that the physiologists were unable to determine the functions of the adrenals the anatomists continued to make progress and several excellent anatomical descriptions of the glands appeared about this time. WINSLOW described them, their relations and their vascular supply in detail and/

and gave the name "glandes surrenalis" (1743). In 1819 CAILLAU reviewed the knowledge of the suprarenals and remarked - "The anatomists have not discovered the function of the suprarenal glands. We are no more advanced to-day, in so far as these glands are concerned, than we were in the time of the famous Eustachius, who first described them".

The comparative anatomy of the adrenals was commenced at the start of the 19th century. MECKEL (1815) introduced these methods and examined and described the adrenals of many species. He advanced the view that the adrenal glands in conjunction with the liver, spleen, thymus and thyroid served to regulate respiratory and tissue metabolism. BERGMANN (1839) was first to remark on the relationship of the adrenal medulla to the nervous system. ECKER in 1846 described the histology of the adrenals and demonstrated the glandular nature of the cells. He pointed out the absence of secretory channels and concluded that the glands must pour some secretion into the blood direct or by way of lymphatics. This work received the general approval of those competent to judge.

In the year 1854 KÖLLICKER promulgated the following/



following views as to the structure and function of the suprarenal glands. "I consider the cortical and medullary portions to be physiologically distinct. The former may be considered as belonging to the category of the so-called vascular glands, and doubtless is in some way related to the process of secretion, while the latter, owing to its extraordinary richness in nerve tissue must be described as an appendage to the nervous system, in which the cellular elements and the plexus of nerves either react, one upon the other, in a manner similar to that obtaining in grey nerve tissue, or else are directly connected". ARNOLD (1866) first introduced the division of the gland into zones.

#### ADDISON AND HIS INFLUENCE

All the observations noted above, although complete in themselves, were practically unrelated and it required the genius of THOMAS ADDISON (1855) to provide the key to the problem. His description of the disease of the adrenals which bears his name served as a stimulus to innumerable physiological researches and clinical studies. Addison not only accurately described the clinical syndrome which is now so widely known but he demonstrated its relationship to a definite disease process in the suprarenal glands. He/

He first described the condition at a meeting of the South London Medical Society on March 15th, 1849 (see WILKS - 1877) when he gave a communication on anaemia and disease of the suprarenal capsules. However, it was not until 1855 that Addison fully detailed the morbid entity that has been named after him. This classical piece of work was so accurate and complete that nothing essential has been added to his original description of the pathological and clinical features and also of the progress of the disease.

The one slightly confusing feature in Addison's original description was the fact that he included anaemia as one of the major diagnostic points. This probably occurred owing to the fact that he was investigating "idiopathic anaemia" when he noted the connection between disease of the suprarenals and the clinical syndrome. Luckily however, it was soon noted that anaemia was not a constant factor in these cases (WILKS, 1862). Addison did not, however, stress the therapeutic measures adopted in his various cases, and it is in this direction that most progress has been made since his famous contribution to medical knowledge.

It is of interest to note that, while Addison/

Addison was the first to detail in its entirety the morbid process that bears his name, a description of the clinical condition by a layman has been found in the files of a Spanish monastery of the 16th century by MARÑON (1922). This, the earliest case on record, is a fragmentary account by JOSÉ DE SIGÜENZA in his "Historia de la Orden del glorioso doctor San Jeronimo".

Addison in his original publication on the disease which now bears his name gives in detail the history and the clinical and autopsy findings of eleven cases. In reading his paper one cannot fail to note that there is little reference to treatment. In three cases stimulants were administered and in one other iron was given as the patient was considered to be suffering from anaemia. Further treatment was merely symptomatic i.e. for cough, hiccup, etc. It is not surprising, however, that the therapy was mainly of a palliative nature as so little was known at that time about the functions of the adrenal.

In 1856 BROWN-SÉQUARD, prompted by Addison's publication, removed the adrenals of a number of animals (BROWN-SÉQUARD 1856 and 1858). The rapid post-operative fatalities in these experiments led him to pronounce the essential nature/

nature of these organs for the maintenance of life. In the same year VULPIAN (1856) noted the green colouration that occurred when the medulla was moistened with ferric chloride. The exact significance of this observation was not, however, fully appreciated until G. OLIVER and SCHAFER (1894 and 1895) noted the presence in extracts of the adrenal medulla of a pressor substance - "adrenaline" - and observed also that the pressor effect was proportional to the intensity of the colour reaction given by the medulla.

The immediate result of Addison's description of the morbid process in the adrenals was that several authorities published notes on cases of Addison's Disease. Unfortunately many of the reports published at this time, owing to insufficient data, cannot be accepted. In 1862 WILKS published an excellent series of twenty-five cases of Addison's Disease, each one confirmed by autopsy. Here also little mention is made of the therapeutic methods adopted. Tonics (iron, quinine and calumba) were given to a few of these patients. However, Case 16 provides an illuminating view of the difficulties that beset the physicians of that time and mentions  
a/

a treatment that was probably unique. It is detailed at length in an interesting and amusing manner in the clinical notes as published by Wilks. An excerpt reads:-

"It is worthy of note that the patient's appearance was attributed by his medical attendants as well as by his friends to jaundice, with a view to cure which, the latter performed several superstitious rites with great assiduity, one of which consisted in the daily evaporation of a portion of his urine".

### DEVELOPMENT OF THERAPEUTICS

#### Early Measures.

In 1875 GREENHOW gave the Croonian Lectures on "Addison's Disease". It is of significance that, despite the fact that three lectures were given, the lecturer, who discussed the minutiae of the pathology and of the clinical examination, made no more than the following remarks regarding treatment:-

"Rest and scrupulous avoidance of bodily and mental excitement, or any causes of nervous exhaustion, form the essential parts of the therapeutic management of all such cases; whilst the diet and medical treatment must be carefully adapted to the inevitably varying phases of the disease".

ZIEMSSSEN in his excellent text-book of medicine (1878) reiterated this opinion and stressed the importance of/

of stimulants in view of the insufficiency of the heart muscle. His treatment would no doubt be acceptable to many of his cases for it is on record that he recommended the stimulants to be given "in the form of good strong wine. Good beer, also, and under certain circumstances, the stronger alcoholic forms, in particular - old brandy, must not be withheld". He deprecated the use of drastic purges in very strong terms owing to the exhaustion they caused to the patient. Iron and quinia were advised and it is to be noted that opiates were also mentioned as being useful. This last is in sharp distinction from modern opinion. The same author also tentatively put forward Potassium Iodide and Galvanism as possible aids, but mentioned that little was known of these newer methods.

In 1879 ANDERSON read a paper before the Glasgow Medico-Chirurgical Society. He pointed out that the treatment in the past had tended to be too symptomatic and that too little attention had been paid to the underlying "scrofulous" affection of the adrenals. He therefore recommended general "antistrumous" remedies. This was a great advance. Anderson gave his cases blisters over the renal regions. He recommended/

mended complete rest combined with good food and the administration of cod liver oil and wine. His results were good, as compared with those of other physicians of the time, but, unfortunately, he does not detail them.

About this period it is apparent from the literature that there existed considerable difficulty in the differentiation of "Addison's Disease of the Suprarenals" from "Idiopathic Anaemia". This latter was investigated by Addison himself and is the condition now known as Pernicious Anaemia. Around 1880 it was frequently termed Addison's Anaemia. As a result of this confusion of names, the therapy adopted for patients with disease of the suprarenals was frequently based on the results of similar treatment which had been used with comparative success in cases of "Addison's Anaemia". An example of this is shown in a communication given by FINNY to the College of Physicians of Ireland in 1882. In this he advocates the use of arsenic in patients suffering from genuine "Addison's Disease" in view "of the great and notable results which followed its administration in cases of 'idiopathic' anaemia'". YOUNGE (1883) published a paper in the following year and/

and in it advocated the use of *Liquor Arsenicalis* in all cases of Addison's Disease. He stated "Arsenic acts in some inexplicable manner on the suprarenal capsules, checking the diseased action that is taking place in them: and it is the only remedy on which any reliance can be placed in these cases".

However, in 1890 NOTHNAGEL, Professor of Medicine at the University of Vienna revealed clearly the trend of medical thought at that celebrated school, when he stated that "The prognosis is 'semper et ubique letalis' and the therapeusis is consequently 'nil'. The chief aim of the physician is to increase and keep up the strength. This he does by giving iron, wine and good food". BERGTOLD reiterated this opinion almost to the word in a paper from America in the following year (1891). The above views summarise clearly medical opinion at that time. Any papers published about 1890 on Addison's Disease were clear and concise regarding the clinical and pathological manifestations of the condition, but the majority omitted treatment entirely or evaded any preciseness on the subject. The notable exception to this was BRAMWELL (1892) who published a beautifully/



beautifully illustrated and most stimulating paper on Addison's Disease in his Atlas of Clinical Medicine. In it he devotes a large section to treatment that, although not perhaps compatible with modern theories in all its features, is logical and expresses with remarkable clarity views that were well in advance of any others published prior to his paper. Summarised, he primarily points out that as the condition is due, in the vast majority of cases, to tuberculous affection of the adrenals, the aim in treatment should be to promote a cure of the tuberculous process or to remove the diseased glands, as he did not consider them to be essential for life in the adult. However, he deprecates operation in view of "the risk in such a case when the most trivial causes are apt to be followed by the most profound and even fatal prostration and collapse". He therefore advocates general treatment for the tuberculosis. The health should be maintained at the highest possible state of efficiency with good housing and good and careful feeding. He recommends a light but appetising diet consisting of chiefly of milk, butter, eggs, farinaceous foods, fish and white meats. Red meat is to be avoided in the majority of cases. Small quantities of alcohol are beneficial/

ficial as a stimulant. No sudden or severe effort is to be allowed. Exhaustion and mental depression are to be avoided. Gastro-intestinal irritation must be prevented and allayed, if it does occur. The avoidance of drastic purgation is essential. All irritating symptoms such as hiccup, vomiting, diarrhoea, etc. should be treated at once. For the last he suggests many remedies, including, it is of interest to note, small doses of morphine. Regarding more specific therapy he recommends cod liver oil where the patient can take it. Iron, arsenic and strychnine are very good in moderate doses but caution in administration is necessary. He advocates mild counter irritation over the adrenals by painting the skin with tincture of iodine. Any complications and associated lesions such as phthisis and spinal caries are to be treated at once with due regard to the fact that the patient is suffering from Addison's Disease and therefore cannot stand drastic measures.

Bramwell's opinion that the suprarenal glands were not essential for life was in keeping with many papers published towards the end of the nineteenth century by competent physiologists (ROLLESTON - 1895).

INTRODUCTION/

INTRODUCTION OF ORGANOTHERAPY

In the last decade of the nineteenth century there was introduced a new form of treatment for Addison's Disease which opened up a new avenue in the development of its therapeusis. It was the utilisation of substitution therapy whereby preparations of suprarenal gland were administered to function in place of the diseased tissue. The use of extracts of the glands parenterally was the most popular, but many other methods were used, whereby the gland was given orally as a fresh or dried preparation, or even in some cases as a graft of living tissue.

As far as can be determined the first to use this form of therapy were ABELOUS, CHARRIN and LANGLOIS (1892) who injected watery extracts of the suprarenal glands of dogs and of horses into two patients suffering from Addison's Disease. They did not persevere with this treatment and they were unable to report any appreciable improvement in the condition of the patients. This preliminary work was rapidly followed by similar therapeutic measures by other workers (CHAUFFARD (1894), T. OLIVER (1894), DYSON (1894)) all of whom obtained results in which no beneficial effects could be recorded.

All/

All these workers were using suprarenal preparations empirically. On reading their papers it is appreciated that they were trying this treatment merely as an experiment, and that they were blindly groping in the dark in an effort to find a cure for this disease of the suprarenal glands. However, in 1894 G. OLIVER and SCHAFER (1894) demonstrated to the Physiological Society the pronounced and rapid physiological effects upon the blood pressure that were produced by the parenteral administration of aqueous, alcoholic or glycerol extracts of the suprarenal glands. They followed this up by a paper a year later (G. OLIVER and SCHAFER 1895 a.) in which they elaborated their findings. Shortly afterwards they (G. OLIVER and SCHAFER 1895 b.) demonstrated that whereas extracts made from healthy human suprarenal glands possessed these physiological properties, those made from the glands of people who had died from Addison's Disease were entirely inactive. This was a most important observation and apparently provided scientific justification for the employment of endocrine therapy in Addison's Disease. Later experience exposed the fallacy of such a deduction. It is now generally agreed that it is the absence of the/

the cortical hormone - "cortin", and not the loss of the medullary hormone - "adrenaline", that is responsible for the clinical syndrome of Addison's Disease.

While the above observations by Oliver and Schafer were proceeding, the different views held regarding adrenal function immediately prior to that period were ably summarised by ROLLESTON (1895) in the Goulstonian Lectures of 1895. In the course of his address he made it evident that there were two main theories advanced. The first - "Detoxifying", postulated that the suprarenals removed pigment and toxic substances from the blood and rendered them innocuous. This supposition was largely founded on experimental work performed by ABELOUS and LANGLOIS (1891) who claimed that after removal of the suprarenal bodies a toxic substance with properties like those of curare appeared in the blood. The researches of many other workers had also pointed in this direction. The second or "Secretory" view suggested that the adrenal glands provided an internal secretion. Oliver and Schafer's experiments supplied the stone that spanned the gap between theory and fact - the secretory function was accepted as the major duty of the adrenals/

adrenals.. The question as to whether or not they acted as detoxifying centres was left in abeyance.

The observations of Oliver and Schafer provided a great stimulus to the physicians of the period and consequently one finds numerous publications about 1895 and the following years, in which the authors had used suprarenal preparations for patients with Addison's Disease. Unfortunately many of these papers require to be regarded with considerable reserve as the diagnosis of many of the cases is open to doubt. It is obvious, for example, that the patient described by JONES (1895) suffered from pernicious anaemia and not from Addison's Disease as claimed. The treatment of this case by suprarenal preparations was given great publicity at the time and the beneficial results which accrued naturally tended to obscure the issue regarding the efficacy of such therapy in Addison's Disease. It is of interest to note that Jones himself admitted in 1903 that the case was one of pernicious anaemia (ADAMS, 1903). Similarly, owing to the natural remissions that occur in the severity of the disease, scepticism prevents acceptance of the verdict "cured" in cases that were observed for a short time only.

DEEKS/

DEEKS (1902) records a well marked case of Addison's Disease as cured by means of oral administration of suprarenal extract. The observation of this case lasted merely through two months. Many other dubious cases similar to the above are recorded, and must now be discounted.

G. OLIVER (1895 a.) himself mentions in his excellent little monograph "Pulse Gauging" two cases of Addison's Disease treated with suprarenal extract. In both of these he noted a clinical improvement with a gain in weight and an increase in blood pressure whilst this therapy was being exhibited. However, very few facts are recorded about either case and it is doubtful if from the data given they would be accepted nowadays as authentic cases of such a relatively rare condition.

SHOEMAKER (1895) records a case of Addison's Disease in which encouraging results followed the hypodermic injections of a glycerol extract of whole suprarenal glands. The equivalent of 10 grains of fresh gland was given daily. The general clinical features of this case as detailed in the report are in keeping with those accepted to-day as being indicative of Addison's Disease. The diagnosis in this case was also corroborated at/

at the time by several competent independent observers. This case, which was published in a somewhat obscure medical periodical, was not recorded, as far as can be ascertained, in any of the statistical tables that were compiled dealing with the utility of suprarenal preparations in Addison's Disease around this period. It may indeed be the first example of a case of this condition in which suprarenal extract was definitely beneficial. This case had been observed for thirty months before publication. Another similar case which is also not recorded in any of the statistics of the time is that put forward by FOSTER (1899). His patient was given 5 gr. tablets of whole suprarenal substance and improved considerably for four months, but then had a sudden relapse and died in a crisis. It will be noted that both these cases received preparations made from the whole gland. It is probable that the beneficial results were due almost entirely to the medullary hormone being present. It is doubtful if any of the cortical hormone would be extracted by the simple glycerol method used by these workers. When one considers the very elaborate techniques used at the present time for the extraction of Cortin it is justifiable to assume that there would not be sufficient "cortin" content in their preparation to produce/



produce the clinical improvement noted by them.

In 1897 in a review of "The Therapeutics of Internal Secretions" before the Triennial Congress of American Physicians, KINNICUTT analysed the results of suprarenal treatment in cases of Addison's Disease. He was able to collect forty-eight of these cases and tabulated them with brief notes of their salient features. Six cases were reported as "cured or practically well", twenty-two "improved", eighteen "unimproved", and in two cases an aggravation of symptoms was stated to have occurred during treatment. It would be advisable to accept these figures with considerable reserve. It has been possible to trace to their source four of the six cases which were stated to have been "cured". Not one of these can withstand a critical analysis. One case is apparently that of a patient suffering from pernicious anaemia (STOCKTON - 1895); another is probably the same (G. OLIVER - 1895 b.); while the remaining two have no clinical details (SHATTUCK - 1896 and WOOD - 1896). WOOD (1896) makes an interesting observation that reveals the difficulties that faced a physician using organotherapy in these days. After discussing the treatment of his case with preparations of suprarenals, he continues as follows/

follows:-

"I know of two or three other cases of Addison's Disease in which benefit was derived, and there have been some cases of failure reported. There is, however, a special reason for failure. Suprarenal capsules are ordered from some apothecary who has a faint notion that the suprarenal capsules consist of fat, and he gets a lump of fat out of the belly of an animal, and the doctor wonders why he don't cure his case of Addison's Disease. Always see that a first-class veterinary surgeon gets the capsules himself from the beef".

CABOT (1896) published a similar review of the results of suprarenal therapy in Addison's Disease, but his cases were not so definitely graded as were those of Kinnicutt. Several individual cases were included in both series of statistics. Cabot collected twenty cases and of these nine showed improvement under adrenal therapy. He states that "The various fluid extracts are evidently very inferior to the gland itself, dry or raw". He also draws attention to the difficulty of coming to an absolute diagnosis of Addison's Disease without a confirmatory autopsy and suggests that some of the so-called cures might be attributed to preceding errors in diagnosis.

In 1897 BRAMWELL recorded three cases of Addison's Disease - all of which were confirmed at post-mortem. In one of these extract of rabbit's/

rabbit's suprarenals was given hypodermically in the renal regions. Later the extract was given by mouth. The patient showed an improvement as a result of this therapy and was able to return to work. However, he suddenly collapsed in a crisis and died the following day. At autopsy no adrenal glands were found, only adipose tissue being present in their usual location. Bramwell puts forward a carefully developed discussion. He suggests that the good response to therapy in this case was due to the fact that the adrenals were atrophied and that a much less successful result would have occurred if the lesion had been tuberculous, with consequent extensive involvement of the neighbouring abdominal sympathetic plexuses. In this way he gives an explanation of the fact that so few cases of Addison's Disease respond to organotherapy. Bramwell published a further paper on the same subject five years later and in it he reiterated and elaborated this opinion (BRAMWELL - 1902).

#### OPERATIVE MEASURES AND THEIR RESULTS

So medical progress continued. Innumerable cases were treated with suprarenal preparations - many of them rightly so, many of them with little justification. In 1897 operative treatment for cases of Addison's Disease was attempted for the first/

first time. Two different procedures were adopted, that of grafting and that of removal.

JABOULAY (1897) transplanted dogs' suprarenals subcutaneously into two patients with Addison's Disease. The results were disastrous - both patients presented similar features. They became very prostrated, developed a hyperpyrexia and died within twenty-four hours.

OESTREICH (1897) records a case in which a patient came to him presenting vague symptoms of nausea, vomiting, etc. On examination a small tumour was felt in the upper abdomen lying close to the spine. This was thought to be a carcinoma of the stomach and a laparotomy was performed. It was then appreciated that the mass was retroperitoneal in position and was lying at the upper pole of the left kidney closely applied to the aorta. It was removed and subsequent microscopic examination revealed that it was a tuberculous suprarenal gland. This attracted attention to the preoperative clinical picture which was now recognised to have resembled that of Addison's Disease. The operation was followed by the complete disappearance of the Addisonian symptoms, and a year later the patient was reported to be fitter than/

than she had been for years. This result was amazing. Normally in cases of Addison's Disease operation is to be avoided as the shock usually kills the patient. ALLBUTT and ROLLESTON (1908) in recording this case point out that if the symptoms were due to the tuberculous adrenal they must have been the result purely of irritation of the sympathetic and not in any way due to suprarenal inadequacy. Jaboulay's attempt at suprarenal transplantation in humans was carried out apparently in ignorance of the fact that several workers had previously failed to obtain satisfactory grafts in experimental animals. The importance of a successful suprarenal transplantation had been readily appreciated and considerable work was performed about this time in an endeavour to obtain a suprarenal graft that not only preserved its viability but also its function.

In view of the importance of such investigations and the interest attached to them it has been considered advisable to set them forth in comparative detail. Even as early as 1887 CANALIS made an attempt at suprarenal transplantation in rabbits. Out of four experiments he succeeded only once in demonstrating surviving suprarenal cortical cells in the cicatrix of the wound where the piece had been transplanted.

LANGLOIS/

LANGLOIS (1897) reported eight successful transplants out of thirty operations in frogs. These frogs, in which the adrenals had "taken", survived the subsequent destruction of their normal suprarenal tissue while control frogs, after their adrenals were destroyed died at once. When later the successful grafts were destroyed seven of these grafted frogs died. The eighth survived.

Doubt is expressed about the significance of these results by later workers (H. and A. CHRISTIANI, 1902). GOURFEIN (1895) experimenting on frogs, BOINET (1895) on rats, HULTGREN and ANDERSSON (1899) on cats and dogs and STREHL and WEISS (1901) on numerous animals all failed to obtain survival of suprarenal grafts. These different workers transplanted the adrenal tissue to many varied sites, such as the dorsal muscles, the kidneys, the liver, etc. POLL (1899) made an extensive histological study of suprarenal transplants. A remnant of the gland was found in twenty-three out of fifty-four grafts after intervals that varied from three to thirteen weeks from the date of planting. In each case the surviving tissue consisted of cortex only - the medullary portion being entirely replaced by fibrous tissue.

H. and A. CHRISTIANI (1902) conducted a series/

series of carefully controlled experiments in which they made suprarenal grafts in rats. They found that, although macroscopically the transplants took well and apparently developed, the medulla actually showed atrophic changes microscopically and did not grow in the graft. Only the cortical portion developed. At a later date they removed the normal adrenals from some of these animals and invariably found that death occurred, so demonstrating that the function of the graft was inadequate to maintain life. SCHMIEDEN (1902) reported the successful transplantation of a suprarenal of an animal into one of its own kidneys, but he did not demonstrate continuance of function of the transplanted portion by the critical test of removal of the remaining normal suprarenal tissue. PARODI (1903) grafted adrenals from embryo rabbits into the kidney and liver of adult rabbits. The cortex survived but the medulla fibrosed. STILLING (1903 and 1905) succeeded in demonstrating living suprarenal tissue in the testicle of the rabbit over three years after transplantation into that organ. This consisted only of the cortical portion, however, the medulla having disappeared. The cortical cells had not only been preserved, but had multiplied. His/

His results demonstrated the possibility of the indefinite survival of certain portions of adrenal transplants, though he apparently did not endeavour to estimate the degree of adrenal function retained by them.

The most elaborate and successful work of this kind was that of BUSCH and VAN BERGEN (1906) who succeeded in transplanting adrenals in rabbits and also in demonstrating a preservation of suprarenal function in some, at least, of their transplants. Their experiments were performed in three stages. (a) A suprarenal of an animal was removed and grafted into one of its own kidneys. (b) Several weeks after this operation the second adrenal was removed. In the successful cases the animals survived after the removal of this, their sole remaining normal adrenal tissue. However, they all died immediately after (c) the removal of the kidney containing the adrenal transplant. Microscopic examination of the transplanted adrenals revealed a somewhat mixed picture in which it was difficult to identify all the cells. Many of these bore a strong resemblance in structure and arrangement to the cells found in the zone reticularis of the cortex, while others, which were larger, had a/



a plentiful cytoplasm and small nuclei and were presumed to be medullary in type. A confirmatory feature was the fact that these latter cells gave a positive reaction with chrome salts. Further similar and more detailed results were published later (BUSCH, LEONARD and WRIGHT - 1908). In this paper not only were successful results obtained in homo-grafting, i.e. transplanting a piece of suprarenal into some other part of the same animal, but also in hetero-grafting. However, it was only found possible to obtain successful results when the graft was made into another animal of the same species as the donor. Also the grafts took successfully only when the transplants were made into the kidney. Grafts made into the thyroid and testes were complete failures.

Two years later BUSCH and WRIGHT (1910) recorded three cases of Addison's Disease - one of which was treated by suprarenal transplantation. The patient was admitted to hospital in a moderate state of severity and in view of the comparative lack of urgency it was decided to perform a suprarenal transplantation. There was no human gland available at the time, but while waiting for one the patient's condition became alarming, and consequently/

consequently it was considered expedient to remove an adrenal gland from a female shoat weighing 40 pounds. The edges and ends of the gland were shaved off, exposing the medulla and it was then grafted into a cavity of an equivalent size that had been cut in the testicle, which was exposed by being drawn up to an inguinal incision, made under local anaesthesia. It was originally intended to use the kidney, in view of these workers' own experimental results, but, in view of the patient's precarious condition, this was considered impracticable on account of the probable shock which would ensue. Subsequent to the operation the patient was given desiccated adrenal gland which had later to be stopped on account of the nausea. Adrenalin was also given hypodermically. For several days after the operation evident improvement occurred. The patient became less despondent, ate better, felt somewhat stronger, and the vascular tonus increased. The pigmentation also decreased. However, after fourteen days the weakness became more pronounced, the blood pressure fell and the pigmentation deepened. On the sixteenth day collapse occurred with shivering. This went on to coma and death on the following day.

Microscopic/

Microscopic examination of the transplant showed good adherence with moderate vascularisation. A few medulla cells survived in groups but the major portion of the medulla had degenerated. A large part of the cortex remained and was apparently viable. The workers considered the result highly satisfactory and encouraging as the operation had, in their opinion at least, delayed death. They pointed out that the obligatory use of an adrenal from another species and also of the testicle as a site for the graft were not contributory to success.

In one of their other cases the patient had a positive Wassermann Reaction and anti-luetic treatment was adopted in the form of Protoiodide of Mercury. This undoubtedly hastened death and the authors issued a general warning regarding the use of mercurial preparations in Addison's Disease.

These results of adrenal grafting are of exceptional interest and value in view of the renewal in recent years of attempts at transplantation in cases of Addison's Disease.

#### THE RESULTS FROM ORGANO THERAPY PRIOR TO 1900.

The introduction of organotherapy at the end of the nineteenth century was received with a considerable/

considerable degree of unwarranted enthusiasm and at the same time was treated with scepticism by many authorities. It was only natural therefore that several papers were published about this time critically analysing the different results claimed. In addition many of the periodicals contained long articles elaborating the uses and abuses of the endocrine preparations. Such a paper appeared in the Practitioner on "The Therapeutic Value of Suprarenal Preparations in Addison's Disease" (BOX - 1901). In this the author reiterates strongly the difficulties in diagnosis between Pernicious Anaemia and Addison's Disease and points out that many of the so-called "cures" had to be rejected on the ground of incomplete examination and lack of detail. He quotes from his own clinical experience eight cases of Addison's Disease treated by the oral or rectal administration of fresh whole adrenal gland. Seven of these cases failed to respond to this therapy and in the eighth case the beneficial result was doubtful. As a result, he naturally viewed the use of adrenal preparations in cases of Addison's Disease with some disfavour. He makes a suggestion that the symptoms of Addison's Disease may be due in some cases to the physical involvement of the thoracic duct by the inflammatory process of the adjacent/

adjacent adrenals.

In 1903 ADAMS published a very carefully compiled paper on "The Results of Organotherapy in Addison's Disease". In this he presents a critical analysis of all the then available published cases of this syndrome that had been treated by some form of suprarenal therapy. He records ninety-seven cases. He divides these into four groups. Class I, "Cases in which alarming or fatal results were presumably or possibly due to the treatment", is composed of seven cases. In three of these adrenal transplantation was attempted with rapidly fatal results. (These include the two cases of Jaboulay noted above). In the other four cases adrenal extracts were exhibited orally and parenterally. This administration was followed by collapse of the patient in each case. In one of these improvement occurred after this form of therapy had been stopped. Two of these patients died shortly after their course of treatment with adrenal preparations, but, as Adams points out, this could not be attributed to the therapy adopted, as sudden death is a well recognised mode of termination of Addison's Disease, treated or untreated. Adams concludes "On the whole there is no evidence to show that any serious risk/

risk is incurred in the treatment of Addison's Disease by the ordinary methods of opotherapy". It is probable that the alarming results obtained with some of these cases were due either to a high adrenaline content of the extract or to non-purification of the extract so that foreign proteins or other toxic substances were administered unwittingly.

Class II comprises those "cases which were uninfluenced by or derived but doubtful benefit from the organotherapy". In all, there are forty-four cases in this group, which in Adams' words represents "a large and dispiriting succession of failures". Class III, "Cases in which marked improvement coincided with the treatment", totalled thirty-one. Adams at once hastens to remind his readers of the natural remissions that occur so suddenly in this condition and that the extended observations necessary in such cases were not always possible or forthcoming. He also points out that it was impossible to confirm the diagnosis of the majority of cases in Class III. A few of the cases recorded by him actually had sudden spontaneous remissions while they were not receiving adrenal therapy. Similar reservations are necessary when considering Class IV, composed of "cases in which permanent benefit (? cures) accrued/

accrued apparently as a result of the suprarenal feeding". These total seventeen and were treated by oral administration with one exception where extract was given hypodermically. Each of these cases was observed for at least a year after the commencement of organotherapy. Adams treated his subject so exhaustively and critically that his final conclusions are worthy of quotation in full.

- (1) "There would appear to be a certain class of case of Addison's Disease which derives indubitable benefit from the exhibition of some form of suprarenal substance, though in any given case it remains up to now impossible to determine its probable response to the treatment".
- (2) "In any given case of the disease, selected haphazard, the probability obtains that disappointment will follow on the institution of organotherapy: but that probability is very distinctly less than that attaching to any alternative method of treatment at present known".
- (3) "The last word upon the preparation to be used and its method of administration remains yet to be said. The problem seems to be to get a sufficient and continuous dose of the pure and active principle unchanged into the blood stream. Intravenous injection is impracticable".

WELLS (1903), while advising the administration of suprarenal preparations either as the gland itself or in the form of its active principle adrenaline, expresses little confidence in these forms of therapy. He points out nevertheless that/

that the underlying principle of supplying the system with a vitally necessary secretion which it lacks is correct, and suggests that the indifferent success attending such therapeutic measures in the past was probably due to the fact that the methods of administration were defective. He predicts that success would almost certainly attend the perfection of some obscure details in technique. BATTY SHAW in 1905 published a monograph on Organotherapy and he was even less enthusiastic than Wells on the use of suprarenal preparations in cases of Addison's Disease. He devotes the section on the Adrenals mainly to quoting unsuccessful cases of suprarenal therapy, and then goes on to issue a warning regarding the uncontrolled use of suprarenal preparations, in view of their toxic effects. It was perhaps natural that these preparations were used without due care by certain workers as the dangers attached to them were as yet unappreciated. In consequence several cases were reported about the beginning of the twentieth century in which severe toxic effects had occurred. BOINET (1903) points out the dangers of using adrenaline in any case of advanced Addison's Disease and suggests that in early and mild cases only small (not more than 0.3 mgm.) well spaced doses should be used.

He/



He quotes two cases of his own in which death occurred shortly after adrenaline had been administered hypodermically (1 mgm. to one patient and 0.3 mgm. to the other). On both occasions the patients were very tired from excessive exertion when the injections were given, and Boinet suggests that this fatigue was perhaps the cause of the alarming results. He describes several experiments in which the injection of adrenal extracts into adrenalectomised rats caused generalised nervous excitability with a tremor of the upper extremities. This passed on to cardiac and respiratory embarrassment and death of the animals. RENDU (1899) administered orally the fresh suprarenal glands of calves to a patient suffering from Addison's Disease. On the second day the urine became loaded with albumen and on the eighth day the patient died suddenly. In this case it is recorded that as much as 15 - 20 gm. of the fresh gland were administered daily.

#### TREATMENT WITH TUBERCULIN AND GENERAL

##### SANATORIUM MEASURES.

It is understandable that with the advent of the organotherapy the clinicians would be apt to neglect the older and more general measures used prior/

prior to its introduction. However, early in the twentieth century the Scottish Medical School attempted to direct the attention once more to the underlying disease process. In 1904 ANDERSON read a paper before the Medico-Chirurgical Society of Glasgow in which he described a typical case of Addison's Disease that he had treated with tuberculin. He used a 1 in 1000 solution of Koch's Old Tuberculin and gave two injections of 0.5 cc. and six of 1.0 cc. at four to eight day intervals. The course of therapy extended in all over six weeks. Prior to this treatment the patient's condition had steadily deteriorated, but subsequent to the commencement of the tuberculin therapy there was an appreciable improvement in the clinical state of the patient with a definite fading of the pigmentation.

In the following year BRAMWELL (1905) in a paper on Addison's Disease recalls the known beneficial effects of open-air treatment in many tuberculous affections and suggests that patients with the former condition should be nursed in the open under sanatorium conditions. He records two cases. The first was treated out of doors in Edinburgh throughout a very inclement winter. The patient stood the weather well and did not complain/

complain. He felt comfortable, gained 20 lbs. in four months and improved generally with a decrease in his pigmentation and a lessening of his general asthenia. In addition to the general therapy this patient received 15 gr. of "Supra-renal Extract" daily. The second patient who was treated in the same manner was unable to stand the cold and the therapy had to be stopped.

In 1912 there appeared the report of a case of Addison's Disease treated successfully with Tuberculin. This was published by MUNRO (1912) and was by far the most complete and detailed record of such therapy that had appeared by that time. In view of the importance of this case it has been considered justifiable to abstract it in comparative detail:-

"The patient was a spinster, aged 34, whose history and clinical features were typical of moderately severe Addison's Disease. There was a family history of tuberculosis. The patient's condition was becoming progressively worse. It was decided that, in view of her tuberculous history and her flagrant condition, the diagnosis of which was confirmed by several independent physicians including H. D. Rolleston and Sir A. Wright, she should be treated immediately by a course of tuberculin. The first injection was one of 1/1500 mgm. Human Tuberculin T.R. On the following day the patient felt worse, there was increased nausea and diarrhoea and there was aggravation of several vague pains in the chest and lumbar region from which the patient suffered. Next day these disappeared and returned only at rare intervals and/

and in a very transient manner. The nausea, mental depression and asthenia persisted longer but all were greatly alleviated by the ninth day after the initial injection. The tuberculin injection was repeated every tenth day and was later increased to 1/1000 mgm. and given at weekly intervals for many months. From the second to fourth month of treatment the patient was also given 15 gr. daily of suprarenal extract but, as this had no appreciable effect, it was discontinued. During the first year of treatment every injection of tuberculin produced slight malaise for about twenty-four hours. This effect, however, became less manifest and the tuberculin was gradually increased until towards the end of the second year 1/500 mgm. was being given every second day. Slow but steady progress was apparent from the start, but from approximately the eighteenth month onwards much more rapid improvement set in. The depression and diarrhoea disappeared, the asthenia became negligible and the pigmentation faded rapidly. At this time the patient had to return home and, as it was considered essential to supervise carefully the tuberculin therapy, it was stopped and she once again took suprarenal extract. However, this produced no apparent favourable effects and consequently it in turn was stopped after two months, as the patient felt that it upset her. After four months with no treatment the patient had lapsed considerably in her general state. She was then admitted to hospital and given a course of thirty-four injections of 1/1000 mgm. Tuberculin during the next four months. This caused a complete relief from all symptoms and she was able to return home and take her part in somewhat anxious and arduous household duties. Her weight was then six pounds more than it was when first admitted. She continued to have short courses of tuberculin inoculations, and was very fit and in an apparently healthy condition when the case was published exactly five years after the date on which she was first seen. The pigmentation of the buccal mucosa, which was easily detected at the commencement of treatment, had by now completely disappeared.

Such a result afforded considerable support

to/

to the claims of those who sponsored tuberculin therapy in cases of Addison's Disease. Nevertheless, this form of treatment was apparently unpopular and comparatively few cases have been recorded since in which it was adopted.

GUTHRIE (1913) records another case of Addison's Disease treated with Tuberculin with very good results. This patient had failed entirely to respond to any of the "usual therapeutic measures - iron, digitalis, tonics, etc.", and in view of a positive reaction with von Pirquet's test she was given Koch's Tuberculin T.O. and later T.E. in increasing doses with little or no benefit. This was followed "by somewhat large doses of Friedman's Turtle Tuberculin" for which the author claims good results. The patient began to put on flesh rapidly; the pigmentation quickly cleared up. The weight increased from 9 st. 1 lb. to 9 st. 11 lb. in six weeks and a steady improvement is recorded. From the scanty data supplied this case must be regarded with some dubiety.

#### FURTHER REVIEWS ON THE EFFECT OF THERAPY.

In 1909 BOINET reviewed the use of organo-therapy in Addison's Disease. He cites several cases with very variable results. Two of these are claimed as "cured". Both patients were given/

given fresh whole suprarenal gland by mouth (10 - 15 gm. daily) and in addition were given daily injections of a glycerol extract of the gland. From the published reports the results in these cases are very good - one of the patients was alive and very well six years after the commencement of treatment; the other was in excellent health ten years after his first symptoms.

Three cases gave a moderate response to organotherapy. These were treated with adrenaline or extracts of the adrenals. This was followed by some reduction in the asthenia but little change in the pigmentation. Their general state remained much the same.

Four other cases are detailed in each of which death occurred. In the first the patient ingested almost thirty grams a day of fresh suprarenal gland, with comparatively little effect on the Addisonian symptoms. However, this massive dosage brought on various bad side effects, insomnia, nightmares, tremors and cramps, which all stopped with the cessation of therapy. However, the patient's symptoms suddenly flared up and she died in a crisis. Each of the other three cases did not receive fresh suprarenal gland preparations but was treated with adrenaline itself either/

either by mouth or hypodermically. The beneficial results were negligible and were insufficient in every case to prevent the patients passing into a crisis and dying. Boinet reiterates the view expressed by him six years previously (1903) that adrenal preparations had to be administered with the greatest care to any case of Addison's Disease. He concludes by expressing the opinion, which Bramwell had already enunciated in 1897, that it was probable that the better responses with organotherapy were obtained in cases of Addison's Disease due to simple atrophy, and that the results to be expected in cases caused by tuberculosis were less favourable. He suggests the terminology "Addisonism" for cases of Adrenal atrophy as he was not of the opinion that they were true cases of Addison's Disease.

SAJOUS in 1907 completed the second of the two volumes of his book on "The Internal Secretions and the Principles of Medicine". This publication was a comprehensive production and reviewed in detail all the then known branches of endocrinology. In addition to a large portion devoted to the clinical pathology of Addison's Disease there was included a small but most stimulating/

stimulating section on the therapeutics of this condition in which the author advocates the use of intravenous salines three times weekly "as toxic wastes are inadequately catabolised". As far as can be determined this is the first reference to the use of intravenous salines in the treatment of Addison's Disease. It is now, of course, appreciated that such a form of medication exerts its beneficial effect by alleviating the gross anhydraemia that occurs at the time of the crises, and not so much by eliminating toxic substances from the blood as propounded by Sajous. Nevertheless, the introduction of such a measure is worthy of the highest commendation, notwithstanding the fact that the rationale advanced by its originator might be considered faulty according to modern conceptions. Sajous goes on to say that the only remedy of value is adrenaline and that cure is hardly to be expected, the purpose being to carry on artificially the functions of the adrenals as long as possible. In order to avoid excess of toxic metabolites he advocates rest and the abstention from foods rich in nucleins. He is definitely opposed to the use of thyroid which, he says, serves only to excite the diseased structures; also arsenic, "which further depresses the already deficient adrenal functions". He condemns/



condemns the use of alcohol, as it "deprives the blood of some of its oxygen", and is against stimulants in general "which hasten the morbid process". It will be seen from the above that Sajous effectively deprecates many of the therapeutic measures most zealously advocated in the past.

In an elaborate paper published in 1912 SERGENT puts forward the idea that many cases of adrenal insufficiency passed unnoticed, as the symptoms were not gross enough to warrant a diagnosis of Addison's Disease. The gravity of these cases was latent and was frequently not appreciated, and occasionally they might inter alia be subjected to an operation with consequent collapse and death. He suggests that many of the cases of fatality described as "post-operative" shock and "acute dilatation of the stomach" should really be regarded as cases of Addisonism, and says that it is in this type of patient that suprarenal therapy can be utilised most advantageously. He points out the great variation in effect produced on different patients with the same adrenal preparation, and recommends that fresh gland or, better still, extract of whole gland, should be administered to those patients in which the asthenia is the predominant feature. When hypotension is the/  
the/

the major problem adrenaline should be given, and only in the event of its failure should one utilise whole gland preparations. Regarding the method of administration he holds that the whole gland is best given by mouth as hypodermic injections occasionally cause severe pain. Sergent also recommends that adrenaline should be given orally and not by injection. This is to be given in very small doses spread over the day. He then goes on to point out that while organo-therapy is the obvious measure in a crisis, the general treatment to be adopted varies from case to case. In patients with a tuberculous diathesis a sanatorium régime is advocated with various adjuvants such as cod liver oil, phosphates, etc. Similarly, if syphilis is suspected as the cause of the disease one should adopt general anti-luetic therapy - with great care and restraint, however, on account of the intolerance of these patients to many of the preparations used for this purpose - particularly those with a mercurial base. Any distressing symptoms such as diarrhoea or vomiting should be treated at once with the relevant measures, but here Sergent stresses that opiates must on no account be administered. He continues by pointing out that the prophylaxis of crises in cases/

cases of Addison's Disease is just as important as their alleviation. All causes of fatigue must be avoided. These patients must be sheltered from infections and intoxications of either an endogenous or exogenous nature. Pregnancy and surgical procedures should be avoided. It should be borne in mind that the toxic effects of many drugs appear in Addison's Disease at a much lower level than in normal people. This is especially exhibited in the case of arsenic "which is a violent poison for the suprarenals". This paper by Sergent was by far the most comprehensive that had yet been produced on Addison's Disease. On considering it, one appreciates the exceptional clinical acumen of the author who propounded views that are not only compatible with modern opinion but were so complete that little has been added to them, despite the many supplementary methods of investigation that are now available.

#### SUCCESSFUL TRANSPLANTATION OF SUPRARENAL GLAND.

In 1912 an Australian surgeon MORTON recorded a case of Addison's Disease that was apparently successfully treated by transplantation of a suprarenal gland from a human. As far as can be determined this is the first reported case of such a procedure in which there was a favourable result, and, in view of the interest attached to it/



it, the liberty has been taken to abstract the case in comparative detail.

The patient was a woman aged 35 whose general clinical features as presented in the case notes are very suggestive indeed of Addison's Disease. There was recurrent nausea, vomiting and diarrhoea, well marked pigmentation, severe asthenia, subnormal temperature and a systolic blood pressure of 90 - 95 m.m. Hg. The blood counts were normal except that a differential white count showed 47% lymphocytes. There was no anaemia. The von Pirquet test was positive. Under oral treatment with suprarenal gland (B.W.), tuberculin every ten days and also iron and arsenic, the patient gradually improved, although each injection of tuberculin was followed by a marked reaction with headache and vomiting lasting from 24 to 36 hours. The blood pressure rose with this therapy to 110 m.m. However, each menstrual period was accompanied by a severe attack of nausea and vomiting. These attacks became more prolonged and frequent and appeared between the menses so that eventually the patient was unable to rise without severe vomiting and a feeling of extreme prostration. The operation was actually performed during a crisis with persistent vomiting that had brought the patient to a very low physical state. The suprarenal gland was taken from the cadaver of a man who had died from cardiac failure. It was removed with complete asepsis immediately after death, was then bisected and a half was buried in each of the patient's recti muscles. These had been exposed under local anaesthesia. For two days following the operation the vomiting of the crisis continued and the patient was very weak and low. However, she then commenced to improve rapidly. Within a fortnight she had lost all feeling of nausea and was able to move about freely. The systolic blood pressure was then 108. Further progress notes reveal that the patient returned to a normal home life, her pigmentation decreased markedly and she continued to show a general improvement with an increase in weight. Subsequent to the operation the menstrual periods no longer brought on any nausea.

In the following year BROWN (1914), who was also/

also an Australian, attempted the same procedure in another case. However, this was an absolute failure - the patient dying within two days of the operation. Brown himself stated that in his opinion death was markedly accelerated by the operative procedure.

#### BIOCHEMICAL ASPECTS.

About this time workers were beginning to appreciate the value of biochemistry and several short articles appeared reporting simple biochemical investigations in cases of Addison's Disease. These papers naturally contained several erroneous conclusions and, although not in themselves of much value, were collectively very important in that they directed medical thought towards the biochemical investigation of such a condition as Addison's Disease, and formed the basis upon which was built much of our present-day knowledge of the malady. Such papers included that of MÜNZER (1914) who investigated the Carbon Dioxide tension of the blood in Addison's Disease and that of WOLF and THACHER (1909) who made a preliminary investigation into Protein Metabolism in the condition.

Several workers had drawn attention to the presence in the cells of the suprarenal cortex, of the doubly refractile cholesterol-esters, and in/

and in consequence the adrenal glands were considered to be closely concerned in the metabolism of cholesterol. (KAISERLING and ORGLER; 1902. PANZER, 1907. ASCHOFF, 1907.) It was suggested that increased cholesterol content of the blood was due to increased adrenal function. ALBRECHT and WELTMANN in 1911 made a morphological study of the cholesterol-ester content of adrenals in various morbid processes, and found that it was possible to divide diseases into two large groups; in one the cortex had a large cholesterin-ester content, in the other the content was poor. They attributed these differences to variations in the activity of the suprarenal function and postulated that these glands supplied the body with cholesterol. LANDAU (1913), however, made a similar pathological study and came to an entirely different opinion. He suggested that the suprarenals did not produce cholesterol themselves and that the cholesterol found in them was deposited there from the blood. In support of this he pointed out that the greater the amount there was of circulating cholesterol in the blood the larger the amount of cholesterol found in the adrenal cortex. Work performed by WACKER and HUECK (1913) and by LANDAU and McNEE (1914) tended to confirm this latter view, which had also been supported by McNEE in a paper he published/

published on Cholesterol Metabolism in 1913. Arising out of this work ELLIOTT published a paper in 1915 in which he stated that it was possible to keep adrenalectomised cats alive by the daily intraperitoneal injection of cholesterol. In consequence he advocated the administration of cholesterol to cases of Addison's Disease, although, as he admitted, there was no known diminution in blood cholesterol in this condition. He suggested that one gramme of cholesterol should be given daily as a 4% solution in olive oil and that in addition yolk of egg and boiled brains should be included in the diet on account of their cholesterol content.

Opinion was still very divided as to the beneficial results accruing from the administration of adrenaline to cases of Addison's Disease. Thus it is recommended strongly for patients with Addison's Disease by HARROWER (1914) in his "Practical Hormone Therapy". On the other hand, ELLIOTT (1915) says "Neither with animal experiments nor in man has treatment with adrenalin proved to be of value in prolonging life. I have used hypodermic and intravenous injections of adrenalin without obvious benefit. Still the substance is worth a trial". Elliott later goes on to point out that the cortex of the adrenal is just/

just as grossly destroyed as the medulla by the tuberculous process in Addison's Disease; further, that it was not known whether it was the cortex or the medulla that was essential for life and that "Every attempt, therefore, needs to be made to find out whether some other extractive of the gland in addition to adrenalin cannot be used for a more successful treatment of Addison's Disease". He states that in his opinion glycerine extracts of the whole gland are no better than adrenalin itself. As far as can be determined this is the first time that it was suggested that Addison's Disease might be due to a cortical lesion and might indeed be better treated by a cortical extract than one made from the medullary portion of the gland. Unfortunately, however, it was many years before such an extract was produced.

#### THE RENAISSANCE OF ENDOCRINOLOGY

#### AND ITS INFLUENCE.

Little advance was made in the therapy of Addison's Disease during the period of the World War. No papers of note appeared apart from those quoted above until 1917, in which year the "Association for the Study of the Internal Secretions" was founded. The formation of this society/



society promoted considerable advancement in our knowledge of the endocrine glands as it brought together physicians whose primary interest was that of the internal secretions. As a result, there was applied to the numerous problems in this branch of medicine the combined thought of many competent authorities. This served to promote discussion and in consequence many of the erroneous beliefs held prior to that time were speedily quashed on account of many fallacious tenets on which they were based being elicited and exposed. The views and papers of the members of this association were published in its journal, "Endocrinology". The early volumes of this periodical contained several excellent articles on the functions of the adrenal glands. The authors endeavoured to correlate the various clinical features associated with pathological conditions of the adrenal with deficiencies or excesses of adrenal function and in this way attempted to determine more definitely the exact rationale underlying the somewhat empirical forms of therapy utilised for Addison's Disease about that time (VINCENT - 1917, SAJOUS - 1918, etc.)

STEWART (1921) produced an excellent paper in "Endocrinology" on "Adrenal Insufficiency" in which he reviews the various theories that had been evolved/

evolved regarding the physiology of the Suprarenal Glands. He indicates the importance of the adrenal cortex for the maintenance of life and stresses the fact that, despite this known physiological property, the majority of physicians were still tending to disregard the cortex as a possible site of the morbid process in Addison's Disease. He tends rather to minimise the physiological importance of the medulla and quotes the work of WHEELER and VINCENT (1917) who destroyed practically all the suprarenal medulla in dogs without causing death. He makes many very scathing remarks regarding the tenets about Addison's Disease held by the physicians of that period, and deprecates the increase in the so-called "hypoadrenic syndromes," in terms which could hardly be more disparaging. These syndromes were being rapidly evolved about this time, mainly by continental workers who, as Stewart points out, had no more grounds for attributing them to adrenal insufficiency than that the administration of adrenaline seemed to do good. He stresses the fact, repeatedly emphasised by physiologists in the past, that the pharmaco-dynamic or therapeutic effects of adrenaline cannot be utilised to prove the existence of a deficiency in the secretion of adrenaline from the suprarenal glands. HOSKINS (1918)/

(1918), the first editor of "Endocrinology", in putting forward the same plea, asks very pointedly whether because cascara was efficacious in relieving constipation, it had to be concluded that the patient was suffering from "hypocascarism".

This paper of Stewart, although mainly destructive in its criticism of the views held by the clinicians of the period, was nevertheless of extreme importance in that it also analysed censoriously the various physiological tenets held then and eliminated many that were fallacious. It naturally provoked considerable discussion and the replies to his condemnation of the dogmas of the clinicians were led by SAJOUS (1922). The latter points out the tremendous difference there is between the chronic hypoadrenalism that occurs clinically and the acute adrenal insufficiency produced by the enucleation of the suprarenals. He said that neither he nor other physicians would endorse Stewart's statement that the majority of clinicians regarded the loss of the adrenal medullary secretion as the major factor in cases of Addison's Disease. "No present day clinician worthy of the name would think of 'epinephrin secretion' as a sole factor in Addison's Disease, being well aware of the fact that both the medulla and cortex may be the seat of lesions." He then passes/

passes on to say that no competent therapist would administer adrenaline in such cases and that it was necessary to use either the fresh gland, the dried gland or a glandular extract if beneficial results were to be expected, quoting some work of his own in support of this contention.

In 1922 there was published a most comprehensive series of volumes entitled "Endocrinology and Metabolism". These were compiled by numerous authors and there is a large section devoted to Addison's Disease. This part was edited by COHOE (1922) and deals with every aspect of the condition in a most exhaustive manner. He reviews in detail the various forms of treatment that had been used up to that time. With regard to the use of glandular therapy the following is found:-

"Only in the earlier stages may any marked degree of improvement be expected, and in the later stages no beneficial result is likely to occur; further, in advanced cases great care should be exercised in the administration of either the gland substance or of the active principle."

Cohoe did not think that any advantage was obtained by using pituitrin in conjunction with adrenaline as was held by several workers about that time (COBB - 1916). Similarly, he condemns the use of tuberculin in Addison's Disease owing to/

to the danger of very violent symptoms occurring due apparently to a local reaction in the region of the suprarenals, resulting in acute insufficiency of the glands. Cohoe makes the suggestion that further development in the knowledge of metabolism might readily enable the clinician to influence the course of the disease by dietetic measures. However, he makes no definite statements as to what modifications he would make in the diet, beyond advocating plenty of carbohydrates. In this connection it is of interest to note that the discovery of a hypoglycaemia in patients with Addison's Disease had stimulated several workers to increase the carbohydrate intake in such cases. As early as 1909 PORGES obtained good results by giving laevulose, while PITRES and GAUTRELET (1910) and GROTE (1916) found the administration of glucose most efficacious.

#### THE MUIRHEAD RÉGIME

In 1921 there occurred a case of Addison's Disease that was unique in several ways, and one which has since become so well known that it might readily be regarded as a landmark in the study of this condition. The subject of the disease was A. L. MUIRHEAD, Professor of Pharmacology in the John A. Creighton Medical College, who published

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a most interesting autograph history of his illness (1921). The clinical features as presented by the patient himself differ in no essential detail from those of a typical case of Addison's Disease.

The particular value of the report lies, however, in the author's description of his reactions to the treatment adopted. This therapy was of such comparative value in this case that it was repeated on many occasions and became widely recognised as the "Muirhead Régime". The treatment was originated and carried out with the cooperation and under the direction of ROWNTREE at the Mayo Clinic and it was he who ultimately reported the case in full (ROWNTREE - 1922). In it a régime of forced therapy was adopted in which adrenaline and desiccated whole gland were administered to the limit of tolerance.  $\frac{1}{2}$  - 1 c.c. of 1 in 10,000 Adrenaline was given hypodermically twice daily. This was sometimes administered in a dilute solution of mucilage of acacia in place of the usual normal saline solution with a view to delaying the absorption of the adrenaline and so prolonging its action. This retardation effect could be seen as a slight lengthening of the brief pressor response that occurred immediately after the adrenaline administration. At the initiation of the/

some cause other than the rise in blood pressure.

In view of a high blood uric acid (6.9 mgm.%) the patient was put on a purin free diet and within two weeks the blood chemistry was back to normal. The patient gained on the average a pound a week during his six weeks' stay in hospital. There was a definite clinical improvement from the start of the adrenaline therapy with a lessening of the abdominal tension, an increased food tolerance, relief of the constipation, decreased pigmentation and an increase in strength and endurance. The patient found, however, that while he had no discomfort from the rectal administration of the desiccated whole gland, he was unable to continue with the adrenaline per rectum owing to severe rectal tenesmus that occurred about an hour after its administration. Professor Muirhead reported his own case about six months after the commencement of therapy. At that time he had returned to work and was following without discomfort his ordinary occupation of a medical teacher. However, about two months later the patient developed a gastric upset, loss of appetite, abdominal discomfort and weakness. The pigmentation once again became marked and his condition became steadily worse despite the fact that the therapy was intensified. He eventually died approximately ten/

ten months after the commencement of treatment. In view of the interest attached to this case and the influence that the "Muirhead Régime" had on the treatment of Addison's Disease during the next ten years it is considered justifiable to present Rowntree's observations on the case in detail:-

"The patient's improvement under treatment with epinephrine and the whole suprarenal gland ..... was striking objectively as well as subjectively. ....Glandular therapy was of unquestionable value in the relief of asthenia and of gastro-intestinal discomfort, and resulted in a temporary clearing up of the pigmentation. For a time, at least, it also checked the general course of the disease. Although the results were only temporary, they were almost miraculous. Such definite relief of symptoms in the chronic form of the disease justifies a thorough trial of such measures in other cases of Addison's disease."

It was indeed ROWNTREE himself who made this "thorough trial" and utilised the "Muirhead Régime" to the greatest extent (ROWNTREE (a) 1924, (b) 1925, and ROWNTREE and SNELL, 1931). He analysed his results very carefully and came to the definite conclusion that the "Muirhead Régime", while by no means the ideal form of therapy, was yet the most efficacious utilised up till that time, and had saved life, temporarily at least, in a considerable number of cases. In all fifty-seven cases were given the Muirhead treatment and of these thirty-two are regarded as being benefited. Twenty of this number had "excellent results/



results in that the patients made rapid improvement, or were definitely rehabilitated for a period of several weeks at least, some for many months and ten of them for periods of three to seven years." In such cases the blood pressure increased 5 - 15 m.m. during five to six days. In contrast to these, twenty-five patients did not improve or did not tolerate the treatment well, and complained of increased weakness, sweating and trembling; the nausea and vomiting persisted or increased and the blood pressure fell. The results as summarised showed that half the patients were somewhat benefited, a third responded with immediate results that were considered excellent, while a sixth were living after three years. Rowntree does not fail to point out the limitations of the Muirhead Régime, in that it is only a form of substitution therapy and is entirely devoid of any effect on the diseases underlying the failure of the glands. He advances the view that the Régime might readily be effective in certain cases of Addison's Disease, namely those due to atrophy of the glands, whilst it might be completely useless in other cases, as, for example, when an active tuberculous lesion is present in the adrenals. From that point of view it is essential that the patient be treated on general lines and the underlying pathological condition be attacked if/

if at all possible. Rowntree stresses that such specific therapy must, however, be carefully supervised and must not be at all drastic or the results might readily be catastrophic and not palliative owing to an exacerbation rather than an alleviation of the morbid processes. The individual symptoms and signs call for their own treatment and every case must be regarded as a separate entity and treated on its own merits. Therapeutic measures which are of optimum value to one case might readily be definitely harmful to another. There was a marked variation in the tolerance of different patients to adrenaline and to whole gland preparations, and, in addition, the individual tolerance was not constant in that several patients showed quite severe toxic effects with doses of the preparations that they had previously taken with impunity. Intolerance to the continued administration of whole gland by mouth was encountered with moderate frequency, the patient complaining of burning in the epigastrium, intestinal cramps, abdominal distress or nausea following its use. Decrease in size of the dose or its omission for a period was necessary in some cases. The toxic effects were less marked when the preparation was taken on a full stomach, although no decrease in efficiency was noted.

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The best results undoubtedly occurred in the patients who had the greatest tolerance to the treatment. An apparent inability to receive any form of suprarenal treatment manifested itself in the more advanced cases, a shock-like condition developing. From Rowntree's description of this latter condition it was apparently one of acute and severe anhydraemia, there being a high haemoglobin content, low blood volume and extremely low blood pressure.

THE EFFECT OF THE ADRENALS ON THE BLOOD PRESSURE  
IN NORMAL INDIVIDUALS

In view of the use made of adrenaline in the treatment of Addison's Disease both in the "Muirhead Régime" and in the various methods utilised prior to its adoption, it is perhaps of value to review at this stage our knowledge concerning the part normally played by adrenaline in the maintenance of the blood pressure. Considerable controversy has arisen in the past over this problem, due to the apparently conflicting results obtained by different research workers.

Early authorities presumed that a constant secretion of adrenaline occurs which helps to maintain the normal blood pressure. STREHL and WEISS (1901) removed one adrenal gland in rabbits and/

and found that when the adrenal vein of the other side was clamped the blood pressure fell at once, sometimes markedly. The pressure returned to normal when the clamps were removed.

YOUNG and LEHMANN (1908) repeated the experiment on dogs and obtained little, if any, fall in blood pressure on clamping the suprarenal veins but the subsequent release of the clamps produced a rise in some of their cases. They suggested that this might be due to the damming back of adrenaline in the suprarenal veins. KAHN (1911) found no fall in blood pressure on tying the adrenal veins in rabbits. HOSKINS and McCLURE (1912) found only transitory changes in the blood pressure on ligating the adrenal veins in dogs. MOORE and PURINTON (1900) demonstrated that very small amounts of adrenaline cause a lowering of the blood pressure. Hence they suggested that the amounts of adrenaline that presumably would be liberated normally from the suprarenals would tend to decrease rather than maintain the blood pressure. CANNON (1914) having failed to show the presence of detectable amounts of adrenaline in the normal vena cava under normal conditions, demonstrated that in times of emotional stress the adrenals secreted considerable quantities of adrenaline, and so/

so established the well-known "emergency" theory. All these later experiments tended to support the view that the adrenals did not normally secrete adrenaline into the blood stream.

However, in 1914 COW showed that the adrenal vein had a collateral circulation. This was later completely corroborated by VINCENT and THOMPSON (1929). As a result of this discovery it was apparent that the older experiments in which only the adrenal veins were clamped or ligated were fallacious, as the adrenaline could still pass from the suprarenals along their accessory venous plexuses. In 1920 BAZETT, in an endeavour to surmount this difficulty, removed the adrenals in their entirety from cats. He found that the pressure began to fall in about an hour and that the animals died approximately six hours after the operation. This work was confirmed by other workers (VINCENT and THOMPSON, 1929). A satisfactory explanation for these results was not advanced until 1930 when VINCENT and THOMPSON published an account of an elaborate series of experiments. In these they found that the clamping of either the adrenal veins or of their complete collateral circulation caused a slight and very transient fall in the blood pressure. Clamping of/  
of/

of both of these drainage routes coincidentally caused invariably a marked but gradual fall in the pressure that was often as much as 50 mm. Hg. This fall persisted for about twenty minutes and then a slow recovery back to the initial pressure occurred. This recovery was markedly accelerated if the clamps were removed from either of the two drainage routes. Exactly the same phenomena - fall and subsequent slow recovery - occurred after complete adrenalectomy. The fall was not due to the operative procedure as various other organs were removed with no variation in the blood pressure. However, if any large portion of the splanchnic viscera was removed prior to the experiment the recovery process was much delayed and was never complete. In view of these results Vincent and Thomson suggested that the vaso-motor mechanism, particularly of the splanchnic region, acts in a compensatory manner so that the pressure returns to normal after the adrenalectomy. They also postulated that the suprarenals should not be regarded as essential for the maintenance of the blood pressure but rather as a normally functioning accessory-mechanism the removal of which causes a transient fall in pressure. With regard to Addison's Disease they put forward the opinion that/

that due to the disease of the adrenal glands there is a lack of adrenaline and that the consequent fall in the blood pressure cannot be compensated because of fibro-caseous involvement of the abdominal ganglia preventing the normal restorative function of the vasomotor nerves in the splanchnic region. They advance the hypothesis that the lowered basal metabolic rate resulting from the adrenaline insufficiency would contribute greatly to the lowered blood pressure. However, as CANNON (1931) has pointed out, there is no direct evidence that the lowered metabolic rate is due to the adrenaline insufficiency. It might readily be due to the damage to the cortex. The fact that the administration of adrenaline increases the metabolism does not necessarily indicate its deficiency in Addison's Disease; the giving of thyroxine would produce a similar effect, and no one claims that it is deficient in Addison's Disease.

HEYMANS (1929), on the basis of his experiments on the carotid sinus, considers that the adrenals play an important role in regulating the cardiac rate and blood pressure. According to him the carotid sinus regulates the vagal cardiac tone, the neurovascular tone and the secretion of adrenaline from the suprarenals. Changes in these/

these functions take place in response to alterations in the blood pressure, to which the carotid sinus is exceedingly sensitive.

The fallacy attached to all these observations is that, of necessity, the animals are not under normal resting conditions and thus the validity of any conclusions drawn from such observations is dubious (CANNON, 1931).

The problem is very complex and, as yet, has not been solved. It will be appreciated that the view put forward in the past that the administration of adrenaline in cases of Addison's Disease is a form of "substitution" therapy might not be upheld at the present time. Although, of course, there is no doubt as to the efficacy of adrenaline as a form of therapy in many cases of Addison's Disease.

#### EPHEDRINE IN ADDISON'S DISEASE

In 1924 CHEN and SCHMIDT drew attention to the pharmacological actions of Ephedrine, the alkaloid obtained from Ma Huang, and suggested its possible use in hypotensive states such as shock and Addison's Disease. They record one case of the latter condition in which considerable improvement occurred after the administration of ephedrine. The blood pressure rose markedly, the pulse rate fell and symptomatically the patient was much better/



better. The efficacy of the drug in Addison's Disease was investigated by ROWNTREE and BROWN (1926) who, however, obtained very disappointing results. They found that, while there was a slight demonstrable increase in both the blood pressure level and the basal metabolic rate following the administration of ephedrine, these changes were seldom accompanied by significant subjective or objective manifestations of clinical improvement. The results which accrued did not compare in value to those gained by using the "Muirhead Régime."

MILLER (1925) found that the use of ephedrine in such cases tended to upset the patients rather than to help them.

### SUPRARENAL CORTICAL EXTRACTS

#### EARLY PREPARATIONS

As a result of work by SHAPIRO and MARINE in 1921 who demonstrated a definite thyroid - suprarenal relationship, it was suggested that suprarenal cortical extracts might be of extreme value in the treatment of Graves' Disease. In consequence of this and with, in addition, a growing body of medical opinion tending to the view that the morbid changes in the suprarenal cortex were responsible for Addison's Disease, it was natural that an endeavour should be made to prepare/

prepare a potent cortical extract. However, such a procedure was, and is, exceedingly difficult for various reasons. The glands, which contain comparatively little cortical hormone, undergo post-mortem autolysis very rapidly with consequent destruction of the autacoid. Also, it is difficult to remove from the cortical extract every trace of adrenaline, and as both it and its oxidation products are exceedingly toxic, it is essential that none should remain in the finished product. Many of the toxic effects and the failures that arose could be attributed to these difficulties, which were only partially appreciated by the early workers who attempted cortical extraction (BAUMANN, 1923, and BARLOW and SOLLMANN, 1925). It is apparent also from the present day knowledge regarding the intricacies of cortical hormone extraction that many of the preparations made in these experiments must have contained only an infinitesimal amount of the hormone in addition to many impurities.

One of the first extracts to be made, whose potency was clearly demonstrated, was that of HARTMAN and co-workers, who announced in October 1927 the preparation of an adrenaline-free substance from the suprarenal cortex that was capable of prolonging the life of adrenalectomised cats. This/

This was made by a process of salting out from watery extracts of the gland with sodium chloride. Although capable of prolonging life, it is unlikely that this contained any appreciable amount of the hormone (GROLLMAN - 1936). These workers proposed the name "Cortin" for the hormone of the adrenal cortex. A further more elaborate paper appeared in the following year giving their results in detail (HARTMAN et al. 1928). In 1930 the same workers described a case of Addison's Disease that was maintained alive for five months (i.e. up to the time of publication) by means of their extract "Cortin". The data show quite definitely the efficacy of their preparation. Not only was its administration followed by the revival of the patient from an apparently moribund condition, but a pronounced relapse occurred with a fall in the blood pressure and a rise in the blood urea on four occasions on which the cortin was reduced or discontinued. Recovery from these relapses occurred when full doses of cortin were administered. The improvement was obvious within a few hours and the patient was back to a normal condition in two to three days after the renewal of the cortical hormone therapy in adequate amounts (HARTMAN et al., 1930). The patient eventually died of pneumonia 238 days after the institution of treatment. An autopsy/

autopsy revealed that the adrenal cortices were almost completely atrophied, while the medullae were almost normal (HARTMAN and AARON, 1932).

Subsequent experience with some twenty patients confirmed the efficacy of their extract (HARTMAN et al., 1932 a.).

Coincidentally with this work by Hartman and his collaborators, several other teams of research workers were endeavouring to isolate potent suprarenal cortical extracts. The technique adopted differed considerably and the efficacy of the products was correspondingly varied. The fact that there were such groups of workers all endeavouring to solve the same problem led, not unnaturally, to many somewhat polemical papers. There was an apparent race for priority of publication or scientific achievement and in consequence observation was not always tempered with wisdom and sound judgment. It is therefore necessary to accept some of the claims advanced by these experimenters with a moderate degree of caution. Considerable doubt has recently been cast upon the efficacy of the original preparations made by Hartman (ROGOFF, 1934) on the grounds that several other workers, by using the salting out process detailed by Hartman, failed entirely to produce extracts with a clearly demonstrable activity. It is perhaps worthy of note that Hartman later discarded this method/

method and adopted that elaborated by Swingle and Pfiffner in which lipid solvents are used, as described below.

In the same month that Hartman first let it be known that he could prolong life in adrenalectomised cats with his cortical extract ROGOFF and STEWART (1927 and 1928) published a paper claiming similar good results in dogs with preparations made from the adrenals. They had previously demonstrated in 1925 to the American Physiological Society a series of adrenalectomised animals, some of which were benefited by the administration of cortical extracts. They did not, however, give any indication as to their method of preparation of the extract, which was made from the whole gland, and not from the cortex only. On their own admission, it contained varying quantities of adrenaline. They discounted the possibility of the adrenaline causing the prolongation of life produced by the extract because the injection of adrenaline alone, in greater quantity than could have been contained in any dose of extract injected, gave no such result. The authors were content to limit their claim to the fact that they had demonstrated the presence of an essential factor in the adrenal cortex, and not to having isolated this principle for/

for which they suggested the name "Interrenalin". In 1929 they asserted that the use of their preparation in Addison's Disease was beneficial and quoted seven cases in support of this (ROGOFF and STEWART, 1929). A critical analysis of their cases, however, leads to dubiety as to the diagnosis in most, if not all, of them, and, in any event, their results as set forth are not so convincing as are those of Hartman and his coworkers (HARROW and SHERWIN, 1934).

More encouraging results were, however, forthcoming from the work of SWINGLE and PFIFFNER, who, utilising different techniques, produced various extracts from the adrenal cortex. Their first preparation was in the form of a crude lipoid extract made by alcoholic-benzene extraction of bovine suprarenal glands. This, however, had two severe disadvantages in that it contained adrenaline and also on account of its nature was unsuitable for repeated injection, as it caused severe local irritation (SWINGLE and PFIFFNER, 1929 and 1931 a.). Despite these handicaps it was, however, able to prolong life in adrenalectomised cats and maintain them in apparently normal condition. It was found possible to eliminate the irritative factor by making an aqueous solution of an active fraction of this/

this crude extract (SWINGLE and PFIFFNER, 1930 a. and 1931 b.). This still contained a very small quantity of adrenaline, but was sufficiently active to maintain life in adrenalectomised cats. In addition, it was capable, when given in larger doses by daily injection, of reviving comatose animals that were prostrate and on the verge of death from adrenal insufficiency, and also of restoring them to an apparently normal condition and keeping them in a semblance of perfect health, (SWINGLE and PFIFFNER, 1930 b. and 1931 c.). It was but a brief time before these workers announced that they had managed to separate off the adrenaline entirely, leaving the potent cortical extract (SWINGLE and PFIFFNER, 1931 d.).

The significance of this announcement was appreciated at once and the interest aroused by it was profound. It was perhaps fitting that the physician who had the privilege of first reporting its use clinically should be Rowntree (ROWNTREE, GREENE, SWINGLE and PFIFFNER, 1930 and 1931). Extensive experience with the Muirhead Régime, extending over almost ten years, had convinced him that while the latter form of therapy was very good indeed in mild cases of Addison's Disease, it was useless in the crises of acute adrenal insufficiency that are such a feature of this condition. In his/

his own words there was a "great need for a more active cortical preparation that could be administered either subcutaneously or intravenously." Such a requirement was satisfied with the production of the cortical extract by Swingle and Pfiffner and Rowntree demonstrated its potency in no uncertain manner when he administered it to several cases of Addison's Disease in crises with eminently successful results. The following notes about the first recorded case are illustrative:

"The patient was in a state of complete collapse, and was given daily doses of 20 c.c. subcutaneously (1 c.c. being the equivalent of 30 gm. of fresh beef cortex). Within 36 hours a marked effect on appetite and strength were apparent. The patient, who had been so nauseated as to retain water with difficulty, now asked for weiners and sauerkraut and in lieu of the latter ate a double order of beef-steak with relish."

He found that in most cases it proved effective in 48 to 72 hours. It is worthy of note, however, that in several of the more acutely ill cases the patient also received large amounts of intravenous glucose salines, as Rowntree was convinced by this time that the treatment of this "dehydration" was a most important factor if a successful result was desired.

In 1934 ROGOFF reviewed the subject of cortical hormone therapy and came to the conclusion that very little was known beyond the fact that such/



such a hormone was present in the gland. He cast doubt upon the value of many of the extracts, and suggested that the beneficial effects attributed to them would be better credited to the physiological fluids that were usually administered concurrently. Such an opinion is held in many quarters at the present time with considerable justification.

In view of the fact that Rogoff and Stewart made their original preparations of "cortical extract" from the whole gland it may not be without interest to note a paper by PFIFFNER, SWINGLE and their associates in 1932 in which they point out that extracts obtained by them from the whole gland were much more potent than those prepared from dissected cortex. On an equivalent weight basis they found that the yield of cortical extract from the whole gland was eight to ten times that from dissected cortex (as measured in "dog units").

#### COMMERCIAL PREPARATIONS

The clinical demonstration of an apparently active adrenal cortical extract by Rowntree revealed clearly the potentialities of this preparation. Its production was immediately undertaken as a commercial proposition. With the passage of time and the increase in knowledge that experience has given, many varied modifications have been made on the methods of extraction, so that/

that now each firm has developed its own technique. Many of these are essentially the same, while others are widely different. It is a natural sequel that the efficacy of the different preparations should vary correspondingly, and even now there is controversy as to which is the best method of preparation and which is the best product. On the whole, the results with commercial preparations have not been nearly so good as those obtained with the extracts made in research laboratories (LOEB et al., 1935). The fact that many of the commercial extracts are produced in entirely different concentrations is an important feature which is not always appreciated by those who endeavour to estimate their relative values.

#### CHEMISTRY OF THE CORTICAL HORMONE

In 1934 KENDALL and his collaborators announced that they had managed to separate from the suprarenal cortex a crystalline fraction that possessed the essential physiological activity as demonstrated in adrenalectomised dogs and in patients with Addison's Disease. This crystalline preparation was a hydroxy aldehyde but had not actually been produced in the pure form or synthesised. In the following year (KENDALL et al., 1935) these workers were able to demonstrate the presence of two active fractions in the adrenal cortex/

cortex extracts. The first, which corresponded to the crystalline form already separated by them, was not able to restore a raised blood urea (in adrenal deficiency) to the normal level unless sodium chloride was administered along with it. However, this fraction was apparently concerned in the control of muscle activity, as in its presence muscles could respond to prolonged stimulation without the onset of the usual fatigue. The second fraction had little effect on the muscle activity but was capable on its own accord, without the addition of salt, of reducing the blood urea to the normal level and returning the adrenalectomised dog to an apparently normal state, except in so far as its capacity for exertion was concerned. The exact nature of these two active fractions and whether or not they were two separate entities was obscure. The most potent preparation of the adrenal cortex was one that combined the physiological properties of both fractions (KENDALL, 1935). Further more elaborate papers have been published by these workers in which they announce considerable progress in the elucidation of the exact structure of the fractions. (MASON et al., 1936. KENDALL et al., 1937 a. and 1937 b.).

Several other authorities have been studying the same problem and have made similar advances. LAQUEUR, REICHSTEIN et al. (1937) have succeeded in/

in isolating a crystallised compound in pure form which possesses the biological activity of the adrenal cortical hormone. They have suggested the name "Corticosterone" for this and have advanced a provisional formula for it. More recently still it has been reported that they have managed partially to synthesise it (STEIGER and REICHSTEIN, 1937). From the claims advanced it appears to be merely a matter of time before the detailed physical chemistry of the complex cortical hormone fractions is known.

#### CORTICAL EXTRACTS - RECENT APPLICATIONS

From the point of view of recent advances in the clinical application of our growing knowledge of this hormone ALLOTT (1936), in an elaborate investigation into the "Chemical Changes in the Blood in Addison's Disease" noted that in addition to having an appreciable general effect on the patients' clinical state the administration of cortical extracts caused definite changes in the blood chemistry. If given in adequate amounts the extracts bring down the high blood urea and potassium to normal levels, but have little effect in raising the blood sodium and chloride. These last, however, return to their normal level if salt is administered along with the cortical extracts. The use of either salt alone or/

or cortical extract by itself is not always sufficient to maintain the normal level of the blood chloride and blood sodium.

WILKINSON (1937) conducted an investigation on behalf of the Therapeutic Trials Committee of the Medical Research Council during the Years 1934 to 1937 into the value of suprarenal cortical extracts in the treatment of Addison's Disease. He noted the same changes in the blood chemistry during treatment as did Allott. He also found the extracts of great service.

"Suprarenal cortical extracts are of very definite value in the treatment of Addison's Disease if given in adequate dosage. It is the only treatment of any real value in acute crises.....Using these cortical extracts symptoms of asthenia, muscular weakness, digestive disorders (particularly nausea and vomiting and diarrhoea) are promptly relieved; appetite returns, weight increases, mental outlook improves, pigmentation slowly fades."

In all, nine cases are reported and, of these, three died in sudden crises with pyrexia. Five cases had excellent remissions and continued in practically normal health on a maintenance therapy of sodium chloride daily without any cortical extract. The sixth case died from an intercurrent condition during a period of steady remission that had been brought on by cortical extract therapy and had lasted for eight months.

FUNCTIONS OF THE ADRENAL CORTEX HORMONE/

FUNCTIONS OF THE ADRENAL CORTEX HORMONE

From the time that the presence of a cortical hormone was first shown, considerable investigation has been carried out in many laboratories into the physiological effects produced by it. In keeping with the general diversity of opinion that has always existed regarding matters relating to the adrenal, several widely divergent views have been advanced regarding the function of this hormone. Several of the theories have been put forward with very little justification and in consequence are unable to withstand a critical analysis. A few of the more important of the views expressed are given herewith.

1. GENERAL TISSUE HORMONE

HARTMAN, BROWNELL and LOCKWOOD suggested in 1932 that "Cortin is a general tissue hormone." They advance the view that the cortical hormone must have a generalised tonic effect throughout the body as it eliminates the lowered resistance to heat and cold and to mental and physical fatigue found in animals whose adrenals have been extirpated. In addition they postulate "a relationship to metabolism, growth, fluid balance and probably renal function." However, the arguments they advance are not very convincing, and while their hypothesis cannot be denied, it lacks demonstration/

demonstration, and one feels that the authors have avoided the main issue in that they fail to advance any theory as to the exact manner in which the hormone carries out this general tonic effect which they postulate. (HARTMAN et al. 1932 b.).

## 2. CONTROL OF CARBOHYDRATE METABOLISM

In the same year BRITTON and SILVETTE (1932) advanced the theory that the adrenal cortical hormone plays its part by controlling the carbohydrate metabolism, as they noted that both the blood glucose and the liver and muscle glycogen levels were reduced in adrenalectomised dogs and could be restored to normal by the administration of cortical extract. These workers showed that this effect was not due to any adrenaline present in the extract. Further, the decrease in sugar levels in the body did not occur in an animal in which extirpation of the adrenal medulla alone, without removal of the cortex, had been carried out. Their view as to the exact influence exerted by the suprarenal cortical hormone on carbohydrate metabolism is vague, but they apparently considered that the hormone is capable of increasing both the circulating and depot body sugar, and that the glands are primarily concerned in conjunction with other endocrine organs in the maintenance of normal glucose and glycogen levels in the body. They postulated/

postulated that the regaining of muscular energy at the end of a crisis in a case of Addison's Disease is due essentially to the restitution of the glycogen level in the muscles.

BRITTON and SILVETTE for some reason disregarded entirely the changes that occur in the levels of the inorganic ions in the blood in adrenal insufficiency and have thus laid open their theories to considerable criticism. Further, it has been pointed out that all adrenalectomised dogs do not have hypoglycaemia, and that hypoglycaemia may occur in adrenalectomised dogs that are receiving adequate amounts of cortical hormone. Several authorities believe that the hypoglycaemia is merely secondary to the profound anorexia that frequently occurs in cases of adrenal insufficiency, (HARROP, SOFFER et al., 1935).

In a more recent article SILVETTE (1934) stresses the shift in the water and chloride balance that occurs in adrenalectomised animals. This shift is manifested by an increased content of water in the liver and muscles and by a decreased concentration of chloride in the tissues. Silvette expresses the opinion that lack of hormone indirectly produces some fundamental condition or factor that is responsible for the shift in the water and chloride balance and this factor seems to be/



be a deficiency in glucose and glycogen.

### 3. CONTROL OF BODY FLUIDS

SWINGLE, PFIFFNER and their coworkers (1933) have suggested that "the function of the adrenal cortical hormone is the regulation and maintenance of a normal circulating volume of fluid within the vascular system. In the absence of the hormone fluid is continually lost from the circulation, presumably by transudation through the capillary walls, with the result that the adrenalectomised animal is unable to maintain his normal blood volume and eventually dies from circulatory collapse due to insufficiency of circulating fluid." They attributed the fall in blood pressure to the decrease in blood volume, and suggested that the nitrogen retention was in turn due to an impairment of renal function from the loss of filtration pressure caused by the falling blood pressure. They present convincing graphs showing a reciprocal relationship between the blood urea level and the blood pressure in the adrenalectomised dogs. These workers also, however, neglected entirely the alterations that occur in the inorganic ion concentrations in the blood.

### 4. CONTROL OF INORGANIC CONSTITUENTS

LOEB, ATCHLEY and their coworkers (1933 a.) and HARROP and his collaborators (1933 a.) next advanced/

advanced the view that one of the primary functions of the suprarenal cortical hormone is the control of the sodium and chloride metabolism and consequently of the balance and distribution of water. They suggested that the locus of this regulatory function of the cortical hormone is the kidney, and hold that the haemoconcentration that occurs is due to the loss of fluid through the kidneys mainly and not to its transudation into the tissue spaces, as postulated by Swingle and Pfiffner. They point out that the latter view is fundamentally wrong according to the modern conceptions regarding the transudation of fluid. In order that this may occur there must be either a good "head" of capillary pressure or a low osmotic pressure or the combination of both. In Addison's Disease, on the contrary, the capillary pressure is low and the osmotic pressure is actually raised owing to the haemoconcentration causing an increase in the percentage of plasma proteins.

NILSON (1937) accepts the above view, but in addition suggests that the cortical hormone probably "influences" the permeability of cell membranes. He bases this hypothesis on the fact that he noticed a definite sudden increase in the potassium content of the blood cells of adrenalectomised dogs at times when a crisis was imminent. This/

This change could not possibly be attributed to the introduction of newly formed cells as its rapidity of onset is too great and, in addition, the cell potassium level returns to normal within twenty-four hours during recovery from a severe crisis.

ZWEMER (1934) put forward the theory that the adrenal cortex has a regulative effect on the salt and water metabolism of the cell and that this effect is most marked in these tissues which are "primarily concerned with movements of fluid into, within and out of the body."

#### 5. CONTROL OF TISSUE OXIDATIONS

The most recent and by far the most complex theory is that advanced by VERZÁR and LASZT (1936 a and b). They claim to have demonstrated that many of the phenomena arising in an adrenalectomised rat can be abolished by the administration of lactoflavine phosphate as efficiently as by the use of cortical hormone. No effect occurs, however, if lactoflavine itself (and not the phosphate) is given. Verzář therefore postulates that the cortical hormone plays a major part in the synthesis of lactoflavine phosphate from lactoflavine in the body. In favour of this view he states that the cortical extract is inactive if the substrate (lactoflavine or Vitamin B<sub>2</sub>) necessary for/

for the synthesis of lactoflavine phosphate be omitted from the diet. This work has been corroborated by PIJCAN and OBERG (1937). Lactoflavine phosphate in combination with a protein forms the Yellow Respiratory Ferment of Warburg which is considered essential for proper tissue oxidation (WRIGHT, 1936).

The possibilities behind this work of Verzár are tremendous and if the claims advanced are correct the whole of modern opinion regarding adrenal function and dysfunction will require to be radically altered.

I myself have made an attempt to corroborate this work, but as yet with no success. Various chemical and technical difficulties have occurred the significance of which compels considerable doubt to be cast on Verzár's results. One of these major obstacles is the fact that there is no known way of synthesizing or procuring lactoflavine phosphate with any degree of certainty that the product is not one of the many isomers of this substance. A further problem of no mean proportion is the difficulty of preparing a diet which is completely free from lactoflavine. Both these preparations are essential in order that Verzár's claims may be corroborated, and if it is impossible to obtain them with the resources of many of the major research and commercial laboratories of the world at one's disposal, it is only natural that Verzár's work should be regarded with/

with considerable scepticism. Verzář himself is exceedingly vague regarding his method of preparation of these products.

The paper of Pijoan and Oberg cannot withstand even the slightest criticism. There are several apparent elementary mistakes and omissions in it, as for example the fact that they have administered a crystalline substance (lactoflavine phosphate) in solution and yet make no statement as to its strength. Their paper conveys the impression that they considered lactoflavine phosphate to be a liquid! Such brief information as they give in their paper records results that are too "perfect" to be accepted by a critical mind.

"There is considerable evidence to suggest that the adrenal glands may elaborate other hormones which have not yet been isolated and the impure extracts that are used for experimental purposes may contain variable amounts of these additional hormones."

(KEPLER, 1935).

#### THE ADRENALS AND SALT METABOLISM

It has long been known that salt is essential to life, but the manner of its regulation in the body has been obscure. It is only comparatively recently that a relationship has been appreciated between disturbances in the blood ionic concentration and morbid processes in the adrenals. At first the significance of these alterations was not realised but of late the presence of high or low figures in the blood chemistry values has been utilised/

utilised to indicate the necessity for the administration of less or more of the respective inorganic substances. In this way much has been done to advance the therapeutics of diseases associated with the adrenals and in particular that of Addison's Disease.

#### EXPERIMENTAL WORK

It is difficult to fix with certainty the individuals who first detected the relationship between disturbances in salt metabolism and adrenal cortical deficiencies. The fact that adrenalectomised dogs were benefited by the administration of sodium chloride was demonstrated first by SODDU in 1898. This observation appears to have been entirely neglected, and the connection between the adrenals and salt metabolism was apparently not again appreciated until STEWART and ROGOFF in 1925 noted that, whilst untreated adrenalectomised dogs lived 1 to 16 days after the operation, such dogs when given glucose salines lived 6 to 34 days. The salines were given with a view to increasing the excretion of any toxic substances that might accumulate in the blood as a result of the adrenalectomy.

This was perhaps a somewhat fortuitous observation but in the following year BANTING and GAIRNS (1926) conducted a comprehensive and elaborate/

elaborate investigation into the chemical changes that occur in the blood in cases of suprarenal insufficiency. This latter was artificially produced by removing the adrenals from dogs. These observers noted the definite anhydraemia and the consequent increase in blood concentration that occurs. They observed a well marked rise in the nitrogenous bodies in the blood accompanied by a fall in the chlorides. Both of these changes could be obviated by the administration of salines, but the former only if a diuresis occurred. This led these observers to suspect that in adrenal insufficiency there was some impairment of renal function, a conclusion which was prompted by the fact that an appreciable fall in the excretion of nitrogenous bodies in the urine was noted. The urinary chloride excretion varied widely but it was observed that the dogs were able to excrete nitrogenous and inorganic waste products until the last stage before death, (LUCAS, 1926). Several of these results were confirmed by SWINGLE (1926) who recorded in addition an appreciable fall in the blood sugar. He suggested that the comparative renal failure occurring in cases of adrenal insufficiency gives rise to an acidosis that eventually causes death.

COREY (1926) demonstrated clearly that the oral/

oral administration of fluid to adrenalectomised cats served to prolong life. He noted also that the addition to the fluid of certain substances such as sodium acetate maintained life still longer. The use of sodium chloride or glucose produced by far the best effects. Many other experimenters obtained similar results about this time, using adrenalectomised animals as the subjects for their work. A paper worthy of note is that of BAUMANN and KURLAND (1927), who observed that the sodium in the blood serum of adrenalectomised rabbits was decreased by 15 and the chloride by 9 per cent, while the potassium and the magnesium were respectively 42 and 23 above normal. They also remind their readers of the known fall in blood chloride concentration that occurs in cases of severe burns in which the adrenals usually exhibit marked pathological features. They suggest that the beneficial effects resulting from forcing fluids in such cases are probably due to their sodium chloride content. They make no mention of Addison's Disease, however. MARINE and BAUMANN (1927) suggested that sodium was the important ion as they found that they could prolong life in adrenalectomised cats almost as long by giving sodium acetate as by giving sodium chloride. They also stressed the importance of a good fluid intake.

CLINICAL/



CLINICAL APPLICATIONS

The next and most important step was the application of this knowledge to clinical medicine by LOEB (1932) who made a complete analysis of the inorganic bases of the blood serum in three patients suffering from severe Addison's Disease. He found that the sodium was very low, the contents recorded being 108, 109 and 131 millimoles per litre (normal is about 138). Conversely, the serum potassium was greatly raised, 8.7 and 7.1 millimoles per litre (normal 4.8). The chlorine was reduced also (70 and 73 millimoles per litre as against a normal value of 105). One of the patients was given 12 - 15 g. Sodium Chloride daily and after one week of this therapy the patient became almost entirely free from symptoms. Simultaneously with this, the abnormalities in the patient's blood chemistry practically disappeared. No preparation of the suprarenal cortex was administered to this patient. LOEB, working in conjunction with ATCHLEY, BENEDICT and LELAND (1933) now passed on to make electrolytic balance studies in dogs before and after adrenalectomy with a view to determining the processes involved in bringing about these changes noted by him. He found that the removal of one adrenal caused no alteration in the various balances. However, when both adrenals were/

were removed there was an immediate fall in the blood sodium concentration which was apparently brought on by an increased excretion of sodium in the urine, as both the concentration and the total amount of sodium in the urine were increased. This increase in concentration of sodium occurred despite the fact that the urine volume was itself often considerably augmented. Loeb also noted that there was a decrease in the chloride and bicarbonate concentrations in the blood which together were approximately equivalent to the fall in blood sodium. Coincidentally, there was an increased excretion of chlorine in the urine but the extent of this addition was much less than that which could be accounted for by the increase in sodium. Conversely both the potassium and non-protein nitrogen were increased in the blood following bilateral adrenalectomy. Loeb discounted the hypothesis that the nitrogenous retention was due to the fall in blood pressure causing failure in renal filtration as he found that the rate of water excretion by the kidney was, if anything, increased after adrenalectomy (SWINGLE et al., 1933). Loeb then advances a very sound discussion as to the mechanism of the sodium loss. He puts forward three possible explanations. In the first he suggests that the fixed base has been called on to participate/

participate in the excretion of large amounts of acid as in diabetic acidosis. However, he found no evidence of any increase in acid radicles in the blood and no increased excretion of ammonia in the urine. The next view postulates that the sodium loss is secondary to the loss of water through the kidney, but this was discounted by the fact that the concentration of sodium in the urine was notably increased and hence the relative loss of sodium after adrenalectomy was much more than that of water. In any case, as Loeb points out, if one accepted this view one would expect an increase rather than a decrease in the sodium content of the blood. In consequence, Loeb falls back on a third theory which is apparently unassailable, namely that the adrenal glands control the sodium ion concentration in the blood and that the loss of sodium is of a primary nature.

The results and conclusions attained by Loeb and his fellow workers were all corroborated by HARROP, SOFFER and their collaborators (1933), who went further and showed that in adrenalectomised dogs not only did these changes occur in the blood ionic concentration but that the figures were restored to the normal levels by the administration of cortical extracts.

The final link that connected the morbid process/

process in the adrenals in Addison's Disease and an upset in salt metabolism was provided by LOEB (1933) when he reported in full the progress of his case of Addison's Disease to whom he gave sodium chloride. No hormonal treatment was administered (see above). The patient continued in good health with a gain in weight and an increase in blood pressure. She was discharged from hospital and told to take 7 g. of salt daily in addition to her ordinary diet. All went well for five months and her blood chemistry figures remained at the normal level. However, about this time she noticed slight puffiness about her face and was advised to discontinue her sodium chloride and to take a low salt diet. Within two days she collapsed with extreme weakness and persistent vomiting. She lost almost seven pounds in one week, her blood pressure fell from 122/80 to 86/60 and an examination of her blood revealed a marked fall in her blood sodium and chloride with an increase in her potassium and non-protein nitrogen. There was also a slight fall in her fasting blood sugar. The patient was immediately given sodium chloride by mouth and by enema. She improved at once and was discharged from hospital eight days later with a normal blood chemistry, a gain in weight of four pounds and a blood pressure of 122/80. Similar results were obtained in the same/

same year from another patient (LOEB, ATCHLEY et al. 1933 b.).

HARROP and his colleagues (1933 b.) went even further and demonstrated that in several patients who were receiving cortical extract it was possible to stop this hormone therapy and maintain them in normal condition by giving them sodium chloride. Each of these patients had previously been unable to do without the cortical extract. These workers went so far as to suggest that the use of a salt free diet was of the optimum diagnostic value in determining the presence of Addison's Disease and especially in indicating the danger of a relapse. In another paper in the same year HARROP and his fellow workers (1933 a.) conclude that although sodium chloride is exceedingly beneficial, the cortical hormone, at least in minimal amounts, is indispensable.

LOEB, ATCHLEY and STAHL (1935), working on adrenalectomised dogs, corroborated this opinion about the indispensability of the cortical hormone and show that if the hormone is completely withdrawn it is impossible to maintain the blood sodium at normal levels even with massive doses of salt. Conversely, they state that they found that by giving cortical extract of adequate potency it was possible to withdraw all salt from the diet without causing/

causing a fall in the blood sodium or an increase in the urea.

As previously noted, KENDALL and his associate workers in 1935 demonstrated the presence of the two active fractions in the adrenal cortex extracts. One of these was not capable of restoring the raised blood urea in cases of adrenal insufficiency to normal figures unless sodium chloride was administered along with it in adequate amounts. This work served to strengthen further the evidence in support of the relationship that was being claimed between the function of the adrenal glands and salt metabolism.

THE USE OF SODIUM BICARBONATE IN CONJUNCTION WITH  
SODIUM CHLORIDE

In the same year a still further advance was made in the knowledge regarding adrenal deficiency and disturbance in salt metabolism. This was the production of demonstrable evidence that adrenalectomised dogs could be maintained in apparently normal condition over long periods without the use of any suprarenal gland preparation if they were administered adequate amounts of sodium chloride in conjunction with sodium bicarbonate. This observation was made practically simultaneously by two quite independent sets of workers who arrived at the same final conclusion after approaching the problem along two quite separate paths.

HARROP/

HARROP, SOFFER, NICHOLSON and STRAUSS (1935) were led to try the combination of the two salts through the observation that the sodium ion was excreted in the urine in greater equivalent amount than the chloride ion. In consequence the fall in plasma concentration of the sodium ion is much greater proportionally than that of the chloride ion. This suggested the use of other sodium salts in addition to the chloride. They therefore added sodium bicarbonate and found that they could maintain their dogs in perfect condition without the use of any suprarenal preparation. These workers noted that a fall in plasma sodium is accompanied by haemoconcentration, while a fall in plasma chloride gives rise to anorexia and eventually to a hypoglycaemia. They bring forward evidence to show that the hypoglycaemia is not due to the cortical hormone deficiency as it occurs in dogs which are receiving adequate amounts of the cortical hormone. They offer the explanation that it is secondary to the anorexia.

ALLERS (1935) independently, by direct analysis of the blood, came to the same conclusion as Harrop and his colleagues regarding the necessity of providing more sodium than was possible by giving sodium chloride itself. He showed that dogs which received large amounts of sodium chloride for/

for a few days had a bicarbonate reserve below normal. He therefore gave the dogs sodium bicarbonate in addition to sodium chloride and found that they thrived, put on weight and remained in excellent condition without the administration of any suprarenal cortical therapy. It was later found that the administration of sodium citrate instead of sodium bicarbonate was better, as it did not have such an irritating effect on the stomach (ALLERS and KENDALL, 1937). NILSON (1937) conducted balance studies on adrenalectomised dogs and found that they required a much greater positive balance of sodium and chloride than did intact animals and that they were less able to maintain a uniform daily balance.

#### THE ADRENAL CORTEX

##### AND THE BLOOD POTASSIUM CONCENTRATION

In the course of their examination of the blood of adrenalectomised cats and rabbits BAUMANN and KURLAND (1927) noted that the serum potassium was raised by almost 42%, but they did not correlate this with any of the clinical features in adrenal insufficiency.

In 1931 HASTINGS and COMPERE, using adrenalectomised dogs, were able to confirm the above observation. They pointed out that the high terminal/



terminal concentration of serum potassium which they found in their experiments was approximately the same level as that which resulted in the death of dogs when potassium chloride was injected intravenously. They therefore put forward the view that this high concentration of potassium might be of significance when considering the cause of death following the functional or surgical removal of the suprarenal glands. This claim has since been proved to have been prophetic.

In the following year both LOEB (1932) and GREENE and his collaborators (1932) noticed a similar though less marked rise in the blood potassium in patients who suffered from Addison's Disease. HARROP and his coworkers (1933 a.) next demonstrated that after the discontinuance of injections of cortical hormone into suprarenalectomised dogs there was a rapid urinary loss of sodium and chloride, with retention of potassium. The re-administration of the hormone reversed these changes. It was soon appreciated that while the increase in potassium was present in Addison's Disease when a crisis was imminent there was often no abnormality in the ionic pattern of the blood in the chronic or stationary period of the illness (SNELL, 1934).

While discussing the rise in blood potassium  
ZWEMER/

ZWEMER (1934) suggested that it might be due either to an attempt on the part of the body to maintain the osmotic pressure that would drop owing to the fall in blood sodium and chloride, or that it was due to an increased permeability of the tissue cells to intracellular potassium with inadequate excretion through the kidneys. He found that the administration of cortico-adrenal extracts restored the potassium concentration to a normal level (ZWEMER and SULLIVAN, 1934).

HARROP, SOFFER and their coworkers (1935) reiterated the first of the above theories propounded by Zwemer and demonstrated reciprocal variations in the levels of sodium and chloride on the one hand and urea and potassium on the other. NICHOLSON and SOFFER (1935) noted cardiac arrhythmia in adrenalectomised dogs the nature of which they interpret as being a slow auricular fibrillation. They attributed this to the high concentration of potassium in the blood as they found it possible to produce a similar arrhythmia by injecting potassium into normal dogs. Their interpretations, however, are open to argument. The electrocardiograms with which they illustrate their paper, instead of showing the slow auricular fibrillation which they claim, exhibit depression of the auricles with a form of atrio-ventricular rhythm/

rhythm. There is no irregularity in rhythm to be seen in the cardiogram they present. It is of interest to note, however, that these cardiographic findings in their experimental animals are very similar to those that have been demonstrated in some patients with Addison's Disease by DELIUS and OPITZ (1935). Other workers who investigated the electrocardiographic changes in Addison's Disease also failed to find auricular fibrillation in any case, but noted a low voltage with prolongation of the S - T interval (SAMPAYO et al., 1934).

Several workers next demonstrated that the administration of potassium salts to normal individuals caused an increased urinary excretion of sodium, particularly if the sodium intake was high, (KEITH and BINGER, 1935, and MACKAY and BUTLER, 1935).

#### TOXIC EFFECTS OF POTASSIUM

In the following year ALLERS, NILSON and KENDALL (1936) noticed that adrenalectomised dogs which had been maintained successfully with sodium chloride and sodium bicarbonate were very sensitive to small amounts of potassium in their diet. If 0.5 gm. of potassium was added to the daily diet of such dogs a state of crisis was produced like that of acute adrenal insufficiency. This occurred even when the animals were receiving liberal/

liberal supplies of the sodium salts. ZWEMER and TRUSZKOWSKI (1936) obtained similar results in adrenalectomised cats and rats.

The significance of these results regarding the possible toxic effect of potassium was at once appreciated and WILDER, SNELL and their coworkers (1936) immediately investigated this problem from the clinical aspect. They were able to demonstrate clearly the influence that potassium had on the progress of a case of Addison's Disease. The administration of a high potassium content in the diet tended to precipitate a crisis, while conversely, the administration of a diet with a low potassium content permitted the restriction of sodium salts without embarrassment in patients who had formerly required large quantities of sodium salts daily. Further, it was found that patients otherwise requiring cortical hormone could be maintained in good condition by the administration of sodium salts only, if the potassium intake was restricted. Another paper by the same authors (WILDER, SNELL et al., 1937) elaborated this matter still further and gave an optimum diet containing the minimal amount of potassium. VICTOR in the same year (1937) pointed out the difficulties of preparing palatable diets of this nature/

nature and described such preparation in detail. By means of special cooking methods that she had evolved she was able to reduce considerably the potassium content of various common food-stuffs without rendering them unappetising.

ZWEMER and TRUSZKOWSKI (1936) in their paper attribute most of the biochemical and functional changes that occur to the high blood potassium and bring forward experimental data to support their view. Thus, they point out that the low sodium could be ascribed to the diuresis due to the high potassium. Similarly the low blood sugar could be attributed to the high potassium as cases had been reported in which the injection of potassium gave rise to a fall in the blood sugar. They also remind their readers that muscular asthenia had long been associated with high blood potassium and in itself probably gave rise to the circulatory disturbances that occur in adrenal deficiency. They then discuss the lesions found in the kidneys in this latter condition and point out their similarity to those that are found in potassium poisoning. They suggest that these might readily play a part in bringing on the uraemic stage of late adrenal insufficiency. Finally they recommend that

"in the therapy of Addison's Disease it might be of greater importance to eliminate potassium/

potassium from the diet than to administer high doses of sodium chloride, and probably the best results could be expected if both these measures were used."

In 1937 SANDBERG, PERLA and HOLLY made some interesting balance studies of mineral salts. They found that in adrenalectomised rats there was a drop in the potassium intake and in the percentage retained, the absolute value of potassium excreted in the urine remaining constant. They do not attempt to explain why an increased blood potassium occurs if this is the case, but apparently one must postulate that it arises from the intracellular potassium which is probably released into circulation. RICHTER and ECKERT (1938), who have made a study of the mineral metabolism of adrenalectomised rats by the "appetite method", have noted, on the other hand, a slight increase in the intake of potassium after adrenalectomy. This is, however, in keeping with a general increase in appetite that occurs, and is much less than the increase that occurs in the other radicles such as sodium.

A most important recent work that throws considerable light on the part played by Cortin in the control of potassium metabolism is that of INGLE, NILSON and KENDALL (1937). In order to dissociate the probable influence of cortin on the tissues of the rat from its possible action on the kidney, the effect/

effect of cortin was determined on adrenalectomised rats after nephrectomy. Cortin did not prevent the increase in the amount of blood urea and did not change the concentration of sodium or chloride which remained within normal limits. It had little effect on the blood sugar. However, it produced a definite lowering of the blood potassium, which had risen slightly after the double operation of adrenalectomy and nephrectomy. Ingle and his co-workers therefore postulate that the cortin has a definite effect on the distribution of potassium between the tissues and the blood serum. They suggest that cortin influences the permeability of cell membranes.

#### THE ADRENAL GLANDS AND VITAMIN C

The earliest work that demonstrated a connection between the adrenal glands and Vitamin C was that of McCARRISON (1919), who observed adrenal hypertrophy in Vitamin C deficiency in guinea pigs. IWABUCHI (1922) made a histological study of the adrenals in this condition. He found that the lipoids were diminished in the zone fasciculata and increased in the zone reticularis, while the medulla had almost completely lost its chromaffinity.

In 1928 SZENT-GYÖRGYI isolated from the cortex of adrenal glands, as well as from cabbages and oranges/

oranges, a tissue respiratory factor which was a "six-carbon sugar acid". To this he gave the name "Hexuronic Acid". In 1932 WAUGH and KING (1932 a and b) reported the identification of Vitamin C and it was speedily shown to be identical in structure and all its physical chemical properties with Hexuronic Acid, (SVIRBELY & SZENT-GYÖRGYI, 1932).

HARRIS and RAY (1932) and ZILVA (1932) fed the cortex of ox-adrenals to guinea pigs and thereby established the antiscorbutic activity of the tissue. The former workers established that 2 gm. of raw adrenal cortex corresponded in activity with 6 c.c. of orange juice.

The early observation that the cortex of the suprarenals contained large amounts of "Hexuronic Acid" led to much speculation as to a possible relationship between this vitamin and the functions of the cortex. These speculations were prompted by the belief that the suprarenal medulla did not contain hexuronic (ascorbic) acid (SZENT-GYÖRGYI, 1930). However, it was soon demonstrated that other organs in the body, including the adrenal medulla (HUSZAK, 1933), contained appreciable amounts of this acid. In consequence, it was felt that such a wide distribution eliminated the possibility/



possibility of a specific relationship between the Vitamin and the cortical hormone. Nevertheless, about 1930 there were recorded several cases of Addison's Disease which were treated on an empirical bases with Ascorbic Acid. Little benefit was noted (SZENT-GYÖRGYI, 1930).

VARS and PFIFFNER (1933) tried to determine some connection between the adrenal gland and the synthesis or metabolism of Vitamin C. They could find no evidence to support this possibility.

The administration of cortical extracts by injection in large amounts failed entirely to allay the onset of scurvy in guinea pigs that were fed on a

Vitamin C - free diet. LOCKWOOD and HARTMAN

(1933) reported a slight extension of the survival period when guinea pigs which were on a Vitamin C - free diet were given cortical hormone extracts, but GROLLMAN and FIROR (1934) and SVIRBELY (1935) failed to corroborate this.

KING (1936), who discusses in detail all the known physiological functions of Vitamin C, suggests that any function in the adrenal is general rather than specific. He obviously does not consider the presence of ascorbic acid in the adrenal of any particular significance.

#### VITAMIN C AND THE PIGMENTATION OF ADDISON'S

##### DISEASE

WILKINSON and ASHFORD (1936) using the test described/

described by HARRIS and RAY (1933), claimed that they could demonstrate Vitamin C subnutrition in three cases of Addison's Disease. The degree of undernutrition was said to run parallel to the severity of the illness. SIWE (1935) had already obtained very similar results and had noted the low excretion of ascorbic acid that was present in patients with Addison's Disease. Wilkinson and Ashford put forward a tentative suggestion that the pigmentation might be due to deficiency of ascorbic acid. This whole matter will be discussed in detail in a later paper on the pathological changes that occur in Addison's Disease and is outwith the scope of the present thesis. However, it is of exceptional interest to quote a statement written by SZENT-GYÖRGYI in 1930 to the effect that

"Hexuronic acid completely inhibits the formation of pigment in all systems in which a melanoid pigment is formed through the oxidation of a phenol.... The absence of hexuronic acid in Addison's Disease could thus give a clear explanation of the mechanism of formation of pigment."

Wilkinson and Ashford, however, failed to note any appreciable change in the pigmentation of their patients during a course of intensive oral ascorbic acid therapy. HOFF (1936), however, states that he was able to decrease appreciably the pigmentation of Addison's Disease by oral and intramuscular ascorbic acid therapy. This was my own experience/

experience in two cases of Addison's Disease. In one of these the oral administration of 300 mgm. of Ascorbic Acid daily for a period of two weeks was accompanied by such an obvious diminution in the pigmentation on the patient's face that many caustic remarks were made by fellow patients regarding the subject's ablutionary habits in the past.

#### MISCELLANEOUS THERAPEUTIC MEASURES

##### IN ADDISON'S DISEASE

In addition to the more generally recognised forms of treatment in Addison's Disease which have been given in detail in the preceding pages, there are one or two other forms of therapy which have been attempted in the past. These were usually of little benefit and somewhat naturally have passed into desuetude.

##### THE USE OF ANTERIOR PITUITARY

The demonstration by KRAUS (1927) of regressive changes in the chromophil cells of the anterior lobe of the pituitary in cases of Addison's Disease suggested a possible pituitary functional defect in this condition. The experimental work by MARTIN (1932), who found that the cytological picture in the pituitary changed following adrenalectomy in rats, helped to strengthen this view. In consequence WILDER (1934)/

(1934) administered an extract of the anterior lobe of the pituitary to two cases of Addison's Disease who were being already treated by suprarenal cortical extract and abundant sodium chloride. He found that the patients required less salt during this therapy, and that they were very much improved symptomatically, and, in consequence, suggested that anterior pituitary might be a good supplementary form of treatment. He was, however, unable to produce any objective evidence in favour of this combination, and the anterior pituitary therapy has never been used to any extent.

#### RADIATION OF THE ADRENALS

The first recorded case of radiation of the adrenal glands as a therapeutic measure for Addison's was that of GOLUBININ (1905). This case was apparently due to tuberculous invasion of the glands in a man aged 27, and after fifty exposures in sixty days to small roentgen-ray doses (strength not stated) striking clinical improvement was noted. This was evidenced by an amelioration of the general condition, increase in weight and disappearance of the cutaneous pigmentation. WETTERER (1908) also reported a case of Addison's Disease in which improvement is said to have occurred following X-Ray therapy. The use of deep X-Ray therapy in Addison's Disease was not taken/

taken up with any enthusiasm, and no other recorded cases in which it was used have been found in the literature. Considerable work has been done on the effect of radiation on the adrenal cells in experimental animals. This served to show that, in place of stimulating the glands, the rays frequently caused moderately severe toxic changes, particularly in the cortex. However, the usual doses necessary to bring about such a pathological picture were well beyond the therapeutic range for human beings and smaller doses caused little in the way of functional benefit. Two excellent reviews of the subject of therapeutic X-Ray Radiation of the Adrenal Glands have been made by DESJARDINS (1928) and GORDON (1930). Both these authors are, however, rather non-committal in their final conclusions and neither is apparently in favour of Deep X-Ray Therapy as a method of increasing the function of the adrenal cortex.

THE THERAPY OF ADDISON'S DISEASE

AS REPORTED IN EDINBURGH

FROM THE FILES OF THE EASTERN GENERAL HOSPITAL

INTRODUCTION

An analysis has been made of every case admitted as suffering from Addison's Disease to any public hospital in Edinburgh since 1927. For this purpose the

P A R T II

Infirmary, Edinburgh, and the General Hospital, Edinburgh.

THE THERAPY OF ADDISON'S DISEASE

Eastern General Hospital, Edinburgh, 1927 - 1938

IN EDINBURGH

as reported in the files of the Eastern General Hospital, Edinburgh

carefully examined 1927 - 1938

up and it has been possible to trace the ultimate history of every case diagnosed during the period 1927 - 1938. During this time 40 cases of Addison's Disease were treated.

Over this length of time 1070 cases of Addison's Disease admitted to these hospitals. In 1927 the clinical diagnosis was that of Addison's Disease. Of these, it has been possible to trace the ultimate history of 40 cases of Addison's Disease. In that year 10 cases of Addison's Disease were treated. In 1928 10 cases of Addison's Disease were treated. In 1929 10 cases of Addison's Disease were treated. In 1930 10 cases of Addison's Disease were treated. In 1931 10 cases of Addison's Disease were treated. In 1932 10 cases of Addison's Disease were treated. In 1933 10 cases of Addison's Disease were treated. In 1934 10 cases of Addison's Disease were treated. In 1935 10 cases of Addison's Disease were treated. In 1936 10 cases of Addison's Disease were treated. In 1937 10 cases of Addison's Disease were treated. In 1938 10 cases of Addison's Disease were treated.

THE THERAPEUTICS OF ADDISON'S DISEASE  
AS ADOPTED IN EDINBURGH  
DURING THE PERIOD 1927 - 1938

INTRODUCTION

An analysis has been made of every case diagnosed as suffering from Addison's Disease entering any public hospital in Edinburgh since 1927. For this purpose the records of these hospitals (Royal Infirmary, Edinburgh, Leith Hospital, Western General Hospital, Northern General Hospital and Eastern General Hospital, Edinburgh) have been scrutinised and the protocols of any likely case carefully examined. All cases have been followed up and it has been possible, with one exception, to trace the ultimate history of every patient who was diagnosed during the period 1927 to 1938 as suffering from Addison's Disease.

Over this lapse of time there were in all 45 cases admitted to these hospitals in which the clinical diagnosis was that of Addison's Disease. Of these, it has been considered advisable to exclude 10 cases as not being true cases of Addison's Disease, in that their clinical features, their future progress or their autopsy findings did not substantiate the diagnosis made. Twenty-two of the remaining 35 cases were autopsied and in each instance the post-mortem examination revealed such pathological changes in the adrenal glands that the diagnosis/

diagnosis of Addison's Disease has been considered justifiable. As far as possible (16 out of the 22 cases) the macroscopic and microscopic specimens from these patients have been examined and a full report of the various pathological findings will be issued in a further paper on "The Pathological Changes in Addison's Disease," that is being prepared by myself. Only the relevant pathological details have been given in this paper. In 13 cases it has not been possible to corroborate from the pathological viewpoint the diagnosis of Addison's Disease either because no post-mortem examination was held (7 cases) or because the patient is still alive (6 cases).

In this paper I have reviewed the therapeutic measures adopted in these thirty-five cases. I have selected several illustrative cases to show the effect, or non-effect, of the various forms of treatment.

The case histories of these patients have not been presented in full, and no attempt has been made to introduce or discuss any but those significant clinical features the alterations in which could be correlated with the treatment. Also, it has not been considered advisable to enter into any discussion as to the reasons for accepting or rejecting the diagnosis made in the various cases. It was felt/



felt that the introduction of such details was entirely outwith the scope of this paper which is concerned solely in the therapeutic aspects of Addison's Disease. The case notes will be recorded in full in a further paper on "The Clinical Aspects and Diagnosis of Addison's Disease" which is also in preparation.

In the following records the cases have been presented wherever possible in a graphical or tabular form in order that the essential facts pertaining to the results of the different forms of therapy employed may be more readily seen (Tables I and II). It has been considered advisable to put forward the cases in a chronological order as far as possible. A definite notation has been adopted in the numbering of these cases. Any whose number has the prefix "A" is one which was autopsied and proved to be an Addison's Disease. Those with the prefix "B" have not been autopsied, either because they are still alive or because there were no facilities. Those with the prefix "C", which have not been discussed to any length in this paper, were autopsied and were shown to be suffering from some other condition than disease of the suprarenal glands, although diagnosed clinically as being Addison's Disease.

Since 1936, owing to the kindness of the  
Physicians/

## T A B L E I.

Showing the relevant details of all cases in which the diagnosis of Addison's Disease has been accepted.

## (a) Completed Cases.

Year first seen	Case No.	Name	Age	Sex	Clinical Diagnosis	Pathological Diagnosis. i.e. Type of Addison's Disease	Specific Treatment adopted	Survival Period.		Remarks
								From 1st. symptom suggestive of Addison's Disease	From start of specific therapy	
1928	B.3	J.P.	31	M	Addison's Disease	-	None	4 years	- (3 years after admission)	Died at home of "intense weakness."
	B.4	W.S.	55	M	Addison's Disease	-	Ephedrine gr. $\frac{1}{4}$ b.i.d.	? It has not been possible to trace this patient	? ?	Ephedrine helped general condition. No effect on the B.P.
	A.1	C.G.	24	F	Addison's Disease	Tuberculous	Adrenaline M.v. H.I. 2-4 hourly	3 months	3 weeks	Therapy had no effect. Patient died in "crisis".
	A.2	W.Y.	34	M	Addison's Disease	Tuberculous	Adrenaline M.v. H.I. Pituitrin 0.5cc. H.I.	3 months	1 day	Therapy only used terminally. No effect. Patient died in "crisis".
	A.23	Mrs. I.C.	50	F	Gastric Carcinoma	Tuberculous	None	3 months	- (1 month after admission)	B.P. 112/76. Heroin gr. 1/6 given. Patient became much worse next day and died 3 days later.
1930	A.4	C.D.	26	F	Undiagnosed.	Tuberculous	None	"months"	-	Developed empyema of gall bladder. Died immediately after a cholecystectomy.
	A.5	C.G.	40	M	Addison's Disease	Tuberculous	Ephedrine, Adrenaline & Whole Gland Supra-renal tablets by mouth. Pitressin 1.0cc. daily	2 years	2 weeks	Modified "Muirhead régime". Steady downhill course. Died in "crisis". Morphine on day before death.
	A.6	A.P.	58	M	Undiagnosed	Tuberculous	None	?	-	Admitted moribund. No history obtained.

Year first seen	Case No.	Name	Age	Sex	Clinical Diagnosis	Pathological Diagnosis. i.e. Type of Addison's Disease	Specific Treatment Adopted	Survival Period.		Remarks
								From 1st. symptom suggestive of Addison's Disease	From start of specific therapy	
1930	A.7	R.C.	53	M	Gastric Carcinoma	Tuberculous	None	8 months	-	Operated on for gastric carcinoma. Died immediately after operation.
	A.8	Mrs M.R.	22	F	Undiagnosed	Tuberculous	Adrenaline M.vii. H.I. Digitalis gr. 1/50.	2 years	Hours	3 months pregnant. Admitted moribund.
1931	B.6	G.B.	43	M	Addison's Disease	-	Whole Gland Suprarenal tablets. Adrenaline. Eucortone, 470cc.	2½ years	5 months	Eucortone delayed but could not prevent death. Other forms of therapy used had no appreciable effect.
	B.7	Mrs G.G.	47	F	Addison's Disease	-	Cortical Extract, 13cc. in 8 days.	3½ years	2 weeks	Only minute doses of cortical extract were given. No effect. Died in "crisis" 3 days after discharge from hospital
	A.25	M.H.	17	F	Addison's Disease	"Primary Atrophy"	Eucortone 1057cc. in 4 months. Suprarenal tablets.	8 months	4 months	Eucortone produced definite improvement, both in B.P. and clinically. Died in "crisis". (Graph I.)
1932	A.9	Mrs C.H.	30	F	Addison's Disease	Tuberculous	Intravenous salines. Adrenaline 0.5cc. 4 hrly.	10 weeks	7 weeks	Much benefitted by the empirical use of salines and adrenaline. Had several "crises" and eventually died in a "crisis".
	A.10	W.S.	34	M	Addison's Disease	Tuberculous	Eucortone 68cc. in 12 days.	7½ months	12 days	The dose of cortical ex. used in this patient is hopelessly inadequate, as judged by present standard. Patient died in a "crisis". (Graph II.)

Year first seen	Case No.	Name	Age	Sex	Clinical Diagnosis	Pathological Diagnosis. i.e. Type of Addison's Disease.	Specific Treatment adopted	Survival Period.		Remarks
								From 1st. symptom suggestive of Addison's Disease	From start of specific therapy	
1932	A.12	Mrs J.M.	32	F	Addison's Disease	Tuberculous	Eucortone 990cc. in 3 months. I.V. salines at "crisis". Adrenalin M.viii b.i.d.	3 years	3 months	Eucortone and adrenaline had little effect on the B.P. I.V. salines appeared to be as effective as Eucortone at the "crisis". Patient died in a "crisis". (Graph III.)
1933	A.13	T.O.	35	M	Lymph-adenoma	Tuberculous	Pituitrin 0.5cc. 4 hourly	5 months	1 day	Patient critically ill when admitted. Given morphine for hiccough. Died in "crisis" next day.
	A.14	Mrs M.F.	43	F	Addison's Disease	Tuberculous	Eucortone 630cc. in 6 weeks. (Max. dose 50cc. in 1 day. Suprarenal tablets	14 months	8 weeks	Cortical extract therapy had no effect. (Graph IV.)
	B.10	W.M.	65	M	Addison's Disease	-	None	2 years	- (20 months after admission)	Died at home of "extreme exhaustion" after a steady downward course.
	B.11	A.E.	44	F	Addison's Disease	-	Eucortone 37cc. in 16 days. I.V. saline.	1 year	3 weeks	Eucortone had no effect on either B.P. or on general condition. Patient left hospital on own accord and died in "crisis" on following day.
1934	A.15	Mrs I.S.	25	F	Addison's Disease	Tuberculous	None	?	-	Admitted moribund. No history obtained.
1935	B.12	Mrs E.S.	58	F	Addison's Disease	-	Eucortone 272cc. in 30 days. Adrenaline M.v. b.i.d. Ascorbic acid 150 mgm. daily.	7 months	10 weeks	Good subjective improvement to adrenal therapy with increase in B.P. and decrease in pigmentation. No particular effect attributed to Ascorbic Acid. Died in "crisis" a month after leaving hospital.

TABLE I. Contd.

Year first seen	Case No.	Name	Age	Sex	Clinical Diagnosis	Pathological Diagnosis. i.e. Type of Addison's Disease.	Specific Treatment Adopted	Survival Period.		Remarks
								From 1st. symptom suggestive of Addison's Disease	From start of specific therapy	
1935	A.16	Mrs. E.L.	38	F	Addison's Disease	Tuberculous	Eucortone 145cc. in 20 days. Supra-renal Gland Ex. gr. x. Adrenaline M.xii. Salines I.V. and P.R.	4 months	3 weeks	Therapy had little effect on patient. Vomiting increased N <sub>2</sub> retention. Low blood sodium. Death in a "crisis".
1935	A.17	A.L.	36	M	Addison's Disease	Tuberculous	Cortin 560cc. in 36 days. Sod. chloride	4 months	7 weeks	Combination of cortin and Na Cl. quite effective in larger doses but patient gradually sank and died in "crisis". (Graph V.)
1936	A.19	G.T.	36	M	Addison's Disease	Tuberculous	Eucortone 4cc. in last 2 days. Salines.	5 weeks	2 days	Diagnosis only made terminally. Died in "crisis".
	A.20	A.T.	50	F	Addison's Disease	"Primary Atrophy"	Insulin and Glucose. Eucortone 36cc. in last 3 days. Salines.	6 years	3 weeks	Sudden severe "crisis" and died.
	A.21	R.H.	38	M	Addison's Disease	"Primary Atrophy"	Eucortone - 2 courses. Sod. Chloride by Mouth and I.V. drip.	1 year	7 months	Sudden severe "crisis" with death on day fixed for discharge. Adrenals could not be found macroscopically. (Graph VI.)
	A.22	Mrs. W.J.	50	F	Undiagnosed	"Primary Atrophy"	I.V. Glucose salines.	?	4 hours	Admitted moribund. No history obtained.
1937	A.26	M.V.	13	F	Undiagnosed	"Primary Atrophy"	I.V. Glucose salines	5 months	6 hours	Admitted moribund

(b) Cases still under observation.

Case No.	Name	Age	Sex	Clinical Diagnosis	Pathological Diagnosis. i.e. Type of Addison's Disease	Specific Treatment adopted	Survival Period.		Remarks
							From 1st. symptom suggestive of Addison's Disease	From start of specific therapy	
B.13	Mrs M.D.	44	F	Addison's Disease	-	Ascorbic Acid 150 mgm. daily	3+ years	2+ years	Still alive. Now in a sanatorium with Pott's disease of spine.
B.14	Mrs J.W.	55	F	Addison's Disease	-	Salines. Cortical Ex-tract &c.	4+ years	2+ years	Still alive. Frequent investigations being carried out. (Graphs VII. & VIII.)
B.15	J.O.	20	M	Addison's Disease	-	Salines. Diets. Cortical Exts. &c.	5+ years	3+ years	Still alive. Frequent investigations being carried out. (Graphs IX, X, & XI.)
B.17	Mrs C.S.	50	F	Addison's Disease	-	Salines. Diets. Cortical Ext. &c.	6+ years	1+ years	Still alive. Frequent investigations being carried out. (Graphs XII, XIII, XIV, and XV).
B.18	J.C.	55	M	Addison's Disease	-	Salines. Diets. Cortical Ext. &c.	3+ years	5+ months	Recently admitted. Has active tuberculosis. Under investigation
B.19	Mrs M.S.	36	F	Addison's Disease	-	Salines. Diets.	6+ years	3 weeks	Just admitted. Not yet investigated.

Showing the relevant details of those cases in which it has been considered advisable to reject or not to accept the clinical diagnosis of Addison's Disease as definite.

Year first seen	Case No.	Name	Age	Sex	Pathological Diagnosis	Specific Treatment adopted	Survival period.		Remarks. Reasons for rejection, etc.
							From 1st. symptom suggestive of Addison's Disease	From start of specific therapy	
1927	B.1	E.M.	34	F	-	Adrenaline. Adrenal ext. Ext. Thyroid Sic.	14+ years	11+ years	Still alive. Working daily in tweed mill. Examined recently. No evidence of Addison's Disease.
	B.2	Mrs C.D.	38	F	-	Pituitrin.	12+ years	11+ years	Still alive. Housewife. Examined this year. Slightly anaemic. No evidence of Addison's Disease.
1929	B.5	J.L.	62	M	-	None	-	-	Severe Exfoliative Dermatitis. No symptoms suggestive of Addison's Dis. Died 1930.
	C.1	D.B.	40	M	Pneumonia	None	2 years	-	Adrenals normal at autopsy.
1931	B.8	J.P.	51	M	-	50cc. Eucortone in 5cc. doses I.V.	8+ years	7+ years	Still alive. Working as a miner. Examined this year. No evidence of Addis. Dis.
1932	B.9	Mrs C.R.	39	F	-	None	9+ years	-	Still alive. Housewife. Diagnosis doubtful. Under investigation.
	B.20	Mrs E.F.	66	F	-	None	7 years	5 years	Died from cerebral haemorrhage in 1937. No clinical features of Addison's Disease.
	C.2	Mrs A.C.	55	F	Coron. Infarct.	Adrenaline	6 years	2 years	Adrenals normal at autopsy
1936	B.16	Mrs E.M.	34	F	-	Eucortone, 524cc. in 2 months. Ephedrine Whole Suprarenal Gld. Sodium Chloride.	1½+ years	1½+ years	Still alive. Housewife. Diagnosis doubtful. Under investigation.
	C.3	Mrs A.D.	45	F	Cardiac Fail. Pulmonary Infarctions.	Adrenaline. Sod. Chloride.	1 year	3 days	Adrenals normal at autopsy

Physicians in the Royal Infirmary, Edinburgh it has been possible for me to make clinical observation on every case of Addison's Disease that has been treated in that institution. Prior to that time the results of the therapy have been abstracted from the case notes and are, of necessity, less full.

PROTOCOLS OF THOSE CASES IN WHICH THE DIAGNOSIS  
OF ADDISON'S DISEASE  
HAS BEEN CONSIDERED BEYOND DOUBT

(a) COMPLETED CASES

Cases seen first in 1928:

Case B-3 - Male, aet 31. This patient received no specific therapy. He was discharged in statu quo and eventually died of "intense weakness" in 1931.

Case B-4 - Male, aet 55. Ephedrine gr.  $\frac{1}{4}$  b.i.d. was given to this patient with no appreciable effect on his blood pressure (94/60) but causing a slight symptomatic improvement.

These results are in keeping with those of ROWNTREE and BROWN (1926) which were noted in detail in the first part of this paper.

Case A-1 - Female, aet 24. The administration of Adrenaline  $\eta$  V hypodermically two - four hourly had no appreciable effect on this patient. The B.P. (93/74) fell steadily and could not be determined. She had nausea with severe vomiting and died in a "crisis" three weeks after admission. Autopsy report - Tuberculous adrenals.

Case A-2 - Male, aet 34. This patient was treated dietetically for an ulcer in view of his gastric upset. He suddenly became worse and died the same day in a "crisis" despite the hypodermic administration of adrenalin  $\eta$  V and pituitrin 0.5 c.c. Autopsy report - Tuberculous adrenals.

Case/



Case A-23 - Female, aet 50. The recurrent vomiting in this case misled the clinician. A diagnosis of Carcinoma of the Stomach was made and no specific therapy for Addison's Disease was used. Heroin was given four days before death - after which the patient's symptoms were much worse. Autopsy report - Tuberculous adrenals.

Cases seen first in 1930:

Cases A-4 and A-6 - Both of these patients were admitted as acute cases suffering from sudden upper abdominal pain. Case A-4 (female, aet 26) had an empyema of the gall bladder. A cholecystectomy was performed but the patient died immediately after the operation. Case A-6 (male, aet 58) was moribund when admitted and died within six hours before a history could be obtained. Neither case was diagnosed before death. Autopsy report in both cases - Tuberculous adrenals.

Case A-5 - Male, aet 40. A modified "Muirhead Régime" was adopted for this patient with little apparent benefit. Ephedrine, adrenaline and whole gland suprarenal tablets were all given by mouth but the patient went steadily down hill. "The only preparation which appeared to have the slightest effect was whole gland suprarenal tablets." It is of interest to note that this patient had several injections of morphine on the day before death which was recorded as being a "good day". Autopsy report - Tuberculous adrenals.

Case A-7 - Male, aet 53. The gastric symptoms of nausea and vomiting were so marked in this case that a needless operation was carried out for gastric carcinoma. The patient died immediately after the operation. Autopsy report - Tuberculous adrenals.

Case A-8 - Female, aet 22. This case presents one interesting feature. She was three months pregnant when admitted in a moribund state. She had been in hospital four months before complaining of weakness. At that time her skin was quite pigmented and the blood pressure was 100/78 but the diagnosis of Addison's Disease was not suspected. She was given Hyoscine Hydrobromide gr. 1/100 four hours before death. Autopsy report - Tuberculous adrenals.

Cases/

Cases seen first in 1931:

Case B-6 - Male, aet 43. Severe gastric symptoms were the main feature in this patient. He was accordingly treated dietetically at first, but later a diagnosis of Addison's Disease was made and the patient was given whole gland Suprarenal Tablets with little obvious effect either symptomatically or on the blood pressure (100/70). Later he became acutely ill and was given intravenous injections of "Eucortone" (suprarenal cortical extract prepared by Swingle and Pfiffner's method) with dramatic subjective improvement, although there was no appreciable increase in the B.P. which was now 88/56. On two occasions the Eucortone was stopped and the symptoms at once became greatly exaggerated, despite the fact that adrenaline was given hypodermically. However, notwithstanding the Eucortone treatment, the patient continued a steady downhill course and eventually died in a hospital for military pensioners, five months after the commencement of the cortical extract therapy. Permission for an autopsy was refused.

This patient (B-6) was the first recorded case in which cortical extract treatment was used in the Edinburgh Hospital area with beneficial effect. The results were very promising although, unfortunately, they were mainly of a subjective nature, and did not lend themselves readily to demonstration. Despite the administration of large amounts of cortical extract (in all 470 c.c.) the patient's condition gradually deteriorated, although it is apparent that the Eucortone delayed appreciably the fatal termination. No extra salt therapy was given to this patient, as at this date its value in Addison's Disease had not yet been appreciated.

Case B-7 - Female, aet 47. Dietetic measures and rest in bed served to alleviate the severe vomiting which was this patient's major complaint. In/

In view of the asthenia from which she suffered she was given 13 c.c. of Suprarenal Cortical Extract (type not stated) intravenously over a period of eight days with slight subjective improvement but with no alteration in the blood pressure (102/67). She was then discharged, but died in a sudden "crisis" three days later despite the administration of adrenaline and general stimulants.

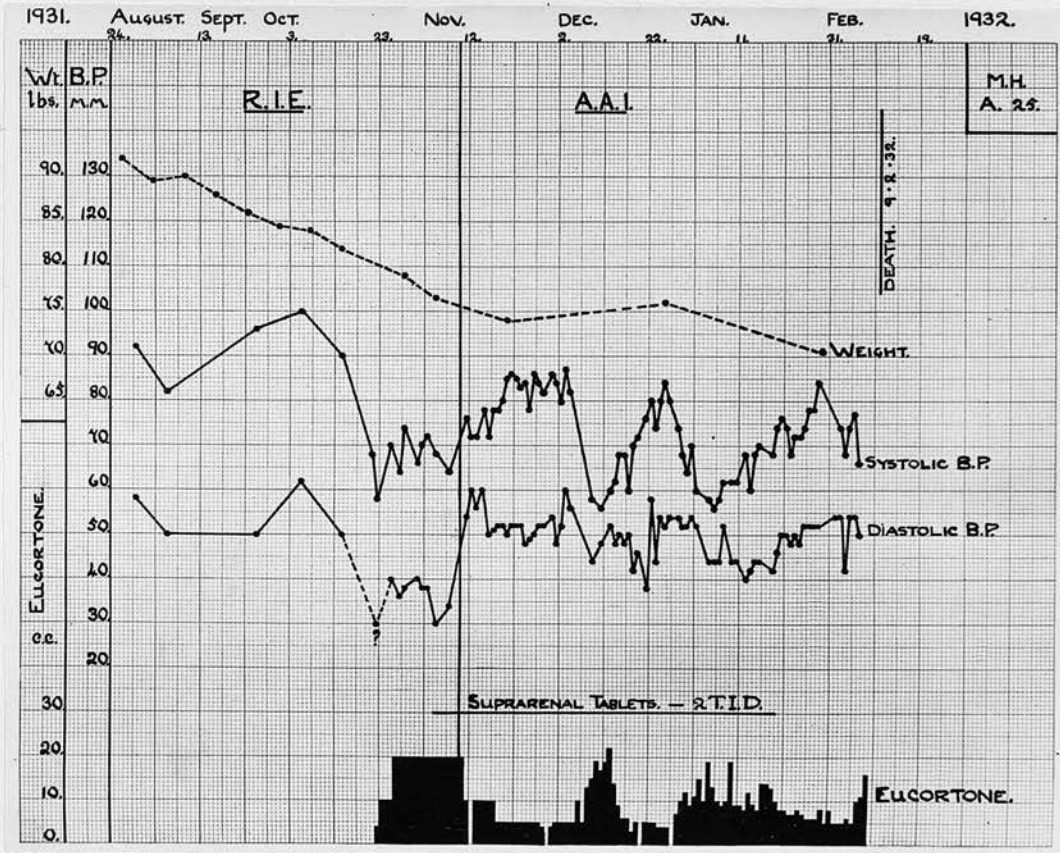
This case (B-7) illustrates clearly the futility of administering infinitesimally small doses of cortical extract. A dose of 13 c.c. in eight days cannot possibly produce any appreciable or lasting effect. This patient was actually treated with cortical extract at an earlier date than case B-6, but the results were hopeless owing to the inadequacy of the dosage administered.

Case A-25 - Female, aet 17. The clinical course of this patient in hospital is shown in Graph I. From it one will appreciate immediately the marked effect that the administration of Eucortone had on this patient's blood pressure. The clinical improvement in the patient was seen immediately after an increased amount of Eucortone was given and preceded the rise in blood pressure usually by one or two days. Several attempts were made to reduce the amount of Eucortone that was given with a view to economy, but on each occasion this reduction was followed by a clinical relapse and a fall in the blood pressure. The terminal relapse that ended fatally was in no way different from the others clinically, but the administration of larger doses was entirely ineffective. It will be noted that the total amount given at this time was less than that given at each of the other relapse periods. The patient died in a typical "crisis" with nausea, vomiting, diarrhoea, etc. The administration of the suprarenal tablets caused no appreciable improvement in this patient (see Graph I).

Autopsy report - Bilateral "primary atrophy" of adrenals.

The pathological findings in this case (A-25)

to/



GRAPH I

Case A-25. Female, aet 17

## "Primary Atrophy of the Adrenals"

- Note
- Steady loss in weight.
  - The uniformly low level of the blood pressure.
  - The increase in blood pressure that occurred following a latent period after the administration of relatively greater amounts of Eucortone.
  - The fact that the suprarenal tablets had apparently no effect on the blood pressure.

(R.I.E. = Royal Infirmary, Edinburgh.  
A.A.I. = Astley Ainslie Institution.)

to the effect that the morbid process was one of "primary atrophy" and not tuberculous as in the majority (83%) of cases may prove of interest. She showed a much better response to cortical therapy than did most of the other similar cases treated about this time. BRAMWELL (1897 and 1902) and BOINET (1903 and 1909), as noted in the previous section of this paper, postulated that the cases which responded best to adrenaline therapy were probably those in which there was no involvement of the sympathetic ganglia near the adrenals (i.e. those cases which were not tuberculous). As far as can be determined, I can find no one who has made similar assertions with regard to the response to cortical extract therapy. However, in view of the dubious nature of many of the cortical extracts marketed about 1931, it is perhaps not justifiable to put forward such a hypothesis on the results from one case. In all, this patient received 1057 c.c. Eucortone in approximately four months.

Cases seen first in 1932:

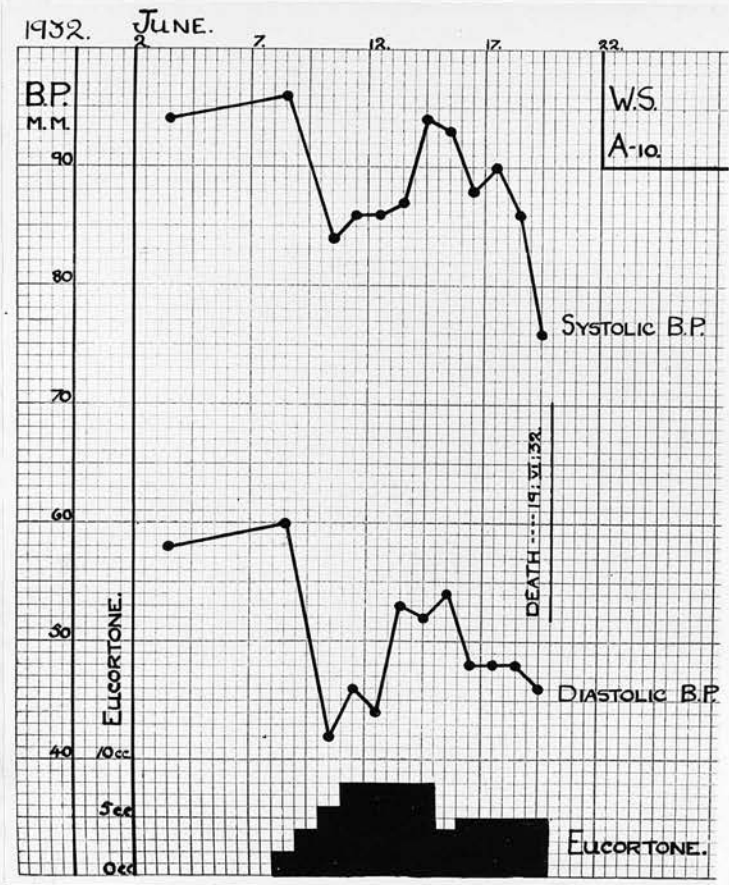
Case A-9 - Female, aet 30. The total duration of the illness in this case was short - 10 weeks. She was treated at first as a gastric case but became so collapsed from vomiting that intravenous salines were given. These helped her considerably and she gradually and slowly improved. However, she has another sudden severe attack of vomiting and became very collapsed. Adrenaline 0.5 c.c. H.I. was given four hourly on account of the low blood pressure (55/30). This helped her slightly and the pressure improved to 65/52. A further crisis was treated similarly with good effect but after this/

this the patient became steadily weaker. Rectal salines were given but were not retained. She had recurrent attacks of severe vomiting and died in a typical crisis.  
Autopsy report - Tuberculous adrenals.

The treatment of this patient by intravenous salines produced most benefit. The salines were given, however, on account of her general collapsed condition, and at the time the peculiar value of sodium chloride in such cases was unfortunately not appreciated, so that this form of therapy was not repeated. It was only after some considerable time that the diagnosis of Addison's Disease was made in this case and consequently there was no time to use cortical extract therapy. The ad-renaline was used empirically on account of the patient's very low blood pressure.

Case A-10 - Male, aet 34. The patient had a typical history of gastric upset and asthenia. After being in the ward a week he had a sudden crisis, and Eucortone was administered intravenously (Graph II). This therapy had a slight effect on the blood pressure, but there was practically no demonstrable clinical improvement. The patient steadily sank and died in a crisis twelve days after the commencement of suprarenal cortical extract therapy.  
Autopsy report - Tuberculous adrenals.

The dose of suprarenal cortical extract given to A-10 was far too small, as judged by present standards. In all, 68 c.c. Eucortone was given in a space of twelve days. The preparation of Eucortone used in 1932 was the older unconcentrated type/



GRAPH II

Case A-10. Male, aet 34.

Tuberculous Adrenals.

Note Temporary rise in blood pressure following administration of suprarenal cortical extract intravenously. There was little sustained effect, and patient died.

type . At the present time the minimum daily dose of such a dilute preparation for a patient in a crisis would be 100 c.c. It will thus be appreciated that the poor result obtained in this case cannot be attributed to the inefficacy of the preparation used.

Case A-12 - Female, aet 32 (Figure 3). In view of the low blood pressure (84/68) on admission, this patient was given adrenaline  $m$  viii b.i.d. This had no appreciable effect, however, on either the B.P. or the general condition. The patient had recurrent attacks of vomiting and Eucortone was accordingly administered (Graph III). This helped the patient's general condition considerably but there was little significant effect on the blood pressure. The Eucortone was gradually reduced owing to its cost, but with this reduction there came a return of symptoms and the patient passed into a "crisis" on 13:X:32. On this date she was retching and vomiting continuously. She was given an intravenous administration of 500 c.c. 6% glucose saline and 64 c.c. of Eucortone. This caused a complete disappearance of all symptoms. Thereafter she was put on a maintenance dose of 10 c.c. Eucortone daily. On 16:XI:32 she again became worse and by 19:XI:32 she had passed into another "crisis". She was given 90 c.c. Eucortone along with 500 c.c. 6% glucose saline intravenously, but this had little effect. The patient's condition became rapidly worse and she died on 27:XI:32.

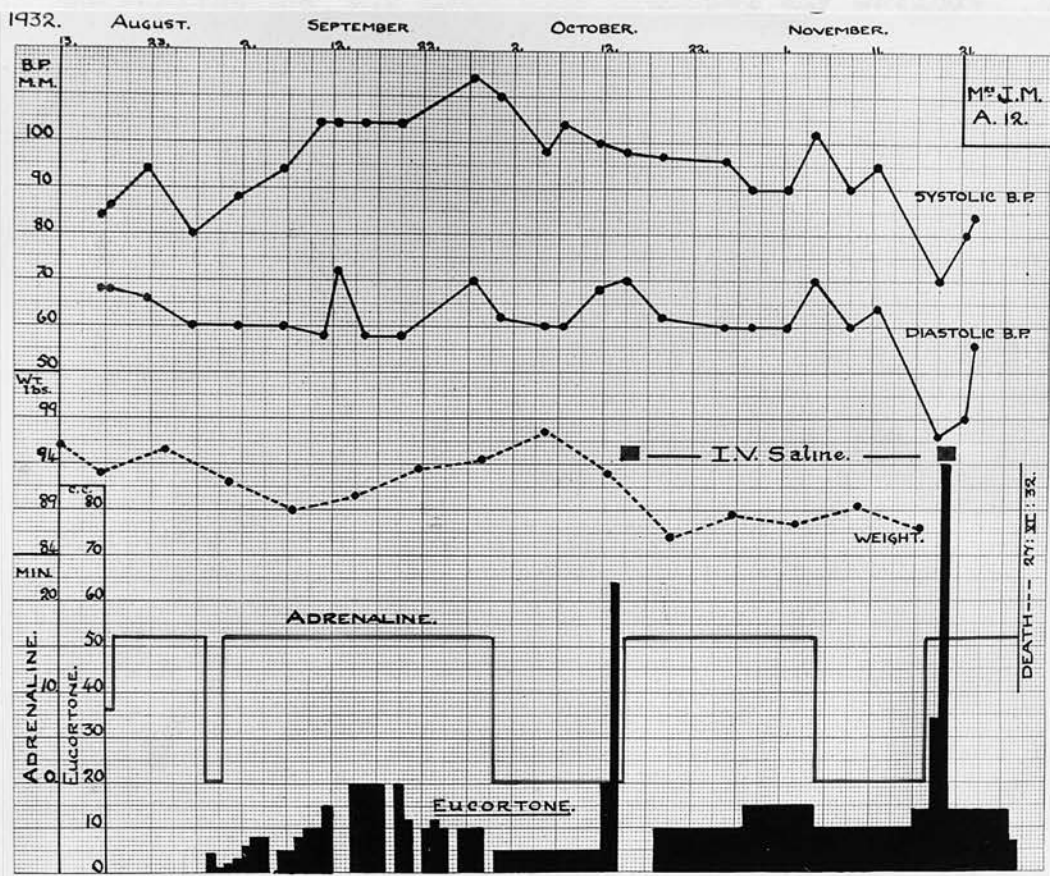
In all, 990 c.c. of Eucortone were given to this patient during her stay in hospital, at a total cost of £61: 11: 6. Despite this tremendous expenditure, the results were disappointing. The Eucortone certainly helped the patient, but in times of real emergency, as, for example, the crisis on 13:X:32 (see case notes), the simultaneous administration of the saline intravenously had probably/





FIGURE 3.

Clinical Photograph - Case A-12.



GRAPH III

Case A-12. Female, aet 32.

Tuberculous adrenals.

Note: No appreciable effect on blood pressure of administration of either suprarenal cortical extract or of adrenaline.

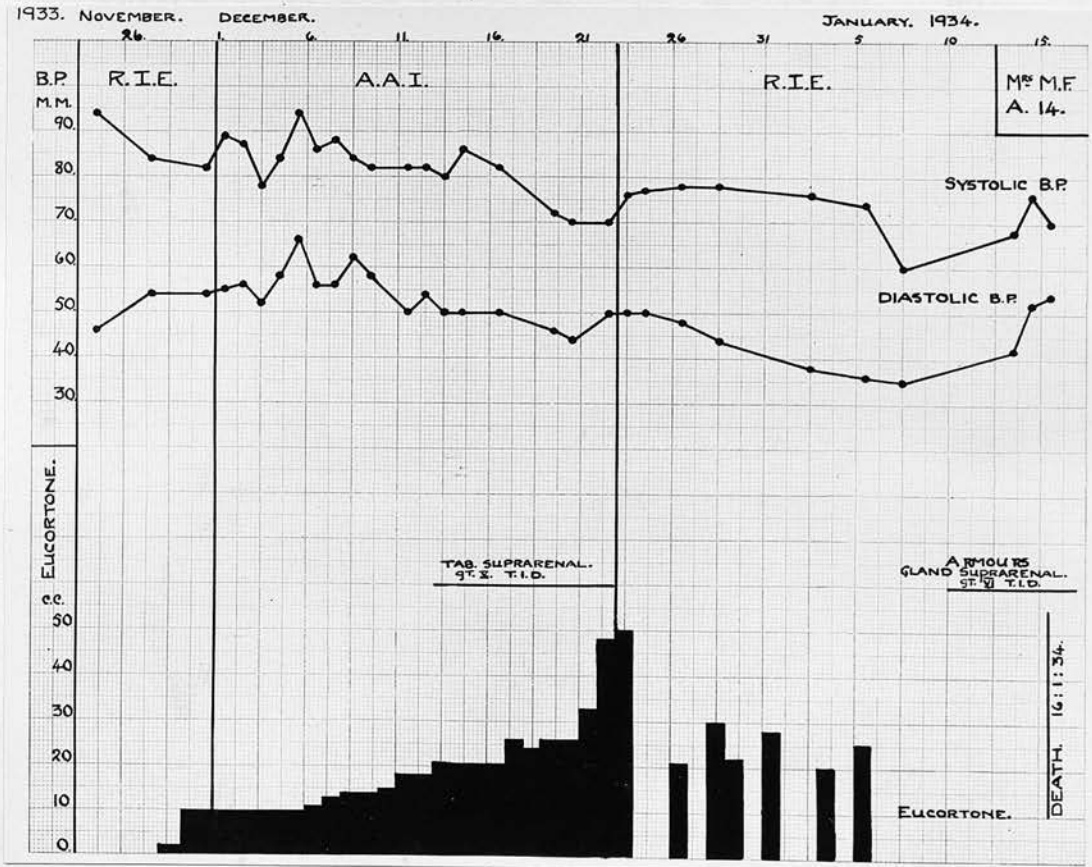
probably as much, if not more, to do with the patient's recovery than the cortical extract. It will be appreciated from the graph that neither the adrenaline nor the Eucortone produced any obvious change in the blood pressure.

Cases seen first in 1933:

Case A-13 - Male, aet 35. This patient was critically ill when admitted. He had severe hiccough. The stomach was washed out and one drachm of Tinct. Chlorof. and Morphine was left in. The blood pressure was so low that it could not be estimated. Accordingly, Pituitrin 0.5 c.c. was given four hourly and in addition gr. 1/40 digitalin was given. The heart slowed and the pulse became stronger, but the patient suddenly lapsed and died on the day following admission. The clinical diagnosis was lymphadenoma.  
Autopsy report - Tuberculous adrenals.

Case A-14 - Female, aet 43. The diagnosis of Addison's Disease was made soon after admission in this case, and she was given comparatively large doses of cortical extract without much demonstrable beneficial effect (Graph IV). The patient's condition became steadily but slowly worse. There was little change in the blood pressure, which remained consistently low (80/40 or thereabouts). Eventually, as the Eucortone was not producing any advantageous effect, it was stopped for economic reasons. The patient's state continued to deteriorate and various stimulants (strychnine, brandy, etc.) were given with practically no effect. Armour's whole gland suprarenal tablets were given with no apparent improvement in the patient. The nausea and vomiting continued and the patient gradually sank and died.  
Autopsy report - Tuberculous adrenals.

This case was very disappointing, as, despite large doses of suprarenal cortical extract, there was no improvement. There was no apparent reason for this failure, as, for example, evidence of active/



GRAPH IV

Case A-14. Female, aet 43.

Tuberculous adrenals.

Note: No appreciable effect on blood pressure from Suprarenal Cortex Therapy.

(R.I.E. = Royal Infirmary, Edinburgh  
A.A.I. = Astley Ainslie Institute.)

active tuberculosis elsewhere in the body.

Case B-10 - Male, aet 65. The feature of this case was the presence on each occasion that it was measured of a very high blood globulin figure (6.0 g.%), while the other proteins (albumen 3.4g.% and fibrinogen 0.38 g.%) were within normal limits. There was no albuminuria. The inorganic constituents of the blood were not estimated. No specific therapy was adopted for this patient as his condition was not considered serious. However, he pursued a steady downhill course and eventually died of "extreme exhaustion" a year and a half after discharge. It was not possible to obtain permission for an autopsy in this case.

Case B-11 - Female, aet 44. A typical case of Addison's Disease that was treated with Eucortone (37 c.c. in 16 days) with little obvious effect on either the general condition or on the B.P. Intra-venous administration of 300 c.c. of 6% glucose saline was very helpful, but on the day following its administration the patient was removed by relatives against the wish of the physician in charge. She died in "crisis" on the next day. Autopsy was not possible.

The dosage of Eucortone used in this case (B-11) was again totally inadequate as judged by present criteria. Despite the fact that there was little obvious improvement in the patient, the cortical extract therapy was apparently able to keep her alive by supplying sufficient extra cortin for the body's requirements. The cessation of the administration of this hormone on the patient's removal from hospital at once brought on the crisis which ended fatally.

Cases seen first in 1934:

Case A-15 - Female, aet 25. This patient was admitted in a moribund condition and died within four hours of admission. No investigations were carried out and the diagnosis was not made before death.  
Autopsy report - Tuberculous adrenals.

Cases/

Cases seen first in 1935:

Case B-12 - Female, aet 56. This woman was diagnosed at first as suffering from chronic constipation. She was treated for this with enemata and mild laxatives with very good results and was then sent home. However, she had only been there for about a month when she had a severe relapse and had recurrent attacks of vomiting. On readmission it was at once appreciated that her pigmentation, which had been mild before, was now very pronounced, particularly over pressure points. The blood pressure was 70/55 and the diagnosis of Addison's Disease was at once made. She was accordingly given a course of Eucortone in which 2 c.c. were given on the first day and the dose was thereafter increased by 1 c.c. per day till 10 c.c. were given daily. This dosage was then continued for 22 days. In all, 272 c.c. of Eucortone were given. At the same time the patient received min. V Adrenaline twice daily. Under this combined therapy she improved rapidly. Subjectively, she became much brighter, the pigmentation cleared considerably and the blood pressure increased slightly. (On the twelfth day of this treatment it was 94/50 and on the twentieth day 100/60.) When the Eucortone was stopped the adrenaline was continued and at the same time 150 mgm. Ascorbic Acid were given daily. The improvement continued with this new treatment and the pressure rose at one stage to 115/70. The patient was discharged and was told to continue the Ascorbic Acid at home. However, shortly after leaving hospital the recurrent attacks of nausea and vomiting recommenced. The patient rapidly sank and died within a month of leaving hospital. No opportunity was given for a post-mortem examination.

The feature in this case (B-12) is the introduction of Ascorbic Acid as a therapeutic measure in Addison's Disease. The success or otherwise of this preparation as a form of treatment cannot be judged from this case, in that the patient also received adrenaline throughout the time in hospital, when she was having the ascorbic acid. It is perhaps significant that the patient died within a month/

month of leaving hospital - i.e. within a month of her last dose of adrenaline, notwithstanding the fact that she was continuing to take the Ascorbic Acid at home. No special note is made in the case notes of this patient regarding any particular fading of the pigmentation after the commencement of the Ascorbic Acid therapy. Lessening in the pigmentation might be expected if there is any significance in the work of SZENT-GYÖRGYI (1930) on pigmentation of the skin as detailed in the first part of this thesis.

Case A-16 - Female, aet 38. The diagnosis of Addison's Disease in this case was made on the day of admission from the history which was absolutely typical. Accordingly, the patient was given an intensive course with treated suprarenal preparations from the start. 2 c.c. of Eucortone were administered daily at first, but this was gradually increased until 10 c.c. were given per day. At the same time gr. X dried Suprarenal Gland and  $\gamma$ XII Adrenaline were given daily. However, despite all this therapy the patient's condition deteriorated. Whereas on admission she had only had severe nausea in the morning, this symptom became progressively worse and she eventually was retching and vomiting continually. The blood pressure remained throughout at a moderate level (104/70). There was, however, a growing retention of nitrogenous bodies (on admission Urea N. 20 mgm.% and a month later Urea N. 53 mgm.%). The blood sodium was taken after the patient had been in hospital for a month and was below normal (296 mgm.%). In view of the continual vomiting, some dubiety was expressed regarding the diagnosis and the possibility of the patient suffering from a gastric neoplasm was reviewed. A fractional test meal was performed and complete achlorhydria was found (Figure 4). As the massive suprarenal therapy was causing no apparent improvement all forms of medicine were stopped after twenty days, by which time 145 c.c. of Eucortone had been given. The vomiting increased in severity. This caused considerable dehydration/

dehydration and epines were accordingly given both intravenously and per rectum. However, these were of no avail, the pressure became 70/55, and the patient slipped into a coma with a temperature of 102.8° and death rapidly ensued.

Autopsy report - Tuberculous adrenals.

This case presents several features of interest. Here we also have a case of an ideal subject for

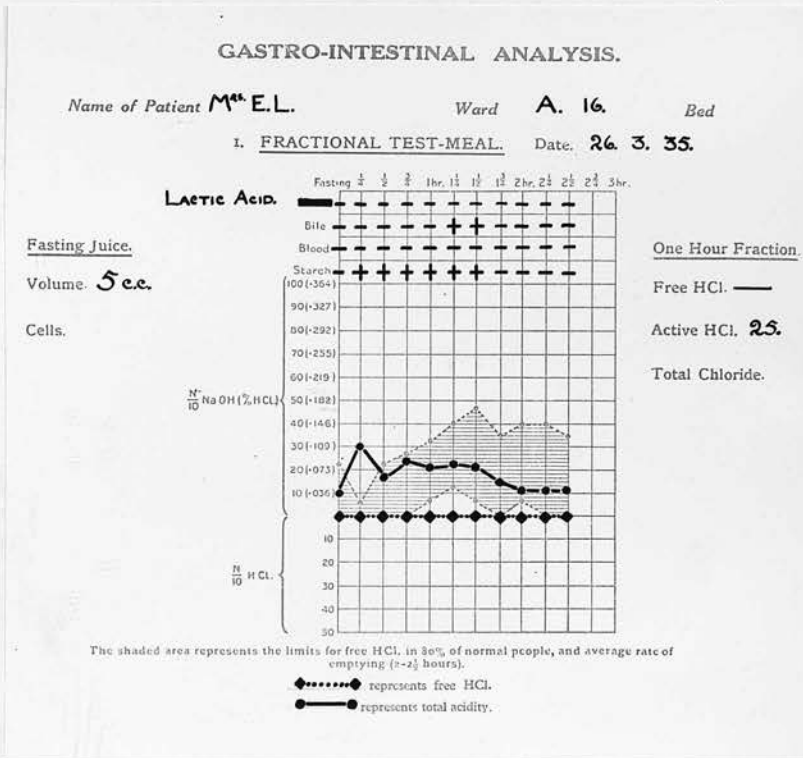


FIGURE 4

Case A-16. Female, aet 38.

Tuberculous adrenals.

Fractional Test Meal Curve.



dehydration and salines were accordingly given both intravenously and per rectum. However, these were of no avail, the pressure became 70/55, and the patient passed into a crisis with a temperature of 105.8° and death rapidly ensued. Autopsy report - Tuberculous adrenals.

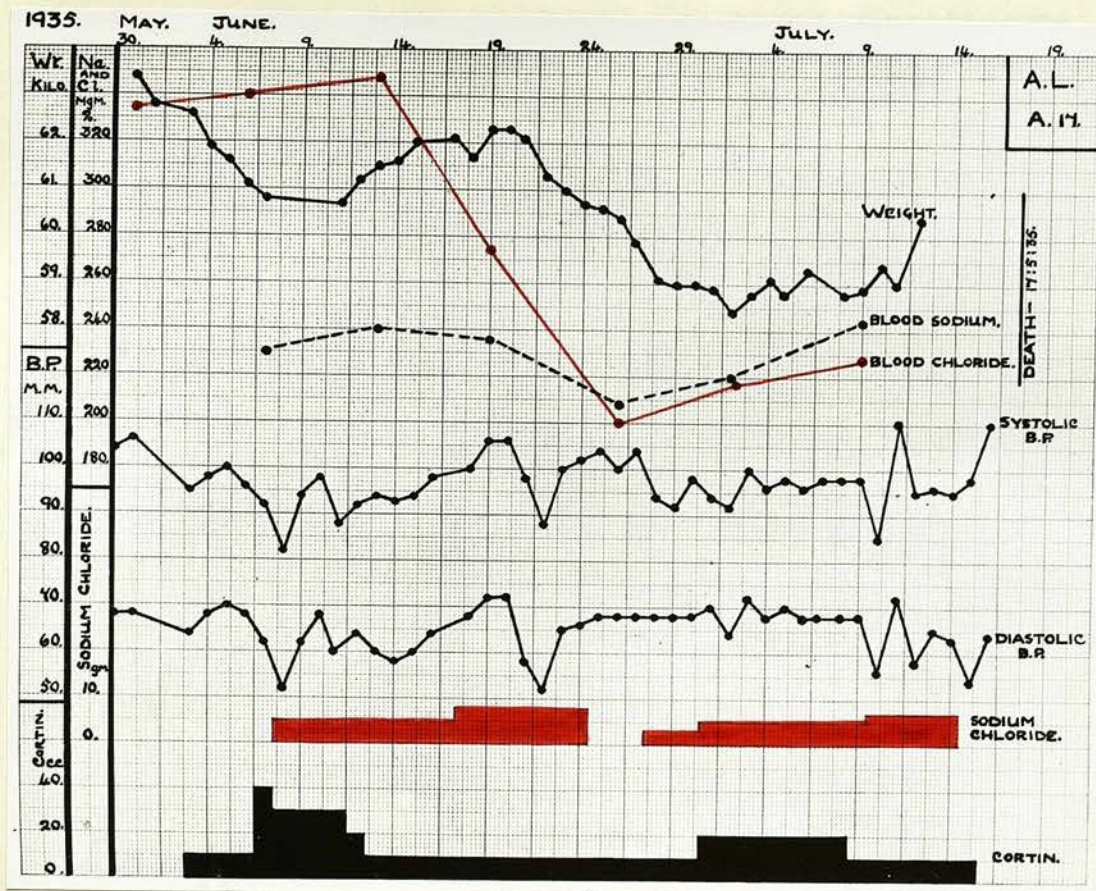
This case presents several features of interest. Here again the dosage of cortical extract preparation was completely inadequate. As far as can be determined this was the first case of Addison's Disease in the Edinburgh Hospital Area in which an estimation of the blood sodium was made. Despite the fact that salines were given in plentiful amounts intravenously and rectally to counteract both the low blood sodium and the "dehydration", there was little apparent benefit to the patient. It is probable that in this case the only thing that would have saved the patient's life would have been the combination of large salines along with massive doses of adrenal cortical preparations. Unfortunately, these were at no time given together, as the cortical preparations had been stopped before the salines were administered. It is usually postulated that in Addison's Disease the fluid loss brings about an "anhydraemia" rather than a true "dehydration". Here in this case, however, from the description of the patient's physical condition and the extent of the fluid loss it is apparent that dehydration itself must have been present to some extent/

extent at least.

Although the diagnosis of Addison's Disease was made from the start, the increasing severity of the gastric symptoms as a result of insufficiency of therapy so predominated in the picture that at one time considerable dubiety arose as to whether the diagnosis was correct or not. This no doubt, along with economic reasons had a great deal to do with the unfortunate decision to stop all treatment with adrenal preparations. One learns from this how closely a case of Addison's Disease can simulate one of Pyloric Obstruction.

Case A-17 - Male, aet 36. The treatment adopted for and the progress of this patient are probably best appreciated by consulting Graph V. The patient received varying amounts of "Cortin" and of Sodium Chloride. A maintenance dose of 10 c.c. Cortin had no appreciable effect on the blood pressure or on the weight, but two short periods of intensive Cortin therapy were followed by a small but appreciable increase in the weight, and, to a lesser extent in the pressure. In both these periods of intensive Cortin therapy intravenous salines were administered at the same time as the patient was acutely ill on each occasion with intense prostration, nausea, vomiting and diarrhoea. These might readily be largely responsible for the rise in weight that occurred on each occasion. The first of these critical periods passed on to a phase in which there was a distinct improvement in the clinical condition of the patient. This took one or two days to become manifest, but then continued for nine days from 10:VI:35 till 19:VI:35. The second course of intensive therapy was not followed by the same extent of improvement in the patient's general condition. He gradually became worse and died in a further crisis a week later. Autopsy report - Tuberculous adrenals.

Examination of the blood chemistry of this patient/



GRAPH V

Case A-17. Male, aet 36.

Tuberculous adrenals.

(For description see context.)

patient reveals a very marked fall in the blood sodium and blood chloride midway through his sojourn in hospital. The exact significance of this fall is doubtful. Some doubt has arisen as to the strict accuracy of the figures for these blood constituents and therefore it has been considered best to ignore them entirely. Otherwise, the blood chemistry showed that the Urea Nitrogen was towards the upper limit of normal (19, 16, 14 and 16 mgm.%) and that this figure tended to increase at those times when the patient's general condition deteriorated. The serum globulin was uniformly high (4.62, 5.12, 4.38 and 3.13 g.%), while the serum albumen was about the normal level (3.22, 3.50, 3.25 and 3.63 g.%). The high blood globulin figure was not fallacious, and as in case B-10, no definite explanation can be brought forward to account for it. There was no albuminuria.

A critical examination of the urine excretion produces one or two interesting facts. The figures as set out in Table III tend to show that Cortin has a definite effect in retaining sodium and fluid in the body. Reference to the table will demonstrate the following points. (1) On comparing period C with period D, it is to be noted that despite the fact that the average fluid intake in the two periods is practically constant, there is  
a/

T A B L E III.

Case A.17. Showing effect of Therapy  
on Chloride Excretion, Etc.

Period	1935 Dates of Period	Duration in days	Weight at end of period	Daily Therapy	Intake. Av. daily fluid	Output. Av. daily urine	Average chloride content of urine	
							g. %	Total daily conten
A	1/6 - 2/6	2	62.7 K.	Nil.	2290 cc.	1310 cc.	0.52	6.80 g.
B	3/6 - 6/6	4	61.1 K	Cortin, 10cc.	2090 cc.	1150 cc.	0.47	5.16 g.
C	7/6 - 12/6	6	61.2 K	Cortin, 30cc. + NaCl, 10.g.	2490 cc.	1500 cc.	0.45	6.83 g.
D	13/6 - 17/6	5	62.1 K	Cortin, 10cc. + NaCl, 10 g.	2300 cc.	1730 cc.	0.79	13.70 g.
E	18/6 - 25/6	8	60.7 K	Cortin, 10cc. + NaCl, 16 g.	2730 cc.	1690 cc.	0.83	14.55 g.
F	26/6 - 27/6	2	59.7 K	Cortin, 10cc.	1160 cc.	960 cc.	1.10	10.45 g.
G	28/6 - 30/6	3	58.9 K	Cortin, 10cc. + NaCl, 5 g.	2180 cc.	1310 cc.	0.81	10.71 g.
H	1/7 - 8/7	8	58.8 K	Cortin, 20cc. + NaCl, 10 g.	2030 cc.	1030 cc.	0.63	6.52 g

a much smaller output of Chloride in the urine when the dose of Cortin is larger. This is seen in both the percentage and the total daily output.

(2) This is also to be observed on comparing periods G and H, despite the fact that the sodium chloride intake is doubled in period H. (3) The fluid intake and urinary output increased when salt was given, but apparently the kidneys failed somewhat latterly. (4) No note was made in this case of the ordinary salt content of the diet, but it can be seen that the excretion of "chloride" was less than the known intake of "sodium chloride" only when (a) large doses of Cortin were given (period C and H), or (b) large amounts of sodium chloride provided (period E).

It is worthy of note that clinical reactions occurred on the two occasions on which it was necessary to administer the cortin with intravenous salines (Table IV). These reactions were identical. About ten minutes after the injection had been completed a rigor occurred. The pulse rate then gradually rose and the blood pressure fell. The pulse rate reached its maximum and the blood pressure its minimum about three hours after the infusion, at which time the patient was in an alarming state of shock. Thereafter a gradual recovery occurred, which was not, however, complete till about 48 hours after/

T A B L E IV.

Case A.17. Record of Reaction on 3:7:35 following on the I.V. administration of 20 cc. Cortin with 400 cc. of 0.9% saline and gum acacia.

Time	Pulse	B.P.	Remarks.
10 a.m.	86	100/72	-
10.15 "			Infusion begun.
11.00 "			Infusion completed.
11.15 "	98	100/70	Rigor.
11.45 "	140	88/60	
12.15 p.m.	132	90/62	
12.45 "	150	76/54	
1.15 "	152	76/50	
2.15 "	136	76/54	Pulse irregular in force. No deficit.
2.35 "	136	76/54	M.v. Adrenaline + gr.1/60 Strychnine Hydrochloride
3.15 "	130	76/55	
4.45 "	120	78/54	
7.00 "	125	80/56	Dicrotic pulse.

after the injection.

Cases seen first in 1936:

Case A-19 - Male, aet 36. For the first few days after admission this patient presented rather a difficult diagnostic problem. His history was that he had been extremely weak for three weeks. Prior to that he had felt perfectly well, though he had never been robust and had been liable to contract any infectious illnesses that were prevalent. He had also suffered from acute rheumatoid arthritis at the age of 25 and had been troubled with a duodenal ulcer for three years. The only clinical feature on admission that was suggestive of Addison's Disease (apart from the asthenia) was a low blood pressure (94/64). There was no pigmentation whatsoever. Apart from an attack of severe epigastric pain on the day after admission, the patient without any special treatment improved slightly in his general condition, although he continued to complain of extreme exhaustion. (The epigastric pain was explained later by the finding at autopsy of a gall-bladder filled with stones.) Seven days after admission the patient had a sudden severe attack of vomiting and diarrhoea that left him very weak. There was no abdominal pain nor discomfort at this time. The blood pressure had fallen slightly and was now 80/50, and this fact, together with the extreme asthenia and vague gastrointestinal symptoms, served to promote a tentative diagnosis of Addison's Disease. Salines were administered both intravenously and per rectum, but the latter were not retained. Sodium chloride was also given by mouth in cachets, but these were promptly vomited. 2 c.c. Eucortone and 1.7 c.c. Coramine were administered on two occasions to the patient with little effect. The blood pressure fell steadily and on the day following the onset of the crisis was recorded as 68/30. An intravenous drip was set up and this helped the patient slightly, although the pulse was almost imperceptible at the wrist. He was somewhat restless and morphine gr. 1/6 and hyoscine gr. 1/100 were given every four hours approximately, but he became steadily worse and died in coma two days after the onset of the "crisis". Autopsy report - Tuberculous adrenals.

The extreme difficulty in making a definite diagnosis in this patient (A-19) contributed greatly to the unsatisfactory treatment adopted. The dosage of/



of Eucortone administered was completely inadequate for a patient in a "crisis". In the two days only 4 c.c. were given of the old unconcentrated Eucortone, whereas the necessary dose of this preparation would be approximately twenty to fifty times this amount. The salines, while undoubtedly necessary, could not be expected to bring a patient out of an "Addisonian Crisis" unless large amounts of the adrenal cortical preparations were administered coincidentally.

The use of the morphine also, in such amounts, while doubtless considered necessary owing to the restless state of the patient, was probably about the worst form of therapy that it was possible to adopt. This view has been expressed by SERGENT (1912) and several other authorities in the past. With a view to determining the nature of the collapse that occurs after the administration of morphine I considered it justifiable to give gr. 1/6 morphine to four patients suffering from Addison's Disease. In one patient (B-15) the blood sugar dropped from a preliminary figure of 83 mgm.% to 56 mgm.% in half an hour and the patient exhibited many of the features associated with hypoglycaemia, such as "shaking", dizziness, feeling of hunger and profuse sweating. He had a severe bout of hiccough lasting/

lasting for about five minutes. At the same time the diastolic pressure fell and the pulse rate increased. The blood sugar had returned to the normal level in two and a half hours, but the patient was somewhat distressed and vomited continually in the afternoon (Table V).

No such hypoglycaemic reaction occurred in any of the other three cases on whom this test was carried out. Two of them were apparently unaffected by the morphine, while the third had severe vomiting about three hours after receiving it, and required intravenous salines to restore her. In this patient (B-14) the blood pressure fell markedly about two hours after the administration of morphine and could not be measured with the sphygmomanometer. The patient became very collapsed (Table VI).

The exact nature of the reaction that occurs after the administration of morphine is consequently vague. It is apparently accompanied in some cases at least by a form of hypoglycaemia, although it is probable that the latter does not play such a large part in the collapse of the patient as does the subsequent bout of vomiting, to which these patients seem peculiarly liable. This problem is still under investigation.

Case A-20 - Female, aet 50. This patient was very weak and emaciated when admitted and was consequently given insulin and extra glucose daily with a view/

T A B L E V.

Showing effect of morphine gr. 1/6 on case of Addison's Disease  
(Case B.15). Note resultant hypoglycaemia.

Time	B.P.	Pulse	Blood Sugar	Remarks
9.00 a.m.	86/66	82	83 mgms. %	Condition good. Given morphine gr. 1/6.
9.30 "	-	84	56 "	Condition unchanged.
10.00 "	84/44	100	78 "	Severe hiccough; sweating profusely; choking felt hungry and dizzy; no vomiting.
10.30 "	80/60	90	71 "	Still dizzy. Very sleepy.
11.00 "	86/66	80	76 "	Not so sleepy; feeling better.
11.30 "	86/66	80	81 "	-
12 noon	-	-	80 "	Sleeping.
1.00 p.m.	-	-	-	Vomited.
3.00 "	-	-	-	Vomited.
4.00 "	-	-	-	Vomited.

T A B L E VI.

Showing effect of Morphine, gr. 1/6, on case of Addison's Disease (B.14). No hypoglycaemia. Extreme Collapse. 20:ix:37.

Time	B.P.	Pulse	Blood Sugar	Remarks
9.00 a.m.	88/66	64	84 mgms.%	Condition good. Given Morphine gr.1/6
9.30 "	78/54	74	"	Condition unchanged.
10.00 "	74/50	100	"	"Feeling very sleepy".
10.30 "	68/ ?	110	"	Nausea. "Feeling cold".
11.00 "	60/ ?	116	"	-
11.30 "	? / ?	110	"	Pale.
12 noon	? / ?	110	"	Very collapsed.
1 p.m.	? / ?	100	-	Vomited.
3 "	64/44	90	-	Vomiting continuously.

view to improving her general condition. This helped her considerably, especially when the glucose was administered intravenously in the form of 6% glucose salines. Apart from the salines, no specific therapy was adopted for the apparent adrenal insufficiency from which the subject suffered. She progressed favourably for approximately three weeks when she had a sudden bout of vomiting. This became progressively more severe. Large glucose-saline intravenous infusions were given along with insulin, but the patient's condition gradually deteriorated. An intravenous saline drip was set up and, in order to supplement the apparently deficient secretion of the diseased adrenals, she was given 20 c.c., 8 c.c. and 8 c.c. of Eucortone on three successive days. However, this did not help her to any appreciable extent and she sank and died four days after the onset of the vomiting. It is of interest to note that this patient received morphine on each of her last two days on account of her extreme restlessness after the drip was set up. Autopsy report - Primary Atrophy of adrenals.

This patient (A-20) died in a sudden relapse that occurred when her general condition was apparently much better than when first admitted. This "crisis" was very severe and consequently gave rise to considerable restlessness which unfortunately was treated with morphia. The dosage of Eucortone used was undoubtedly far too small for such an extreme condition. It may be observed that the adrenals in this case were not tuberculous but were of the "primary atrophy" type. This patient did not respond to the therapy nearly as well as did the first case of adrenal atrophy (A-25, see above) although, of course, her treatment was not so intensive and her relapse was much more acute than was encountered in the former case.

Case/

Case A-21 - Male, aet 38, (Figure 5). The therapy and progress of this patient in hospital may best be appreciated by reference to Graph VI. When admitted, the patient, who had been vomiting continuously for four days, was very collapsed and therefore an intravenous drip saline was immediately set up. This helped him considerably, the vomiting stopping and the asthenia being ameliorated. He was then put on 5 - 10 g. Sodium Chloride daily and he gradually improved so that by August 30th he was able to get up and go about, although still somewhat weak. On September 12th a course of the "new" concentrated Eucortone was commenced, the sodium chloride therapy being maintained. This combined treatment brought about an obvious improvement both in the general condition and the systolic blood pressure, which rose 5 - 10 mm. The blood chemistry also tended to revert to more normal levels (see Graph VI). The patient was now discharged from hospital and returned to his work as a turbine driver. He continued at this for three months, taking extra salt daily but having no cortical extract therapy. At the end of this time he was again admitted to hospital on account of nausea and weakness and was given another course of Eucortone, which was later combined with salt. Here again, as in the first course of treatment, it was the combination of salt and cortical extract that produced the best apparent results. The nausea vanished, the patient felt stronger and the blood pressure rose several mm. It was decided to discharge him and continue his treatment with Eucortone at fortnightly intervals as an out-patient. However, on the evening prior to the day fixed for his discharge he complained of nausea and faintness. During that night he vomited, and while doing so he collapsed suddenly and died within a few minutes. Autopsy report - "Primary Atrophy" of adrenals.

The feature of this case (A-21) was the sudden death that occurred at a time when the patient was apparently in his best possible condition. The marked severity and acuteness of this crisis is all the more astounding when one considers that, apart from the moderate degree of severity of the symptoms when the patient was first admitted, there/

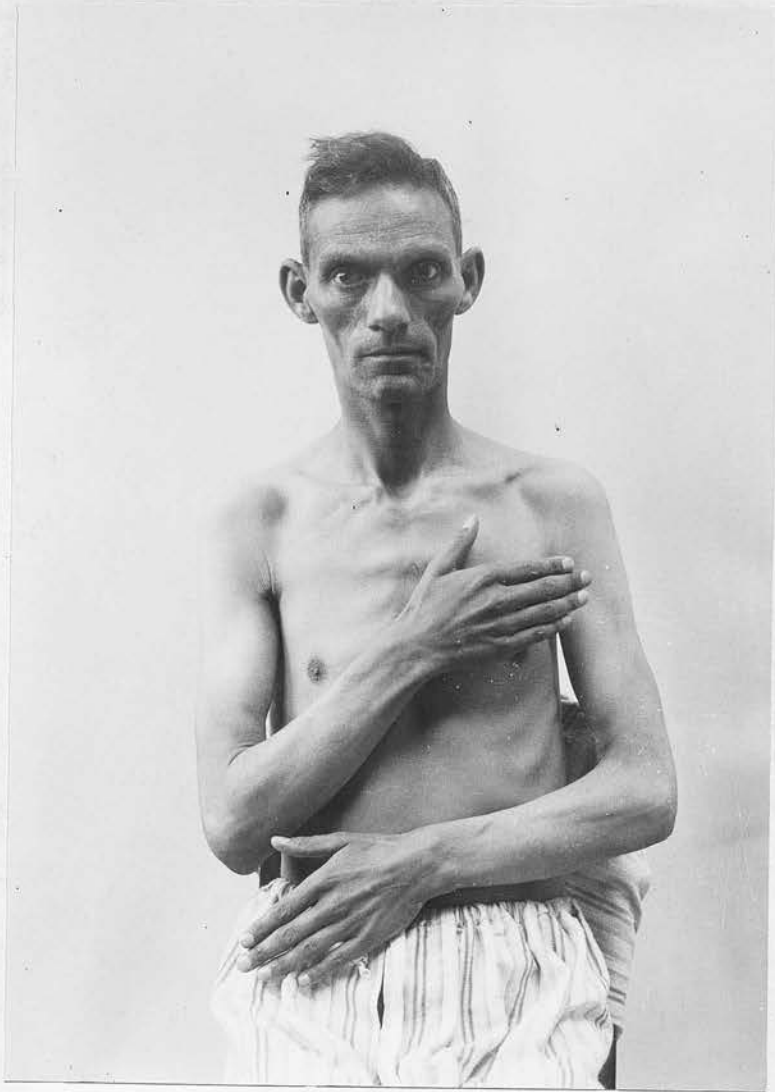
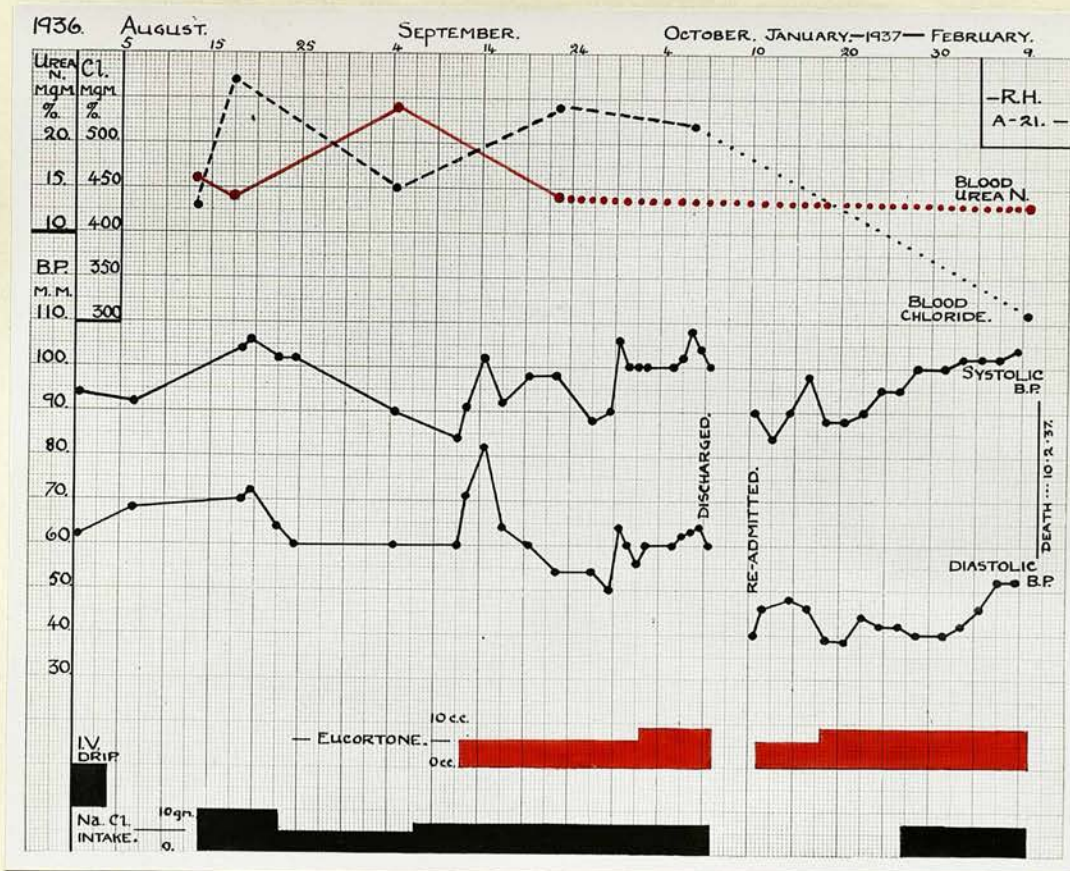


FIGURE 5  
Clinical Photograph  
Case A-21



GRAPH VI

Case A-21. Male, aet 38.

Primary Atrophy of Adrenals.

- Note
- (1) Rise in Blood Chloride and fall in Urea N. following initial NaCl medication, with subsequent return towards original level.
  - (2) Similar change with also rise in B.P. after first course of Eucortone therapy.
  - (3) Slight rise in B.P. after second course of combined Eucortone and salt therapy.
  - (4) Low "chloride" level of the blood taken during the crisis.



there was no indication that he was subject to these acute "crises" of Addison's Disease which are so frequent and so terrible in their effects. An even more amazing fact about this case is that when I performed the autopsy no recognisable adrenal tissue could be located macroscopically. Multiple microscopic sections were made of the perirenal fat and a few small, greatly atrophied adrenal remains were found buried in the adipose tissue. These will be described at length in the further paper that is in preparation. The fact that this patient was able to survive with the comparatively small amounts of adrenal cortical extract supplied suggests that these remnants were, however, functioning to some extent. The preparation used in this patient was the "new" Eucortone which is approximately  $2\frac{1}{2}$  times as concentrated as the "old" Eucortone that was used in all cases described in this paper prior to this case. It is noteworthy that neither the sodium chloride alone, in the first course of treatment, nor the Eucortone alone, in the second course, was nearly so effective in its results as was the use of them in combination (Graph VI).

Case A-22 - Female, aet 50. This patient was admitted in a moribund state. She was grossly dehydrated and intravenous salines were given. However, these had little effect and the patient died in a few hours, with her condition undiagnosed.  
Autopsy/

Autopsy report - Primary Atrophy of the adrenals.

Case seen first in 1937:

Case A-26 - Female, aet 13. Admitted in a moribund state, grossly dehydrated and exceedingly restless. The breath and urine were laden with acetone. There was no glycosuria. The patient was given rectal and intravenous glucose salines with insulin, but she gradually lapsed into coma and died quietly six hours after admission. The illness was undiagnosed.

Autopsy report - Primary atrophy of the adrenals.

The feature in this last case (A-26) is the age of the patient which might naturally mislead any clinical investigator, as it is extraordinarily young for Addison's Disease to occur. At autopsy the adrenals were merely represented by two minute structures whose combined weight was approximately one eighth the normal for the adrenal glands. Microscopically there was revealed a much more acute necrotic picture than is usually the case in the "primary atrophy" type of Addison's Disease.

Both of these last cases (A-22 and A-26) illustrate vividly the difficulties of diagnosis and treatment in a patient who is first seen in the crisis of this illness. It is practically impossible to diagnose the underlying condition in an Addisonian crisis unless a good history is available that might lead one to suspect the cause of the coma. Even then the treatment is by no means easy, as the presence of ketosis may so dominate the picture/

picture that one might be tempted to endeavour to alleviate it as the major disturbance, rather than supply the adrenal cortical hormone that is so manifestly deficient in such a condition.

(b) CASES STILL UNDER OBSERVATION

Case B-13 - Female, aet 44. This patient was admitted on 9:V:36 with a history and clinical picture typical of Addison's Disease. This was, however, only of moderate severity and although the patient had occasional bouts of nausea with vomiting, she apparently had never suffered from a really severe "crisis". The patient was given general tonic treatment at first (Radio-malt, Three Syrups, etc.) and her condition gradually settled. She was then given 150 mgm. Ascorbic Acid daily and her progress continued. There was no appreciable alteration noted in her pigmentation after the adoption of the Vitamin C therapy. There was also no definite increase to be seen in the blood pressure as a result of this treatment. It remained consistently low (96/60 on admission, 94/62 on discharge). The patient was eventually discharged in practically the same state as on admission. Shortly after leaving hospital she developed severe pain in her back and was diagnosed as suffering from Pott's Disease of the Spine. She was therefore admitted to a sanatorium and on inquiring from the superintendent during this year (1938) I have learnt that her general condition is much the same and that she still shows signs of adrenal insufficiency.

The exact diagnosis in this case, owing to the presence of an active tuberculosis lesion, is open to question. When first seen all the clinical features suggested Addison's Disease, but it is possible that the morbid condition in the spine was the sole cause of all her symptoms, although it was not detected on radiological examination when in/

in hospital. It is more probable that there is a definite involvement of the adrenal glands in the tuberculous process, although symptomatically this is certainly secondary now to the bony lesion. The progress of this patient is being carefully watched and in the event of any more definite "Addisonian" symptoms developing the case will be reinvestigated.

Case B-14 - Female, aet 50, (Figure 6). This patient is a typical example of Addison's Disease. She has now been under observation for two years and during that time has had several "crises" which have been successfully treated. She was admitted first in July 1936, and was diagnosed as suffering from Addison's Disease. At that time she had an "Addisonian" history of two years' duration. She was then given the empirical treatment of Potassium Iodide gr. X t.i.d. This therapy made her condition steadily worse and she lost 3.2 Kilo in weight in ten days. The drug was therefore stopped and Calcium Lactate gr. X t.i.d. was next administered. This caused no appreciable effect and she was discharged from hospital a week later with her condition practically the same as on admission.

Unfortunately the data regarding this stay in hospital are very scanty and it has not been possible to present them in graphical form. It was apparent, however, to all who saw the patient at this time that the administration of the potassium increased the severity of the patient's illness.

She was readmitted in January 1937, and her condition was very similar to that on discharge in July 1936. A full investigation of this case was now carried out by me. Various forms of therapy were tried and these have been summarised below. A graphical representation of the patient's treatment and progress is also presented (Graph VII).

Period A. 27th Jan. - 2nd Feb.

Control Period - No treatment.

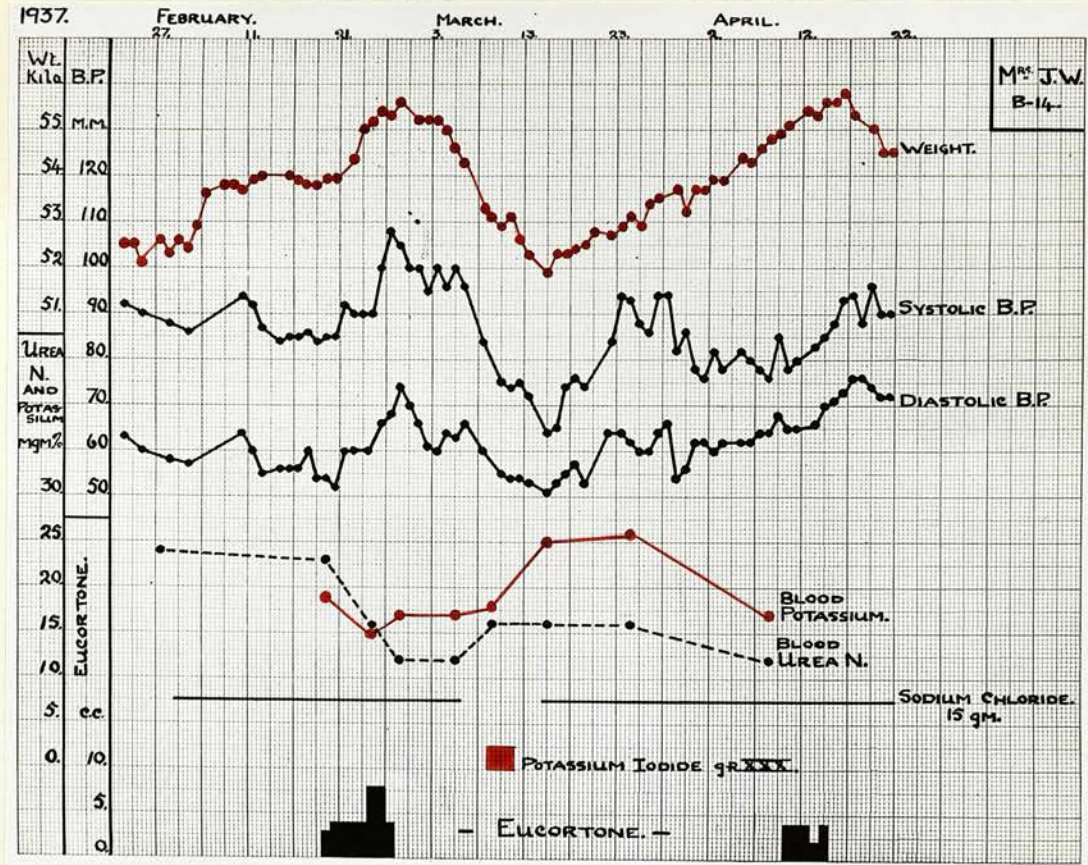
The patient complained of recurrent attacks of neuritis in the arms and legs. There was, however, no obvious change in the patient's general condition during/



FIGURE 6

Clinical Photograph

Case B-14



GRAPH VII

Case B-14. Female, aet 50.

Showing course in hospital after first re-  
admission (27:I:37 to 21:IV:37).

(For explanatory notes see text.)

during this period. On 2:II:37 the B.P. was 88/58 and the weight 52.3 Kilo.

Period B. 3rd Feb. - 18th Feb.

15 g. Sodium Chloride Daily

The patient gradually improved during this period from the clinical aspect. The weight rose to 53.8 Kilo on 18:II:37, but there was little alteration in the B.P. which was 86/60 on that date. On 19:II:37 the blood chemistry showed a low sodium and chloride - 293 mgm.% and 440 mgm.% respectively, while the Urea N. was slightly high 23 mgm.%. The blood potassium was 18 mgm.%. There was a definite increase in the fluid intake and output in this period with a corresponding increase in the chloride excretion (see Table VII).

Period C. 19th Feb. - 26th Feb.

15 g. Sodium Chloride & 4-8 c.c. Eucortone daily.

There was a very marked clinical improvement in the patient and the appetite increased appreciably so that towards the end of this period the patient ate all the food offered to her. The pigmentation became appreciably less. The weight and B.P. rose steadily to 55.3 Kilo and 108/68 mm. respectively on 26:II:37. There was no oedema apparent in this patient at this time that might account for the increase in weight. On 24:II:37 the blood chemistry showed a slight fall in the Urea N. and Potassium - both of which were 15 mgm.%. There was no appreciable change in the Sodium (289 mgm.%) and Chloride (437 mgm.%). The fluid intake and output were practically identical with those in period B, but there was an appreciable increase in the chloride excretion.

Period D, 27th Feb. - 5th Mar.

15 g. Sodium Chloride Daily

The stoppage of the Eucortone caused an immediate lag in the patient's improvement. On 5:III:37 the weight and B.P. had fallen slightly to 54.6 Kilo and 100/64 mm. respectively, whilst the blood chemistry figures revealed no appreciable change from those of 27:II:37. The Urine Chloride content continued at the same high level as in previous period.

Period E. 6th Mar. - 8th Mar.

Control Period - No treatment

The patient exhibited a relapse during this time and many of her symptoms recurred. She complained of feeling tired and of vague pains in the back/

T A B L E VII.

Case B.14. Showing effect of Therapy on Chloride Excretion, Etc.

Period	1937 Dates of Period	Duration in days	Weight at end of Period	Daily Therapy	Intake. Av. daily fluid	Output. Av. daily urine	Average chloride content of urine.	
							g. %	Total daily content
A	28/1-2/2	6	52.3 K.	Nil.	1450cc.	780cc.	0.83	6.26 g.
B	3/2-18/2	16	53.8 K.	Sod. Chlor. 15g.	1860cc.	1140cc.	1.23	13.76 g.
C	19/2 -26/2	8	55.3 K.	Sod. Chlor. 15g. & Eucortone	1890cc.	1195cc.	1.37	16.52 g.
D	27/2 - 5/3	7	54.6 K.	Sod. Chlor. 15g.	1485cc.	1290cc.	1.37	17.49 g.
E	6/3 - 8/3	3	53.4 K	Nil.	1370cc.	860cc.	0.71	6.12 g.
F	9/3 -11/3	3	52.9 K	Pot. Iodide gr. xxx.	1470cc.	1220cc.	0.68	8.26 g.
G	12/3 -14/3	3	52.1 K	Nil.	1490cc.	970cc.	0.59	5.75 g.
H	15/3 - 9/4	26	54.3 K	Sod. Chlor. 15g.	1890cc.	1120cc.	1.08	12.19 g.
I	10/4 -14/4	5	55.6 K	Sod. Chlor. 15g. & Eucortone	2065cc.	1165cc.	1.51	17.45 g.
J	15/4 -19/4	5	55.0 K	Sod. Chlor. 15g.	1940cc.	1330cc.	1.29	17.36 g.



back of her head. She had several restless nights and was very breathless at times. The weight and B.P. dropped sharply to 53.3 Kilo and 84/60 mm. on 8:III:37. The blood chemistry figures revealed little change. The fluid intake and output and the urine chloride content all fell markedly.

Period F. 9th Mar. - 11th Mar.

Potassium Iodide gr. X t.i.d.

The patient became rapidly very much worse and it was thought that she was going to pass into a crisis at one time. In view of her serious state this therapy was not continued for longer than three days. In these there was a continued fall in the weight and blood pressure. The chloride excretion rose slightly.

Period G. 12th Mar. - 14th Mar.

Control Period - No treatment.

No treatment was given in the hope that the patient might show a spontaneous recovery. However, no evidence of this appeared. The patient's condition continued to regress and her symptoms to increase. She suffered from weakness, nausea, flatulence and neuritis in the legs. There was no actual vomiting, however, but the patient suffered from marked insomnia. On 15:III:37 the weight and B.P. had fallen to 51.9 Kilo and 64/50 respectively, while the blood chemistry showed an increase in the potassium to 25 mgm.%. Apart from a slight fall in the already low Sodium, the other figures did not reveal any other significant feature. The urine chloride excretion figure was lower than what it was while the potassium was being administered.

Period H. 15th Mar. - 9th Apr.

15 g. Sodium Chloride Daily.

This therapy caused an immediate though slow improvement in the clinical condition of the patient. The tiredness passed away and the patient became appreciably brighter. The weight rose steadily and on 9:IV:37 was 54.9 Kilo. The B.P. did not rise so markedly and after reaching 93/64 on 23:III:37 fell somewhat and was only 78/64 on 10:IV:37. The blood chemistry on 8:IV:37 exhibited a fall in the Potassium and Urea N. which were 17 mgm.% and 12mgm.% respectively. The Sodium was 306 mgm.% - a definite increase as compared with the level after the administration of the potassium iodide (291mgm.%). The fluid intake and output and the Chloride excretion all showed a definite increase.

Period I. 10th Apr. - 14th Apr./

Period I. 10th Apr. - 14th Apr.

15 g. Sodium Chloride & 2-4 c.c.

Eucortone Daily.

The patient continued to improve. Her weight maintained its upward trend and the B.P. rose sharply. These were 55.6 Kilo and 86/70 mm. respectively on 14:IV:37. No oedema was detected. The other feature in this period was the rise in excretion of chloride with the administration of Eucortone just as in period C.

Period J. 15th Apr. - 19th Apr.

15 g. Sodium Chloride Daily.

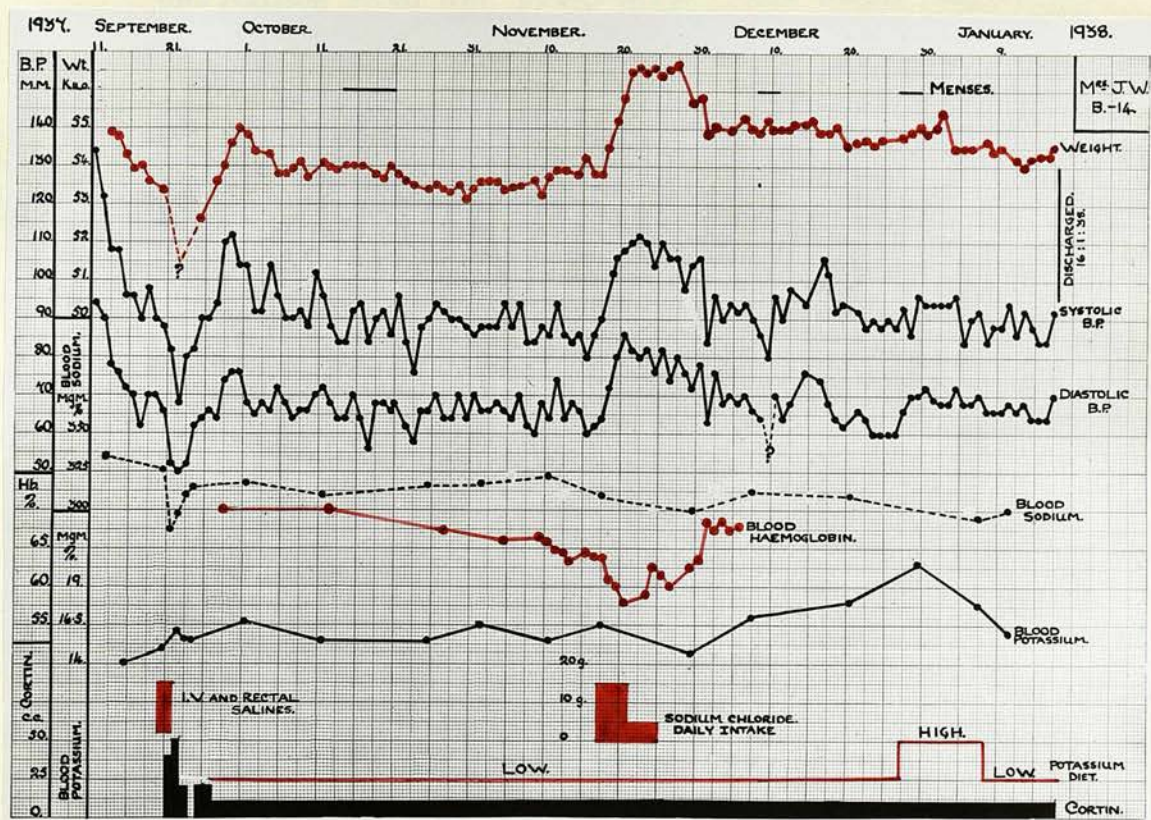
The patient's general progress lagged slightly after the stoppage of the Eucortone. The weight and blood pressure were 55.0 Kilo and 96/72 on 19:IV:37. There was no appreciable change in the total urinary chloride excretion though the percentage fell slightly.

The patient was discharged from hospital two days after the end of this period.

The patient continued to take 15 g. Sodium Chloride daily while at home. Her condition remained good and she was able to go about normally except that she was compelled to remain in bed for several days each month owing to severe menorrhagia. She reported at intervals and was eventually readmitted for a further period of observation. The treatment and course of the patient during this stay in hospital are shown in Graph VIII.

On this readmission on 11:IX:37 the blood pressure was 134/94, but on putting the patient in bed it fell steadily although her condition was unaltered both subjectively and objectively. By 20:IX:37 it was 88/66. On this date the patient was subjected to the Morphine test (Table VI) and as noted previously became very collapsed and required rectal and intravenous salines and large doses of Cortin to resuscitate her. She lost considerable weight during this "crisis" due to the continual vomiting. However, the administration of copious fluids had by 30:IX:37 restored her weight to the level obtaining when she was readmitted. On the same day the blood pressure had risen to 104/76 as compared with the level of 68/50 on 22:IX:37. During the crisis the blood sodium fell to 287 mgm.% as compared with the figure of 327 mgm.% on the previous day. This was restored to a normal level three days after the onset of the crisis as a result of the administration of the salines and the cortin.

After/



GRAPH VIII

Case B-14. Female, aet 50.

Showing course in hospital after second re-admission (11:IX:37 to 16:I:38)

(For explanatory notes see text.)

After she has recovered from the crisis the patient was given a daily dose of 10 c.c. Cortin, and she continued for several weeks with this preparation, having at the same time a diet with a low potassium content (2.16 g. per day). Subjectively she stated that she was in a better condition than she had been for years and was highly delighted with her progress. The major improvement that she noticed was that she was no longer feeling cold, a complaint that she had had since the onset of her illness approximately three years before. Objectively there was no demonstrable improvement in the patient's state. From 14th to 20th October she had a very severe menstrual period which reduced considerably her vitality. However, she soon recovered her former state when the bleeding stopped. Her progress continued in much the same way with a somewhat up and down course though at no time was she really ill. She complained on several occasions of a severe neuritic pain in her arms, and occasionally in the lumbar region. This was usually most marked in the early hours of the morning. A biological assay of the Vitamin B content of her blood showed that it was slightly deficient. There was no tenderness nor other signs of a peripheral neuritis to be found over the affected parts.

On 17:XI:37 the patient was given 15 g. Sodium Chloride daily in addition to the cortin. There was an immediate response to this therapy. Within a day both the blood pressure and the weight began to increase. At the same time there was a well marked increase in the fluid volume of the blood as shown by a fall in the haemoglobin index from 63% to 57% and a coincident fall in the total serum protein from a level of 7.34 g.% on 17:XI:37 to one of 5.31 g.% on 29:XI:37. The patient felt very much stronger as a result of the extra salt. She had, however, one or two mild attacks of vomiting just after taking the salt. On 20:XI:37 (i.e. three days after starting the salt therapy) it was noticed that the patient was "puffy" under the eyes. This oedema gradually increased and consequently the sodium chloride was reduced to 5 g. daily from the following day and finally stopped on 25:XI:37. The weight and blood pressure subsequently fell but became stabilised at slightly higher levels than those at which they stood prior to the administration of the salt.

The/

The patient's progress continued in an uneventful way. She had two further menstrual periods while in the ward and both of these caused considerable exhaustion, and it took several days thereafter for her to regain her basic level.

On 27:XII:37 the patient was put on a diet with a high potassium content (4.9 g. per day). There was no appreciable effect for four days, and then she began to feel weaker and was very easily tired. The blood potassium was 20.6 mgm.% at this time - the highest figure ever recorded with this patient. The weight dropped a trifle and there was a slight rise in the diastolic pressure which was not sustained. Subjectively the patient volunteered the information that she did not feel so well, but objectively there was practically nothing whereby one could demonstrate a deterioration in her general condition. It is, of course, to be noted that the patient was receiving cortin during the whole time that she was having the "high potassium" diet.

On 6:I:38 the patient was put back on the diet with a low potassium content and within three days voluntarily remarked that she was feeling considerably better. She was up and about in a few days and was discharged from the ward on 16:I:38.

The results in this case (B-14) are best compared and contrasted with those of cases B-15 and B-17 and therefore will be discussed at the end of this section after the protocols of the above two cases have been presented.

Case B-15 - Male, aet 20 (Figure 7). This patient was first seen on 19:VIII:35 when he was admitted with a complaint of "lack of energy". This was attributed by him to a crop of boils from which he was suffering. However, on inquiry it was elicited that the patient had noticed that for approximately two years his skin had been much darker than usual. Although there was no history of any nausea or vomiting a diagnosis of Addison's Disease was made.

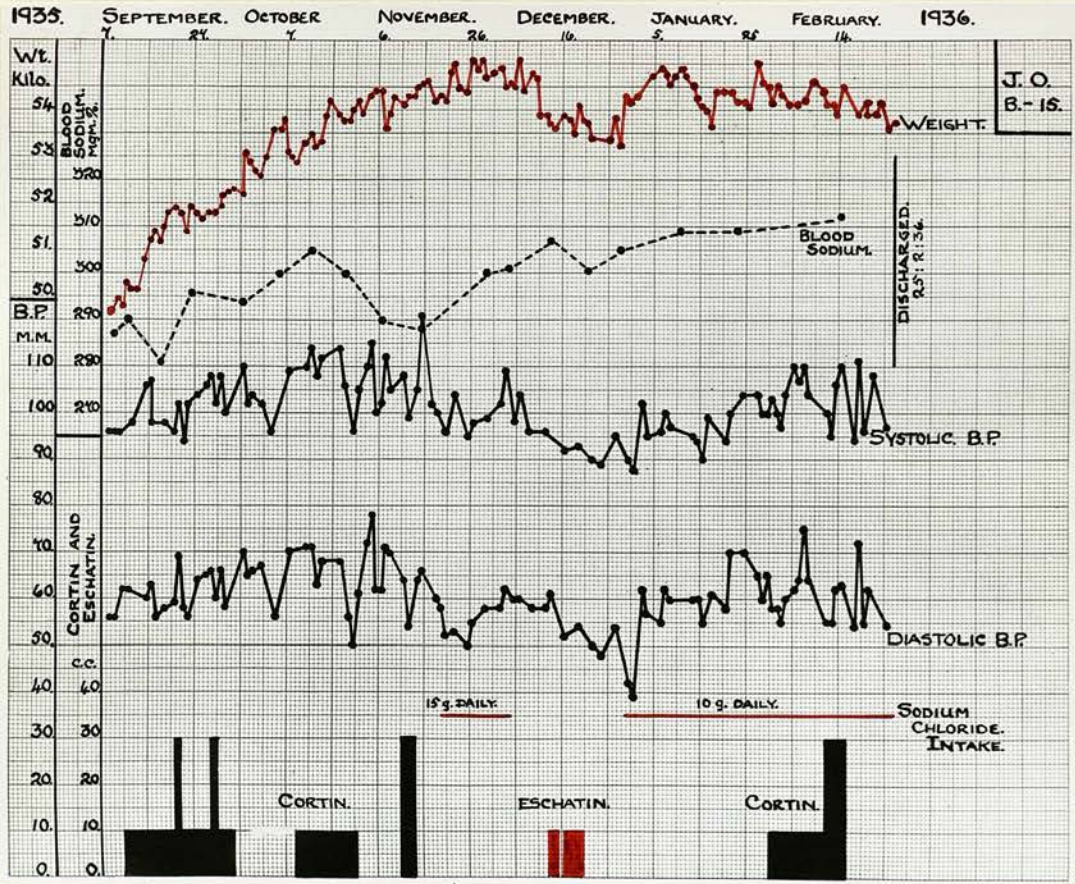
The patient was transferred to the metabolic ward and his further progress is represented in Graph IX. He was given intermittent courses of suprarenal cortical extract. These brought about a/



FIGURE 7

Clinical Photograph

Case B-15.



GRAPH IX

Case B-15. Male, aet 20.

Showing course in hospital after first admission (7:IX:35 to 25:II:36)

a well marked subjective improvement on each occasion they were administered. The patient felt much stronger and was able to get up and go about with ease. The weight steadily increased but there was little alteration in the level of the blood pressure. The gain in weight was most obvious during or immediately after a course of Cortin. This was given either in 10 c.c. or 30 c.c. doses daily (see Graph IX).

The patient was next given a course of 15 g. Sodium Chloride daily commencing on 20:XI:35. This also produced a definite symptomatic improvement and there was a further very slight gain in weight. There was also an appreciable rise in the blood sodium (from 289 mgm.% on 15:XI:35 to 300 mgm.% on 29:XI:35) although it did not reach the normal level.

After some days the patient became nauseated with the excessive salt intake and it was consequently stopped on 4:XII:35. For the next ten days the patient's condition was not so good and he lost 1.5 K. in weight and the blood pressure fell slightly. He was then given a further course of cortical extract therapy. On this occasion Eschatin was used, but it produced no obvious effect. The weight and blood pressure continued to fall. The patient was very listless and complained of feeling tired.

A further course with sodium chloride was commenced on 28:XII:35 and within ten days there was a well marked rise in the weight and in the blood pressure - particularly in the diastolic level. However, this gain in weight was not maintained and the patient soon became stabilised at a level which was slightly above that which he had prior to the salt therapy. On 30:I:36 a course of Cortin was given in addition to the sodium chloride and there was an immediate increase in the blood pressure which, however, swung somewhat during the next few days. There was a coincident slight increase in the weight. Both of these, however, fell again whenever the cortin was stopped. The patient was discharged on 25:II:36 and was told to continue taking 10 g. Sod. Chloride daily.

An estimation of the urinary chloride revealed that there was a definite tendency for a decreased excretion of chloride in the urine during those periods on which cortical extracts were administered. This could be seen most clearly in the total daily urinary chloride content but was also detectable in the/



the percentage of chloride in the urine in the majority of these periods (Table VIII).

The patient continued at home in a satisfactory state of health for about a year. During this time he was taking his daily ration of sodium chloride. At the end of this period he was instructed by his doctor to stop taking the salt. On doing so he felt weaker and became slightly nauseated. Ten days later he began to vomit everything he took including water. He was readmitted to hospital (1:III:37) in a very collapsed state, vomiting continuously and having frequent rigors.

The patient's progress on this occasion is shown in Graph X. A rectal drip was set up at once and large amounts of saline were infused daily both by this route and intravenously. At the same time Eucortone was administered in varying amounts (2 - 12 c.c. per day). This therapy caused an immediate response on the part of the patient. He improved steadily and rapidly. On 12:III:37 a daily administration of 10 g. Sodium Chloride was started. This was continued throughout the patient's stay in hospital. As a result of all this therapy the weight rose rapidly but later declined and continued at a steady level thereafter. The blood pressure exhibited a similar though more delayed rise and fall. Both the blood sodium and chloride, which had been at very low levels when the patient was admitted, rose considerably. Later (8:IV:37) he was given 5 g. Sodium Bicarbonate daily in addition to the Sodium Chloride. This caused no appreciable change in the patient either objectively or subjectively.

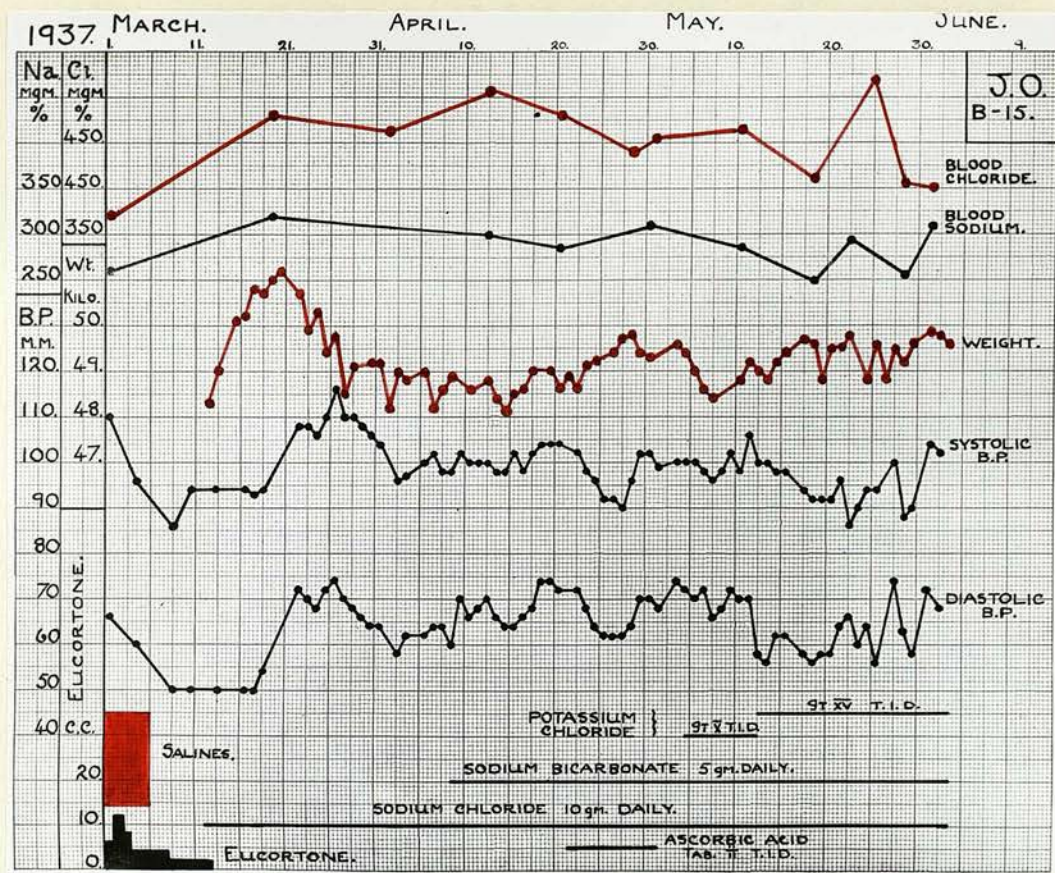
On 21:IV:37 and the subsequent ten days the patient was given 300 mgm. Ascorbic Acid daily. This was followed by an appreciable lessening in the pigmentation although subjectively no difference was noticed.

A course of Potassium Chloride was initiated after the Ascorbic Acid had been stopped (at first 30 gr. and later 45 gr. were administered daily). This was accompanied by a slight fall in the blood pressure and subjectively the patient did not feel so well, although objectively there was little demonstrable change. The blood potassium rose at this time to 32 mgm.%, which was 8 mgm. higher than the level found during the crisis which necessitated his readmission. It is to be noted that during this time that the potassium chloride was being administered/

T A B L E VIII.

Case B.15. Showing effect of Therapy  
on Chloride Excretion, Etc.

Period	1935 Dates of Period	Duration in days	Weight at end of period	Daily Therapy	Intake. Av. daily fluid	Output. Av. Daily urine	Average chloride content.	
							g. %	Total daily content
A	12/9 - 4/10	23	52.3 K.	Cortin, 10cc.	2080 cc.	1350 cc.	0.87	11.78 g.
B	5/10-18/10	14	52.9 K.	None	1910 cc.	1310 cc.	0.91	12.98 g.
C	19/10-31/10	13	54.0 K	Cortin, 10cc.	1730 cc.	1240 cc.	0.96	11.85 g.
D	1/11-10/11	10	54.1 K	None	1440 cc.	1190 cc.	1.12	12.73 g.
E	11/11-13/11	3	54.5 K	Cortin, 30cc.	1550 cc.	850 cc.	1.31	10.57 g.
F	14/11-19/11	6	54.2 K	None	1410 cc.	1180 cc.	1.10	13.00 g.
G	20/11- 4/12	15	54.5 K	Sod. Chlor. 15g.	1850 cc.	1600 cc.	1.08	16.43 g.
H	5/12- 12/12	8	53.7 K	None	1380 cc.	1150 cc.	1.10	12.52 g.
I	13/12-19/12	7	53.7 K	Eschatin, 10cc.	1370 cc.	1140 cc.	0.99	11.08 g.
J	20/12-27/12	8	53.8 K	None	1160 cc.	920 cc.	1.19	10.25 g.
K	28/12-29/1	33	54.5 K	Sod. Chlor. 10g.	1680 cc.	1500 cc.	1.51	21.90 g.
L	30/1 -10/2	12	54.1 K	Sod. Chlor. 10g. & Cortin 10cc.	1170 cc.	1300 cc.	1.46	18.98 g.
M	11/2 -14/2	4	54.2 K	Sod. Chlor. 10g. & Cortin 30cc.	1620 cc.	1320 cc.	1.42	18.70 g.
N	15/2 -24/2	10	53.7 K	Sod. Chlor. 10g.	1870 cc.	1510 cc.	1.43	17.9



- GRAPH X

Case B-15. Male, aet 20.

Showing course in hospital after first  
readmission (1:III:37 to 2:VI:37)

(Note daily dose of Ascorbic Acid = 300 mgm.)

administered he was also receiving sodium chloride and sodium bicarbonate in liberal amounts. The patient was eventually discharged very much improved on 2:VI:37. He was instructed to continue taking 10 g. Sodium Chloride daily.

The patient reported at regular intervals and his progress was carefully watched. He continued to take the salt and all went well until the middle of August. About that time he became somewhat dilatory in the taking of the sodium chloride and on 22:VIII:37 had a sudden fainting attack. He soon recovered from this and at once recommenced his salt diet in full. It was decided to readmit the patient on 9:IX:37 in order that the effect of various diets on his condition might be determined.

The progress of the patient during this stay in hospital is shown in detail in Graph XI. He was put on a diet with a low potassium content (2.6 g. daily) on the day after his readmission. At the same time the 10 g. Sodium Chloride were continued daily. There was a steady improvement in the patient's condition. He put on weight and brightened up considerably. Whereas he was lethargic and listless on admission, he was sitting up and taking considerable interest in his fellow patients by 16:IX:37. On that date the extra salt was stopped.

During the next few days the patient's general condition regressed slightly and he became somewhat depressed. He was inclined to sleep a good deal during the day. On 22:IX:37 and during the next two days the patient complained of a dull pain in his chest situated beneath the left nipple. Physical examination failed to reveal any cause for this. Chemical analysis of the blood taken on 24:IX:37 showed that as compared with the figures found shortly after admission (16:IX:37) the blood sodium and chloride were down (310 to 299 mgm.% and 504 to 460 mgm.% respectively), while the Urea Nitrogen had increased (from 10 mgm.% to 19 mgm.%). All these indicated a slight deterioration in the patient's general state. The blood potassium was practically unchanged. However, with the disappearance of the pain the patient improved visibly and the blood chemistry showed a return of all the inorganic constituents to their former level. During all this time there had been no appreciable alteration in the weight (see Graph XI).

On 27:IX:37 the "low potassium" diet was stopped/



GRAPH XI

Case B-15. Male, aet 20.

Showing course in hospital after second  
readmission (9:IX:37 to 14:II:38)

stopped and the patient was given a diet with a "normal" potassium content (2.9 g. daily) while on 14:X:37 a "high" potassium (4.5 g. daily) diet was started. This latter caused an appreciable deterioration in the subject's condition. Within three days he complained of "feeling tired", and two days later had severe nausea in the morning though there was no actual vomiting. Later still he spontaneously remarked that his new diet did not agree with him as well as did his old (i.e. low potassium diet). Objectively, there were also definite changes. During this time that the patient was on the higher potassium diet his weight fell over 1.5 Kilo. in 8 days. This loss commenced at once and continued throughout the time that the high potassium diet was taken. A corresponding though slight and more tardy fall occurred in the blood pressure. Similarly the blood chemistry showed retrograde changes (i.e. fall in the Sodium and Chloride and rise in the Urea Nitrogen and the Potassium. These changes were, however, not at all marked - see Graph XI).

On 14:X:37 the low potassium diet was recommenced and from 20:X:37 extra salt was given (15 g. Sodium Chloride daily in addition to the salt in the food). This combined therapy of high sodium and low potassium produced a profound effect on the patient. The weight increased by .75 K. in three days; there was a slight rise in the diastolic blood pressure and the blood haemoglobin dropped from 82% to 65% in five days. The blood chemistry showed marked changes, the sodium became higher than had ever been recorded before with this patient and the urea nitrogen fell considerably. Subjectively the patient felt very much better. However, this improvement did not persist for long and he was somewhat listless and depressed during the first week in November. Accordingly on 10:XI:37 a course of suprarenal cortical extract was commenced - 5 c.c. Cortin were given daily. This therapy produced little appreciable subjective change in the patient, but he gained almost 1 Kilo. in weight within five days of its first administration. This gain was, however, only maintained for a few days and then the weight returned to the level at which it had stood prior to the rise. The blood pressure was maintained at a slightly higher figure than what it had been prior to the cortin therapy and the blood chemistry remained at an improved level.

In the first week in December the patient contracted a streptococcal throat infection. This at once brought about a generalised relapse. The weight/

weight and blood pressure both fell; clinically the patient was obviously ill and he became very lethargic and depressed. The throat infection was treated with local applications and with sulphonamide preparations, and although it improved slightly it did not clear up entirely and suddenly flared up again on 19:XII:37. On this date the patient had a rigor and became exceedingly drowsy and irritable. Slight meningismus was present and anorexia was very marked. It was only with the greatest difficulty that the subject could be persuaded to take any fluids. On 20:XII:37 a further rigor occurred. It was very difficult to rouse the patient and he vomited on several occasions. The blood sodium and chloride fell and the urea nitrogen rose - but no appreciable change occurred in the blood potassium. Salines were given per rectum. An attempt to set up an intravenous saline drip failed owing to the restlessness of the patient. On the following day he vomited continuously and could retain nothing. A continuous intravenous drip saline was commenced and was kept going for five days. This was only possible by putting it into the saphenous vein and by strapping the patient to the bed, as he pulled the cannula out of his cubital vein on three occasions. In addition rectal salines were given four hourly and large amounts of Cortin were given intravenously (see Chart XI). The patient's condition was extremely critical at this period and on several occasions his vitality was so low that he was considered moribund. However, each time a slight revival occurred. On 22:XII:37 the blood pressure was 78/44 and the pulse could hardly be detected. It was very soft and irregular at this time but it was not possible to determine the exact nature of the irregularity. Owing to the great restlessness of the patient it was considered hopeless to attempt to obtain an electrocardiographic record. By 24:XII:37 it was just possible to persuade the patient to take some fluids by mouth and by 26:XII:37 he was able to take light nourishment. It was impossible to weigh the subject during this crisis but he was very grossly dehydrated at the time and had obviously lost a tremendous amount. With his improvement after the crisis his tissues rapidly filled up and by 6:I:38 his weight had reached 46.3 K., as compared with 50.6 K. at the beginning of December before the onset of the streptococcal throat infection that brought on the collapse.

It is to be noted that no opiate was used at any time with this patient as it was considered that/

that such a measure would kill him. His nursing during the crisis was exceptionally difficult, and the greatest credit must be given to the nursing staff who so patiently and efficiently carried out their duties without the slightest omission. The patient has complete amnesia of the period of his crisis extending from 20th to 24th December.

After passing the acute phase of the crisis he made steady but slow progress. He was gradually able to eat more and his strength returned somewhat tardily. A daily administration of 5 c.c. Cortin was maintained and on 4:I:38 his daily dose of 15 g. Sodium Chloride was recommenced. He was able to get out of bed on the following day, and was eventually allowed home on 14:I:38. By this time his general condition was very much improved although he had not regained the weight that he had lost during the crisis.

Since his discharge from the ward the patient has been seen at regular intervals. In April 1938 he had a severe bout of toothache and was readmitted to hospital with a view to having a tooth extracted. However, the pain settled down following the administration of analgesics and it was considered inadvisable to attempt any operative procedure on such an obviously frail individual. He was accordingly discharged after a few days. No special investigations nor therapeutic measures were carried out at this time. The patient's general condition was, if anything, slightly better than that on his discharge in January. The blood chemistry figures were very similar to those obtaining on his discharge. There had been a slight increase in weight (47.5 K. as against 46.6 K.). There was no manifest change in the blood pressure.

This case (B-15) will be discussed along with B-14 and B-17 at the end of this section of the paper.

Case B-17 - Female, aet 50 (Figure 8). This patient was first seen on 12:VI:37 when she was admitted with a history of a haematemesis. She was accordingly regarded as a gastric case and treated with a very restricted diet for several days with little effect on her general state, although she had no further haematemesis. Her general condition gradually deteriorated and it was then appreciated that she had several/





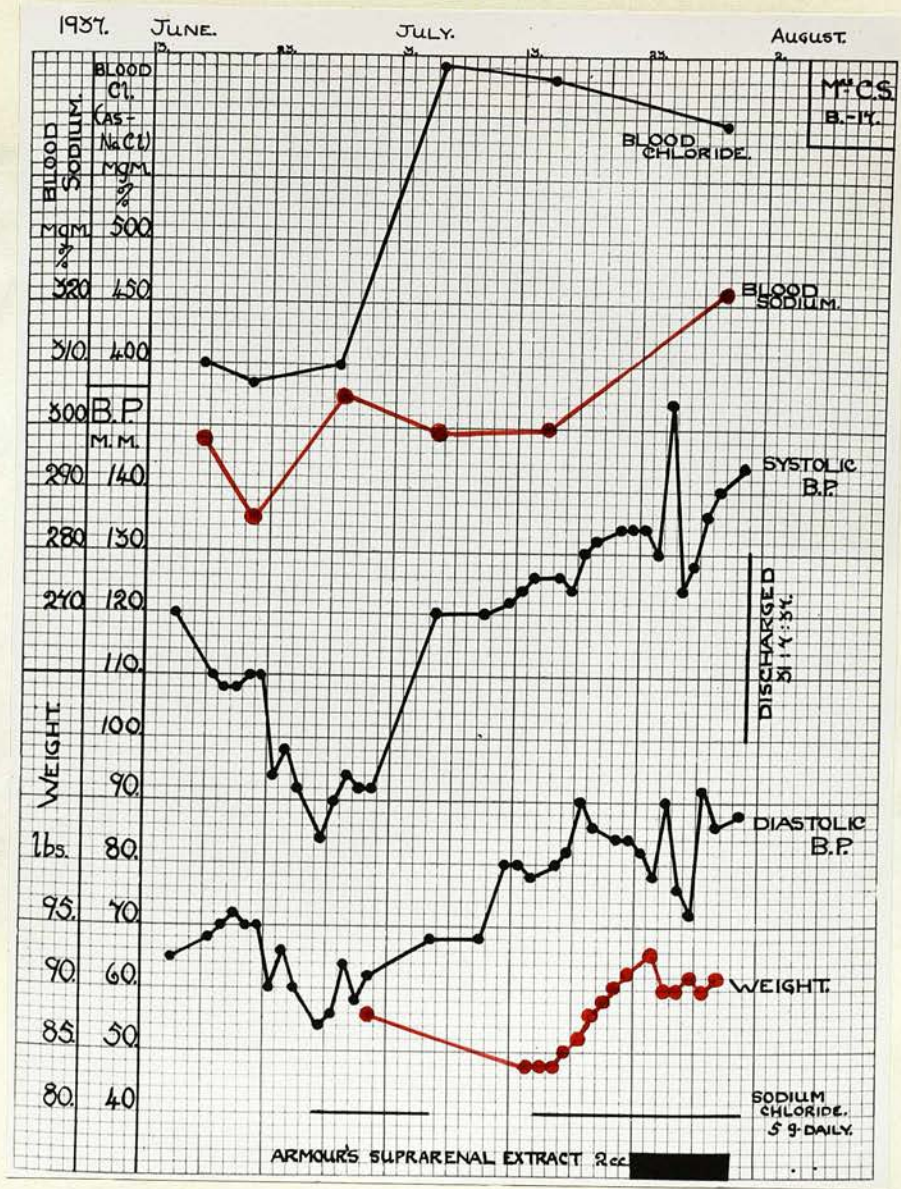
FIGURE 8

Clinical Photograph

Case B-17

several features that could be explained by a diagnosis of Addison's Disease. She exhibited pigmentation and her blood pressure fell steadily so that on 27:VI:37 it was 84/54 as compared with the initial level of 120/65 (Graph XII). Examination of the blood chemistry on 17:VI:37 revealed the changes typical of an adrenal insufficiency (low sodium - 298 mgm.%, low chloride - 400 mgm.%, high Urea Nitrogen - 22 mgm.%). By 21:VI:37 the blood sodium and chloride had fallen further to 285 mgm.% and 387 mgm.% respectively and it was therefore decided to try the effect of salt therapy and she was given a course of 5 g. sodium chloride daily starting on 27:VI:37. This helped her considerably and she became obviously brighter and more energetic, though still confined to bed. There was a sharp and appreciable rise in the blood pressure and in the blood sodium and chloride. On 6:VII:37 the patient had an attack of nausea and vomiting. The sodium chloride was blamed for this and its administration was stopped on that date. The salt was given again from 15:VII:37 and this brought about an appreciable rise in the weight while the blood pressure continued its upward trend and by 22:VII:37 it had reached 134/86, while the weight was 91 lbs. as compared with 84 lbs. prior to the exhibition of the salt. The blood pressure remained at the above level for some days and so from 23:VII:37 the patient was given a course of 2 c.c. of Armour's Suprarenal Extract intramuscularly daily. On 24:VII:37 the blood pressure rose sharply to 154/90 (this reading was corroborated on several occasions throughout the day). On the following day it fell to 124/72, but thereafter rose steadily. The patient's clinical state improved remarkably during this treatment. She was not able to walk, however, as she suffered from chronic arthritis. She was eventually discharged on 31:VII:37 as it was not possible to investigate her fully at the time.

The patient was readmitted to hospital on 8:IX:37 in order that a complete investigation might be carried out on her. She was given various forms of therapy and the results arising from these are shown in full in Graphs XIII, XIV and XV. The various clinical tests that were carried out will be presented in detail in a future paper that is now in preparation. When readmitted the patient was not so well as she was on discharge. The generalised pigmentation appeared to be slightly more marked and the patient was more listless. The weight was 89 lbs. and the blood pressure 110/65 m.m. as compared with the respective values of 91 lbs. and 144/88 m.m. which were found at the time of her discharge/

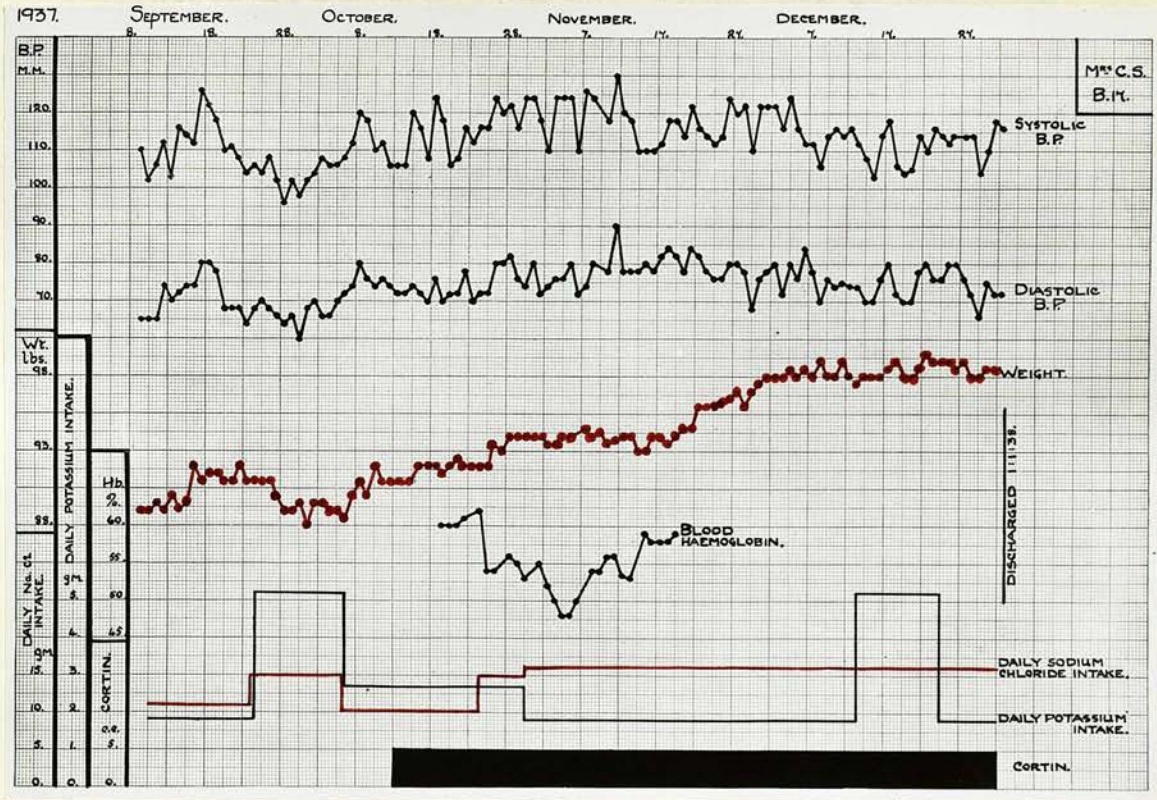


GRAPH XII

Case B-17. Female, aet 50.

Showing effect of salt therapy during the patient's first stay in hospital

(12:VI:37 to 31:VII:37)



GRAPH XIII

Case B-17. Female, aet 50.

Showing clinical course in hospital after  
first readmission (8:IX:37 to 1:I:38)

(For explanatory notes see text)

discharge approximately five weeks before.

Initially an investigation was made regarding the effects brought about by variations in the potassium content of the diet (See Graph XIV). The patient was given in turn, each for periods of 7 to 12 days, a diet with a low, a medium and a high potassium content. No cortical extract was administered at this time and the sodium chloride intake was kept about the normal level. During this time the patient's clinical state was carefully watched. The blood pressure and weight were estimated daily and frequent chemical examinations were made of the blood. The results are set out below:-

Period A. Sept. 8th - Sept. 23rd.  
Low Potassium Diet.

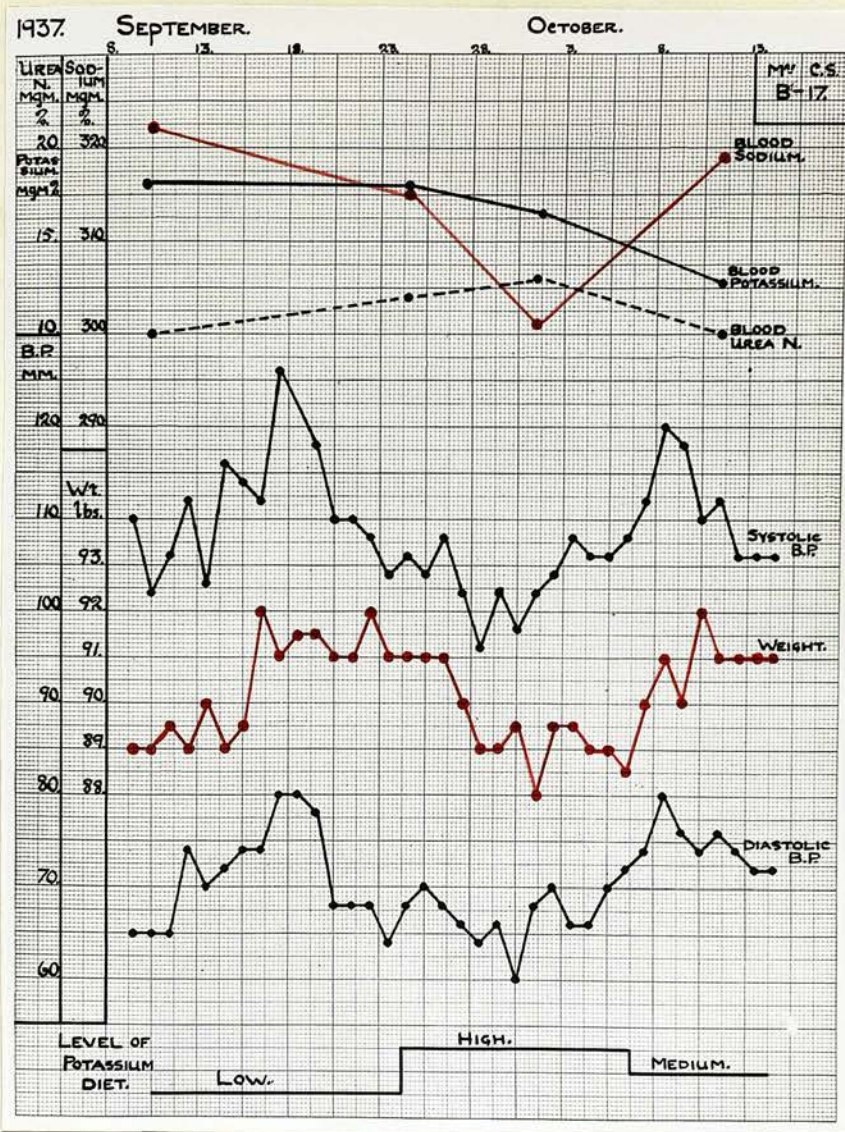
(The daily intakes in the diet were approximately Potassium 1.3 g., Sodium Chloride 10.9 g., Calories 1760.)

This had no appreciable effect for several days and then both the blood pressure and the weight rose (Graph XIV). The increase in B.P. was not maintained and the pressure soon returned to its original level (110/65). The weight, however, remained somewhat elevated and stabilised at 91 lbs. as compared with the 89 lbs. on admission. The patient herself showed quite a noticeable improvement in her clinical condition and became more alert.

Period B. Sept. 24th - Oct. 6th.  
High Potassium Diet.

(Daily values - Potassium 5.2 g., Sodium Chloride 14.9 g., Calories 1890).

Again there was a latent period with no appreciable effect and then on 27:IX:37 the weight began to fall and by 1:X:37 was 88 lbs. It is to be noted that this fall in weight occurred despite the fact that both the sodium content and the caloric value of the diet were slightly higher in Period B than in Period A. There was a corresponding fall in the B.P. but again this returned to the basic level (106/66) spontaneously during the taking of this diet. The patient's condition became obviously worse. She was troubled with flatulence and had frequent attacks of nausea. These latter occurred almost daily and would last 2 - 3 hours. The patient felt very sick during these attacks but never actually vomited. They were often associated with severe epigastric pain. The subject spontaneously remarked that her "new" diet was not so/  
so/



GRAPH XIV

Case B-17.

Showing the effects of variations in the  
Potassium Content of the Diet.

Note:- No Cortical Extract administered -  
Compare with Graphs XV and XVI.

(Calorific Values - Low Potassium Diet	1760
High Potassium Diet	1890
Medium Potassium Diet	1650)

so good for her. She steadily became worse and it was eventually decided that, in view of her state, it was inadvisable to persist with the "high potassium" diet. The blood sodium fell and the urea nitrogen rose slightly during this period.

Period C. Oct. 7th - Oct. 13th.

'Normal' Potassium Diet.

(Daily values - Potassium 2.7 g., Sodium Chloride 10.1 g., Calories 1650.)

The inception of this diet was followed by an immediate increase in the weight (from 88½ lbs. to 92 lbs. in four days) and in the blood pressure. Again the latter improvement was not maintained, and the systolic pressure had fallen back to practically its basic level by 13:X:37 though there was a slight increase in the average diastolic pressure, which then ranged at just over 70 m.m. Clinically there was a tremendous improvement with the stoppage of the high potassium diet. Here again it is to be noted that the weight rose although the salt and calorific intake were lower in this period (C) than in Period B.

Period D. Oct. 14th - Oct. 24th.

Same Diet + Cortin 5 c.c. daily.

Cortin was now given daily throughout the patient's residence in hospital. After a period of four days from the start of the Cortin therapy the weight increased slightly, and this higher level was maintained thereafter. There was no corresponding maintained rise in the B.P. though the systolic pressure exhibited a marked tendency to fluctuate sharply. The diastolic pressure showed no appreciable change. Clinically the greatest improvement noted was a symptomatic one. The patient remarked that for the first time for 2 - 3 years she felt warm. She had constantly been troubled with a feeling that no matter what she did she could not get warm. This impression completely disappeared following the administration of the Cortin. Otherwise the patient's condition showed a definite and generalised improvement. There was a gradual diminution in the degree of pigmentation.

Period E. Oct. 25th - Oct. 29th.

Same Diet. Cortin 5 c.c. daily. Sodium Chloride increased to 15 g. daily.

Within two days the weight began to increase and the patient put on 2 lbs. in 4 days, but thereafter there was a lag.

Period/

Period F. Oct. 30th - Dec. 12th.  
Low Potassium - High Salt Diet, Cortin  
5 c.c. daily.

(Daily values - Potassium 1.8 g., Sodium Chloride 16 g., Calories 1760.)

There was no appreciable effect in this period that was not obvious in Period E. The state of an-hydraemia that had existed prior to the salt administration was well shown by the drop that occurred in the blood haemoglobin level (64% on 24:X:37 to 48% on 4:XI:37). The haemoglobin, however, gradually regained its former level. On 24:XI:37 the weight began to increase once again and rose from 94 lbs. to 98 lbs. in ten days. It then gradually stabilised at that level. About the same time the blood pressure, which had fluctuated considerably, became steadier at a level of 114/74 approximately.

In view of the marked changes that had occurred in this patient both objectively and subjectively as a result of making alterations in the potassium intake (Periods A, B and C) it was thought advisable to find out if the coincident administration of a suprarenal cortical extract could abolish or, at any rate, diminish these fluctuations in the subject's condition. The daily exhibition of 5 c.c. Cortin was continued and by making certain minor alterations in the diet it was found possible to supply both low and high potassium content diets with a uniform sodium chloride level (Graph XV).

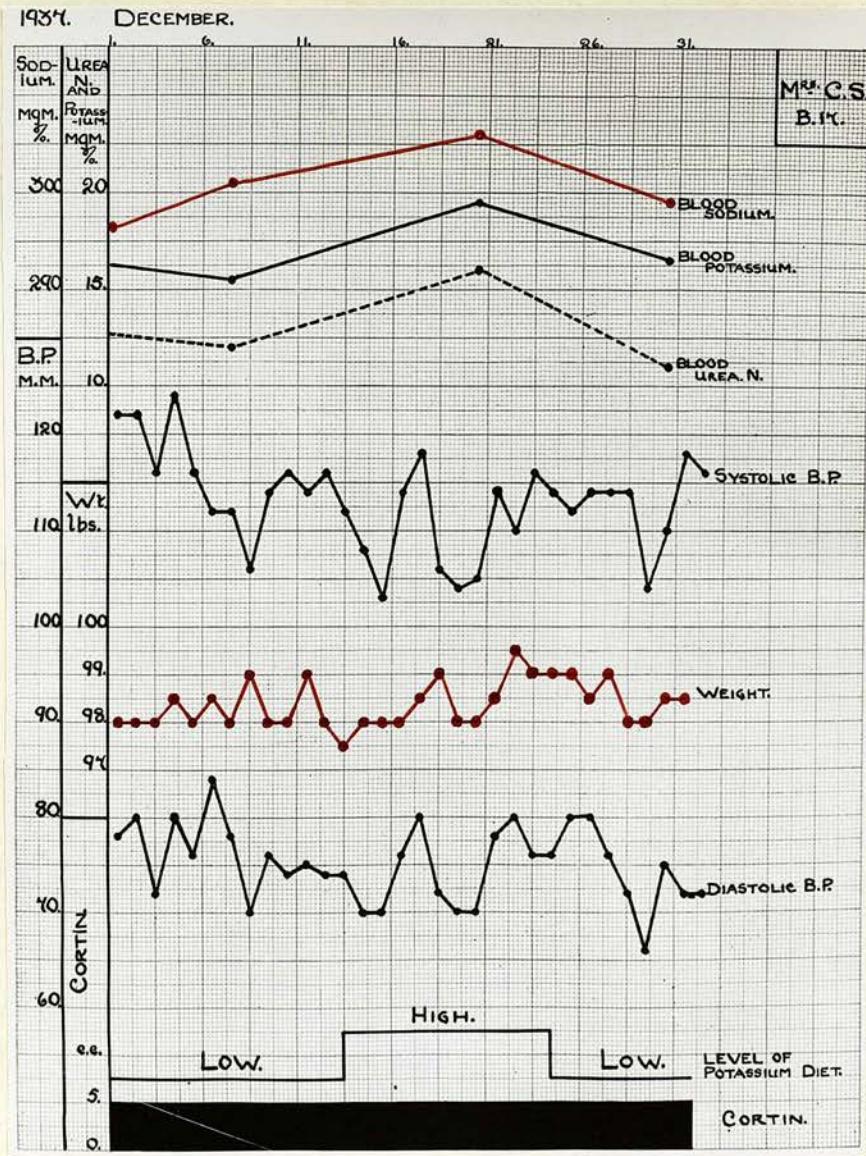
Period G. Dec. 13th - Dec. 21st.  
High Potassium Diet + Cortin 5 c.c. daily.  
 (Daily values - Potassium 5.2 g., Sodium Chloride 16 g., Calories 1890.)

Here also the change in the Potassium content of the diet brought about no appreciable alteration in the patient's condition. Her weight, blood pressure and physical state continued at a uniform level.

As compared with periods A, B and C, the variations in the potassium content of the diets at this time (periods F, G, H) caused no significant change. The only difference between these two experiments was that in the latter Cortin was given throughout (Compare Graphs XIV and XV).

The patient was discharged from hospital on 1:I:38, and, acting on instructions, is taking 10 g. salt daily. Since that date her condition has been satisfactory. She has had several attacks of nausea which are often accompanied by a dull pain in/





GRAPH XV

Case B-17

Showing the effects of variations in the Potassium Content of the Diet during the administration of Suprarenal Cortical Extracts.

Compare with Graphs XIV and XVI

(Calorific Values - Low Potassium Diet - 1760  
 High Potassium Diet - 1890)

in the lumbar region that is most obvious in the early hours of the morning. She has been visited at home on each occasion that these attacks have occurred, but it has not been considered necessary to readmit her, as at no time was there any recurrent vomiting.

Case B-18 - Male, aet 55. This patient is undoubtedly suffering from adrenal insufficiency. He has many of the features of a case of Addison's Disease. However, he has at the same time evidence of an active tuberculous infection. He has had tuberculous adenitis and tuberculous mastitis within the past two years and has recently developed a tuberculous pleurisy. These features have so complicated the clinical picture that it has not been possible to estimate with any degree of certainty the extent of his adrenal deficiency. He is being observed regularly and investigations are being carried out as far as his condition will permit.

Case B-19 - Female, aet 36. The diagnosis in this case has only recently been made (April 1938) and the investigation of the patient is in progress at the moment.

A SURVEY OF THE MODERN TREATMENT OF  
ADDISON'S DISEASE

with particular reference to Cases B-14, B-15 & B-17

During the past three years cases B-14, B-15 and B-17, together with several other patients mentioned above, have provided material for an evaluation of the different methods which are current in the treatment of Addison's Disease. At the outset of this investigation it was decided that an attempt would be made to gauge as far as possible the relative importance of Cortical Extract Therapy and the "High Sodium Diets". Later it became obvious that the potassium content of the diet also influenced the patient's progress considerably.

The/

The comparatively close relationship that exists between these different factors will be readily appreciated on studying the clinical data and graphical progress of the above three subjects. Many interesting features have arisen out of these investigations and several of these are set out briefly below.

#### CORTICAL EXTRACT THERAPY.

Cortical extract was used with each of these three patients and in each case beneficial effects accrued. The best results undoubtedly occurred when it was administered at the same time as large amounts of sodium chloride, but it was obvious that the extract by itself could produce a definite improvement in the patient's condition when administered in adequate dosage.

In Case B-15 the intermittent use of cortical extract without extra salt during the patient's stay in hospital produced temporary phases of clinical improvement with a subsequent relapse when the extract was discontinued (Graph IX). Similar effects have already been demonstrated in Case A-25 (Graph I).

In Case B-14 the beneficial results arising from the coincident exhibition of cortical extract and sodium chloride are clearly seen in the weight and/

and blood pressure curves and in the blood chemistry levels. On two occasions (Graph VII) the cortical extract was stopped while the salt administration was maintained at a uniform level, and immediately there was a deterioration in the general condition of the patient. An analogous picture is apparent on the occasion on which the salt therapy was terminated while the cortical extract was still employed (Graph VIII).

It is worthy of passing notice at this stage that in cases B-15 and A-17 the administration of Suprarenal Cortical Extract caused a decrease in the chloride content of the urine (Tables VIII and III), while in case B-14 a definite increase in the chloride excretion rate was manifest during the use of cortical extract (Table VII). The explanation of this apparent anomaly is being sought. As a tentative investigation the renal function has been estimated in every available case of Addison's Disease. The results, so far, have failed completely to reveal any renal deficiency.

On each occasion that a crisis occurred cortical extract was utilised in large doses along with plentiful amounts of salt in the form of salines. In view of the obvious anhydraemia from which the patients suffered on such occasions it was imperative that fluid should be given and consequently it was never/

never possible to gauge the value of the cortical extract by itself in restoring a patient from a crisis. The combination has been used to resuscitate patients from very severe crises on six occasions, in four of which the subject was unconscious and considered moribund. The fact that that there have been no fatalities in any case in which this combined therapy has been used for the acute phases of adrenal insufficiency is in itself an adequate testimony of its efficacy. It is, however, essential that adequate amounts of both the salt and the extract be given. A major obstacle which overshadows the treatment of the crisis in Addison's Disease is the fact that acute adrenal insufficiency might readily occur in a patient and not be recognised owing to the absence of an adequate history. The subject might be first seen in a collapsed or unconscious state and the presence of Addison's Disease never suspected. At the moment there is no known test whereby such a case can be diagnosed with certainty. Several (A-6, A-8, A-13, A-15, A-22 and A-26) have been noted above in which the patient was admitted to hospital in a moribund state and died before the underlying condition was appreciated. It has also been pointed out already that the ketosis that arises in many of these crises from the recurrent vomiting is a further complicating factor that may readily mislead the clinician as to the cause/

cause of the coma.

The fact that the suprarenal cortex can influence potassium metabolism in some way is already seen in Case B-17 (Graphs XIV and XV) where the definite clinical effects that arose as a result of alterations in the potassium content of the diet were completely abolished by the coincident administration of Cortin. In case B-14 a similar result was present although it was not so manifest. The administration of potassium to this patient had been shown to be very detrimental during her first and second (Graph VII) courses in hospital, and yet its employment during the patient's third course while Cortin was also being given did not produce nearly so marked ill effects on the patient. This matter will be elaborated later in the discussion regarding the effects of potassium in Addison's Disease.

As has been already advanced it is essential that if Cortical Extract is going to be utilised it must be administered freely. The exact dosage depends on the preparation used. The two best known on the British market are probably CORTIN (Organon Laboratories) and EUCORTONE (Allen and Hanburys Ltd.). 1 c.c. of Cortin is made from 50 g. whole fresh adrenal gland, while 1 c.c. Eucortone is derived from 110 g. In a crisis 50 - 100 c.c. Cortin should be given daily while with/

with Eucortone, the makers recommend 20 c.c. Both manufacturers suggest that a daily maintenance dose should be given (Cortin 5 - 10 c.c. and Eucortone 2 - 8 c.c.) but this will be discussed more fully later. Although it is exceptionally difficult to come to a definite opinion regarding the efficacy of these two preparations the general impression formed by clinicians who saw both of them used in the above cases of Addison's Disease was that Cortin is the more potent.

#### THE VALUE OF SODIUM

Cases B-14, B-15 and B-17 each received sodium in copious amounts and in every case its use was followed by good results.

In Case B-14 the administration of sodium chloride after her first readmission in January 1937 brought about an increase in weight and an alleviation of the patient's symptoms (Graph VII). This effect was manifestly increased when Eucortone was used coincidentally. The salt was, however, unable to maintain this improvement when the Eucortone was discontinued. The use of rectal and intravenous salines undoubtedly played a major part in the resuscitation of this patient in the crisis that occurred in September 1937 (Graph VIII).

The development of frank oedema in this patient in November 1937 following the administration of 15 g. Sodium Chloride daily is very unusual in a case/

case of Addison's Disease receiving this therapy. She had received the same amount of salt daily for almost three months previously without the slightest oedema being detected, although it was constantly looked for on account of her increase in weight. The salt undoubtedly brought about an improvement in the physical and mental state of the patient at this time despite the presence of the oedema. A careful search of the literature has revealed only one other recorded case of Addison's Disease in which the administration of extra salt gave rise to oedema (LOEB - 1933).

The use of salt in Case B-15 produced well marked effects. When first seen this patient did not require any salt additional to that contained in his food and in fact its administration in the hospital in November 1935 produced nausea and it had to be discontinued (Graph IX). However, the regression that occurred in the patient's state following this stoppage was so apparent that it was considered necessary to restart the salt therapy which was given in slightly smaller amounts (10 g. daily). He has continued to take the salt ever since.

An interesting fact about this patient is that the discontinuation of the salt on two occasions while at home led to a relapse. On the first occasion it was stopped on the instructions of the patient's own doctor and within three days the crisis ensued that brought the subject into hospital in a serious/



serious state. The patient himself was to blame for the second stoppage, but here, luckily, the premonitory symptoms of faintness were recognised and the salt therapy was restarted before a true crisis could occur. On the occasion of his third sojourn in hospital in September 1937 an opportunity was taken to stop the patient's extra salt at a time when he was on a low potassium diet (Graph XI). Except for the fact that the subject himself was very frightened, because he thought that a crisis was bound to ensue, nothing happened. Once he had regained his confidence he stated that he was feeling perfectly fit. Whenever the level of potassium in his diet was increased, however, there was an immediate fall in weight and an onset of premonitory symptoms of a crisis in the form of marked asthenia and attacks of nausea (see protocol).

This patient (B-15) undoubtedly owes his life to the fact that salines were administered to him. On each occasion that he went into a crisis he received large amounts of saline both intravenously and rectally. The most severe crisis occurred in December 1937 and I am convinced that but for the fact that an intravenous drip saline was kept going for five days, he would not have survived. He became grossly dehydrated and the essentiality for the administration of fluids was apparent to everyone.

The/

The value of sodium chloride in Addison's Disease was also clearly demonstrated in Case B-17 (Graph XII). When the patient was first admitted to hospital and her condition was still undiagnosed she was obviously sinking and it was the use of sodium chloride alone that brought about her revival and, in fact, corroborated the suspicion that had arisen that she might be suffering from Addison's Disease.

Each of the above patients tended to have a low blood sodium level. The figure varied at times and was usually at its lowest when the patient's general condition was poor, particularly at the crises. On several occasions the blood sodium was above the normal minimal value (315 mgm.%) but there was no direct relationship to be seen between it and the sodium intake. Frequently the figure would be normal when no extra salt was being taken and conversely it might be subnormal when 10 - 15 g. Sodium Chloride were being administered daily.

Various methods have been used for the administration of the sodium. It has usually been given in the form of common salt along with some flavouring agent such as Syrup of Orange or Extract of Licorice. However, many patients suffering from adrenal insufficiency are partial to salt and frequently can take much more than a normal individual. Latterly the sodium chloride has been supplied/

supplied in a salt cellar along with the daily food and the patients have taken 5 - 15 g. without the slightest nausea. (A small salt cellar, as for example the size in standard use in the Royal Infirmary, Edinburgh, holds approximately 14 g. of salt.)

#### THE IMPORTANCE OF A LOW POTASSIUM INTAKE.

The dangers underlying the taking of a diet with a high potassium content have been demonstrated in each of the three cases B-14, B-15 and B-17, and the work of WILDER and SNELL and their collaborators (1936 and 1937) has been corroborated.

On the first occasion that Case B-14 was in hospital in July 1936 she was given the empirical treatment of potassium iodide. At that time the ill effects that arose from the use of potassium in Addison's Disease were not generally appreciated, but it is of interest to note that it was soon realised that the potassium iodide was increasing rather than alleviating this patient's symptoms. During her second stay in hospital potassium iodide (gr. XXX daily) was deliberately administered to the patient. However, in view of the ill effects that again rapidly arose it was not possible to continue this drug for more than three days (Graph VII). The patient's condition was, however, deteriorating at the time following the discontinuation of cortical extract therapy, and consequently, it was felt that/

that no infallible conclusion regarding the toxic effects of potassium could be drawn from the results. Accordingly it was felt justifiable at a later date (Graph VIII) to give the patient a high (4.9 g.daily) potassium content diet. Apart from mild subjective changes, the only demonstrable ill effects from this was a slight fall in weight. However, it is to be noted that the patient was receiving 5 c.c. Cortin daily during this time.

The effect of variations in the potassium intake was also to be seen in Case B-15. This patient passed into a crisis on the two occasions on which he stopped his extra salt intake when at home, and yet exhibited no signs of such a condition at the time that his additional salt was discontinued in hospital. On the latter occasion he was receiving a "low potassium diet" (Graph XI), while on each of the former he was eating his ordinary diet at home, which presumably contained a much higher potassium content than the special hospital diet. However, when the hospital diet was experimentally changed from one with a low (2.6 g. daily) potassium content to a high(4.5 g. daily) content there was a definite deterioration in the subject's condition. Within three days he complained of weakness and nausea while there was a fall in weight of 1.5 Kilo. in eight days, and a slight fall in the blood pressure/

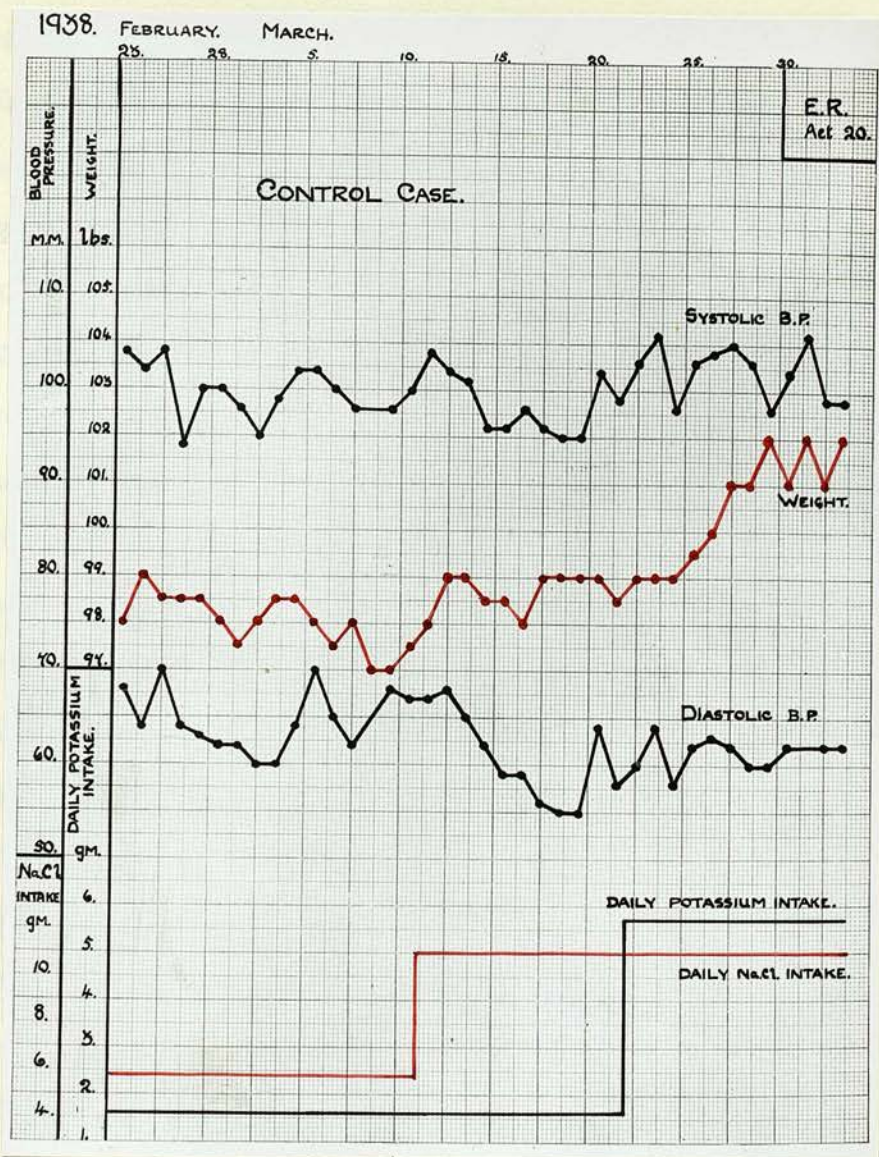
pressure that was later in onset than the fall in weight. Previously the administration of Potassium Iodide (gr. XXX - XLV daily) during ample sodium therapy had produced similar though much less marked features (Graph X - see above). It was thus shown that an adequate sodium intake could diminish appreciably the ill effects arising from a high potassium intake.

Case B-17, however, provided by far the best demonstration of the ill effects of Potassium. The taking of a diet with a high (5.2 g. daily) potassium content produced profound effects on the patient (see protocol). The weight fell and subjectively the patient had frequent attacks of nausea and abdominal pain. Her condition deteriorated appreciably and became so bad that the diet had to be discontinued. On resuming a diet with a normal Potassium content (2.7 g. daily) the patient quickly regained her former state (Graph XIV). A repetition of the same sequence of diets while 5 c.c. Cortin were being administered daily produced no detectable effect (Graph XV), showing clearly that the cortical extract was capable of "covering" the effect of a high potassium intake, as was previously noted in Case B-14 (see above).

A control patient was given the same form and sequence of diets as Case B-17 and the results are presented/

presented in Graph XVI. The patient was suffering from debility and had no evidence whatsoever of adrenal insufficiency. The administration of the high potassium diet produced no ill effects whatsoever - the patient, indeed, voluntarily remarked that she thought it agreed with her better than the "other" (i.e. low potassium) diet. It will be seen from the graph that instead of bringing about a fall in weight the high potassium caused an appreciable increase. This may be attributed to the fact that it had a higher calorific content than the low potassium diet. The same calorific relationships were present in the diets (high Potassium - 1890 Calories, low Potassium - 1760 Calories) given to case B-17, in which an actual loss in weight occurred with the high potassium diet.

The level of the blood potassium was estimated repeatedly in each of the patients on whom a complete investigation was carried out by me (B-14, B-15 and B-17). No complete correlation was found between the blood potassium and the clinical state of the patient although the potassium was unduly high during the occurrence of the crises. The mean value of the high levels found were well below those reported by ALLOTT (1936) and I am unable to support his observation that the crises were/



GRAPH XVI

Control Case

Showing the effect of a high potassium diet in a patient not suffering from Addison's Disease.

- Note:- (1) No ill effects occurred.  
(2) Patient gained weight and did not lose it.  
(Compare Graphs XIV and XV)

were frequently preceded by a rise in the blood potassium (ALLOTT, 1936 and 1938).

The preparation of a low potassium diet presents several obstacles. It is difficult to obtain such a diet that is still palatable and adequate in all the essentials. In addition, the appetite of a person suffering from Addison's Disease is notoriously fickle and it is necessary therefore that the food should be as appetising as possible. VICTOR (1937) of the Mayo Clinic has made a careful study of this matter and has produced an elaborate paper that gives in detail the potassium content of the various common food-stuffs. She has shown also that it is possible to reduce the amount of potassium in many eatables by special methods of cooking. The diets used in this investigation have been largely prepared from the data supplied in her paper and also from those of BRIDGES (1937). Other workers who have made a study of the potassium content of food-stuffs are DAVIDSON and LECLERC (1936) and ABRAHAMS and WIDDOWSON (1937). The latter describe an easily prepared low potassium diet and, as their analyses have been made on British edibles, one should perhaps consider their figures as the most suitable for use in this country. It has been shown that there is considerable variation in the potassium content of the same substances (e.g. vegetables) when/



when grown in different parts of the world. This depends apparently to a large extent on the mineral content of the soil.

Tests are herewith appended of those foods which have a low and those which have a high potassium content. These tables have been compiled from various sources and they represent the average of the values advanced by different authorities (Tables IX and X).

It is, of course, obvious that when constructing a diet one must consider not only the concentration of potassium in each constituent but also the amount of that constituent which is likely to be consumed (e.g. milk, which has a moderately low potassium content, may be taken in such quantities that a large potassium intake will occur.)

The normal daily average potassium content in the diet is about 2.5 - 3.5 g. This is far too high for a case of adrenal insufficiency. If possible not more than 1.5 g. of potassium should be allowed daily. It is difficult to get much below this level and yet provide sufficient protein together with enough of the various essentials. It is comparatively easy to obtain a sufficiency in calories, but the restriction of food-stuffs with a high potassium concentration is apt coincidentally to/

T A B L E IX.

Foods lowest in Potassium.  
(Figures represent mgm. per 100 gm.)

0 - 30	30 - 60	60 - 90	90 - 120	120 - 150	150 - 180
Fresh butter	Buttermilk	Apples	Beef (corned)	Beef (stewed)	Mutton (stewed)
Margarine	Cheese	Asparagus	Berries (stewed)	Bread (white)	Orange
Suet	Cornflower	Beans (French)	Biscuits (cream)	Cauliflower (boiled)	Plums
Sugar	Marmalade	Carrots (boiled)	" (water)	Cherries (stewed)	Rabbit
Tapioca	Onions (boiled)	Cream	Cabbage (boiled)	Flour	Pork
Tripe		Pears	Celery	Kidney	
		Swedes (boiled)	Cucumber	Lemon	
			Egg	Milk	
			Jam	Peas	
			Rice	Turnips (boiled)	

T A B L E X.

Foods highest in Potassium.  
(Figures represent mgm. per 100 gm.)

Over 700	500 - 700	350 - 500
Apricots	Cocoa	Artichokes
Currants	Dates	Bananas
Figs	Lentils	Bacon - fried
Nuts	Mushrooms	Beans - butter
Potatoes - chip	Potatoes - baked	Beef - roast
" - roast		Chicken
Raisins		Chocolate
Sultanas		Cod
Treacle		Ham - boiled
		Herring - fried
		Liver
		Milk - condensed
		Oatmeal
		Peach
		Potatoes - boiled
		Sardines - tinned
		Spinach
		Veal - roast

to produce a deficiency in calcium and iron. The inclusion of cheese in the diet helps to increase the calcium intake considerably without materially adding to the potassium quota. Cheese also contains a small proportion of iron but this element is more conveniently supplied in the form of ferrous sulphate. The content of Vitamins A, C and D is adequate in a low potassium diet, but there is usually a deficiency in Vitamin B. This lack can be made good to a large extent by the introduction of marmite. The addition of this substance fortunately does not increase the potassium content to any appreciable extent.

A typical low potassium diet which was used on several occasions during the present investigation has been set out (Table XI). It will be seen that the total daily calcium intake fulfils the normal requirements. The iron at 8 mgm. approximately is definitely low when compared with the daily requirement of 15 mgm. In practice this is made up by prescribing ferrous sulphate, a measure that possesses the further advantage of being helpful for the anaemia that is frequently present in cases of Addison's Disease.

#### CONCLUSION

From the facts that have been set out above, both in the part that deals with the development of/

T A B L E XI.Typical Low Potassium Diet.

Approximate Contents: Carbohydrate 150 g. Protein 50 g.  
 Fat 100 g. Calories 1700. Potassium 1.7 g.  
 Sodium Chloride 5.8 g.

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Breakfast: Grams.

Bacon - grilled	45
Bread - white	40
Butter	12
Marmalade	20
Two cups (300 cc) Tea with milk and sugar 10 g.	50 g.

10.30a.m. Orange Juice 50

Dinner:

Meat (Roast or mince steak or rabbit or chicken or fish)	45
Vegetable (Cabbage, sprouts, cauliflower, turnip, carrot, or tomato)	50
Potato	50
Butter	8
Cereal pudding (10 g cereal, 10 g. sugar and 150 g. milk)	30
Cream	30

Tea:

1 egg - poached or boiled	40
Bread - white	12
Butter	15
Cheese	15
Two cups (300 cc) Tea with cream 30g. and sugar 10 g.	30 g.

Supper:

1 biscuit (water or cream cracker)	30
Bread - white - toasted	10
Butter	10
Marmite - $\frac{1}{4}$ teaspoonful with 150cc water	10

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(The above diet contains 750 mgm. Calcium and 8 mgm.  
 Iron approximately.)

of therapy and in that which presents several illustrative clinical cases, it will be appreciated that the treatment of cases of Addison's Disease is a very complex matter.

A more complete understanding of mineral metabolism has revealed the close connection between its control and the suprarenal glands. . In the past decade rapid advancement has been made in our treatment of Addison's Disease, and it is difficult to envisage the methods that will be used in a further ten years' time.

In the majority of cases of Addison's Disease it is now apparently possible to keep the patient alive in a moderately fit condition by the administration of adequate amounts of sodium. Chlorine is also necessary, but is of less significance. It is, however, of primary importance that the potassium intake be kept low. The control of the dietary of the patient cannot, however, prevent the onset of crises. These are liable to arise as a result of some apparently insignificant complication such as the occurrence of a mild infection or the taking of some drug which in itself is not toxic to a normal individual. At the time of the crises it is necessary to administer copious salines along with large amounts of a potent cortical extract which must, therefore, always be held in readiness for such/

such an emergency.

Operative procedures must be avoided in patients suffering from Addison's Disease if it is at all possible, and, as will be appreciated from the case records noted in this paper, the use of opiates in such cases may be fraught with considerable danger.

#### SUMMARY

1. The treatment of Addison's Disease is traced from its inception to the present time and the principles underlying the various forms of modern therapy are propounded and discussed.
2. All cases of Addison's Disease that have entered hospitals in the Edinburgh area in the period 1927 - 1938 are reviewed and their treatment analysed.
3. Original investigations into the different forms of modern therapy have been carried out and the results are presented.
4. It is shown that cortical extract is undoubtedly beneficial when administered by itself and that its use is essential in times of "crisis".
5. The effect of Cortical extract is greatly enhanced by the coincident use of sodium chloride or abundant salines.

6. Evidence is produced to show that between the crises the administration of cortical extract is not necessary, provided that a high sodium chloride and a low potassium intake are maintained, and that no intercurrent toxic condition arises.
7. It is demonstrated that a high potassium intake in Addison's Disease is detrimental, but this may be "covered" if ample cortical extract is given or if the sodium intake is sufficiently high.
8. It is suggested that all cases of Addison's Disease should have a diet with a low potassium content, and the difficulties underlying the preparation of such a diet are discussed.
9. Several typical food-stuffs are tabulated according to their potassium content and a suggested low potassium diet is outlined.
10. Cases of Addison's Disease are described illustrating the application of the above conclusions.

I desire to express my gratitude to the Physicians and Surgeons of the Edinburgh Hospitals for their permission to utilise their case records and in several instances for access to their patients. In particular, I am greatly indebted to Professor D. M. Dunlop and Dr W. D. D. Small for the/



the freedom of action that they allowed me in their charges, to Professor A. M. Drennan for his help in enabling me to carry out the experimental work connected with this study, and to all three for their advice and kindly encouragement at all times.

My thanks are also due to many individuals possessed of special ability and facilities who placed their services at my disposal and without whose help this paper would have been lacking in many details necessary for the compilation of the historical and clinical surveys presented. These include Mr T. W. Graham and Miss M. P. Russell of the Library of the Royal College of Physicians; Miss Charlton of the Central Medical Library; Sister A. Buchan and Miss O. Jehu of the Dietetic Department, Royal Infirmary, and Dr C. P. Stewart and the technicians of the Biochemistry Department of the same institution.

In the preparation of the illustrations for this work I have been fortunate in having at my disposal the photographic skill and experience of Mr T. C. Dodds of the University Pathology Department. The clinical photographs were taken by Mr R. P. Danskin.

Part of the above work was carried out during the currency of a Crichton Scholarship and during the half-year tenure of a Houldsworth Scholarship.

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