RECENT ADVANCES IN THE TREATMENT OF ADDISON'S DISEASE.

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The researches of the last few years have added greatly to our knowledge of the functions of the cortex of the adrenal, and have increased the interest taken in the rare condition called Addison's disease. The description written by Thomas Addison⁽¹⁾ in 1855 is worth reading again, as it gives such a clear cut picture.

"The patient, in most cases I have seen, has been observed gradually to fall off in general health; he becomes languid and weak, indisposed to either bodily or mental exertion; the appetite is impaired or entirely lost; the whites of the eyes become pearly; the pulse small and feeble, or perhaps somewhat large, but excessively soft and compressible; the body wastes, without however presenting the dry and shrivelled skin and extreme emaciation usually attendant on protracted malignant disease; slight pain or uneasiness is from time to time referred to the region of the stomach, and there is occasionally actual vomiting, which in one instance was both urgent and distressing; and it is by no means uncommon for the patient to manifest indications of disturbed cerebral circulation We discover a most remarkable, and, so far as I know, characteristic discolouration taking place in the skin—sufficiently marked indeed, as generally to have attracted the attention of the patient himself or the patient's friends. This discolouration pervades the whole surface of the body, but it is commonly most strongly manifested on the face, neck, superior extremities, penis and scrotum, and in the flexures of the axillæ and around the navel. It may be said to present a dingy or smoky appearance or various tints or shades of deep amber or chestnut brown; and in one instance the skin was so universally and so deeply darkened that but for the features, the patient might have been mistaken for a mulatto This singular discolouration usually increases with the advance of the disease, the anæmia, languor, failure of appetite, and feebleness of the heart becomes aggravated, a darkish streak usually appears upon the commissure of the lips; the body wastes, but without the emaciation and dry, harsh condition of the surface so often observed in ordinary malignant disease; the pulse becomes smaller and weaker; and without any special complaint of pain or uneasiness the patient at length sinks and expires."

Addison pointed out that the chief pathological lesion at autopsy was the change in the adrenal gland. We now know that the gland may either be atrophied or affected by tuberculosis. In the latter case the disease is always secondary to a tuberculous lesion elsewhere, which may be active or obsolete. The cause of the atrophy of the gland was a mystery, but the recent advances in our knowledge of the functions of the anterior lobe of the pituitary gland suggests an explanation. When the anterior lobe is removed, the adrenal gland, the thyroid, testes and ovaries, and breast tissues, all atrophy. Further, an extract has been prepared from the anterior lobe, the adrenotropic hormone, which has a specific effect in preventing the atrophy of the adrenal. Nicholson⁽²⁾ has examined the pituitary gland in seven cases of Addison's disease; in four the adrenal cortex was affected by tuberculosis, and the pituitary was quite normal; in three cases where the cortex was atrophied, there was a great reduction of the ordinary basophil cells in the pituitary gland, and an increase in the abnormal basophil cells. This work suggests that the atrophy of the cortex may be primarily due to some lesion of the anterior lobe of the pituitary gland.

When Oliver and Shafer showed that the extract of the adrenal gland, now called adrenalin, which is present in the medulla, raised the blood pressure, it was thought it would be of great value in the treatment of Addison's disease. This belief was soon proved erroneous and we now know from animal experiments that the medulla of both glands can be completely destroyed with the electro-cautery without causing any symptoms of ill health. Since the animals die when both the adrenals are removed, the cortex must be essential to life, and the symptoms of Addison's disease due to a failure of the adrenal cortex. Many attempts were made to prepare extracts of the adrenal, but for a long time these were fruitless. In 1930 Rogoff and Stewart, Hartman, Swingle and Pfiffner, independently prepared extracts which were potent, and since then great improvements have been made in these extracts, though they are still not as potent or as cheap as could be wished. The experiments have been carried out on dogs and cats, and at first it was found that the average life of the animal after adrenalectomy was from 16 to 48 hours, but with greatly improved methods of technique and especially of nursing, the average life of an adrenalectomized dog has been prolonged to 8 days, and some may live as long as 14 days. When the animals are injected with potent extracts life is prolonged indefinitely, and many elaborate studies have been made. The changes which take place when the potent extract is withheld from a dog which is in apparently perfect health are well shown in the diagram given by Harrop, Weinstein, Soffer and Trescher⁽³⁾.

FIG. 1.

Characteristic changes in metabolism, circulation, and blood concentration in a group of supra-renalectomized animals following withdrawal of extract.

(By permission from "Studies on the Suprarenal Cortex," by Harrop, Weinstein, Soffer, and Trescher. *Journal of Experimental Medicine*, 1933, 58, 13.)

On the first day the volume of the plasma begins to decrease and by the sixth day is only 30 or 40% of its original volume. The blood urea also begins to increase on this day, and by the sixth day has increased by 100 to 300%, thus showing that renal failure occurs. On the second day the oxygen

capacity of the blood begins to increase and by the sixth day is 2-5 vols. % greater than it was. The plasma protein also increases by 15 to 20% on the sixth day. The rate of the blood flow begins to decrease on the second day. The body weight begins to fall, and by the sixth day has decreased by 10%. On the fourth day the basal metabolic rate begins to decrease, and by the sixth day has fallen by 20%. The rectal temperature also decreases on this day and may be 5-6°F. less than normal on the sixth day. Contrary to expectation the blood pressure does not show any decrease until the sixth day, when it falls rapidly and may be 60-80 mg. of Hg. less in the course of 24 hours. The animal begins to refuse to take food on the fifth day; on the seventh day develops muscular weakness and a spastic gait, and usually dies on the eighth day. The clinical picture is very striking and interesting. Swingle and Piffner⁽⁴⁾ suggest that it is closely allied to that called "surgical shock." They found that if a small amount of blood, say 1-20 of the blood volume, was removed from a healthy dog, or one which is kept in perfect health by means of a potent extract, no symptoms of ill health develop. If, however, the same volume of blood is extracted from an adrenalectomized dog which had had no cortical extract for three days, the animal dies within 24 hours, although it can be restored to health if some extract is injected. The condition of the dog is not identical with that of a dog dying of surgical shock as the dogs continue to pass urine and there is no increase of red cells in the capillary blood which is a constant finding in surgical shock. The resemblance is however sufficiently close to advocate the administration of cortical extract and intravenous injections of 5 or 10% of sodium chloride to all cases of surgical shock.

The treatment of patients suffering from Addison's disease with cortical extract has been striking but also disappointing. Levy Simpson⁽⁵⁾ gave an interesting account of its use on six patients in 1932. They were all improved in health, although three died of other serious complications. Snell⁽⁶⁾ has analysed the results of the treatment of a large series of cases. These results are not very good, although they are a considerable advance, as it is practically certain that all the patients would have died if the extract had not been available.

TABLE I.
MAYO CLINIC 1930-31.

TOTAL CASES 48.

Died 32.

- 2 admitted very ill.
- 4 improved but discontinued treatment.
- 14 could not get enough extract.
- 12 died in spite of the best treatment available at that time.

Alive 16.

- 7 quite well for more than 1 year.
- 6 fairly well after 6 months.
- 3 poor health because of inadequate amount of extract.

There are two main difficulties in the use of the extract. (1) A small dose is 10 c.c. and the price of this varies from 11/- to 30/-. If the patient is very ill two or five times the amount must be injected. This expense is almost prohibitive except for those patients who are very rich or who are being treated in hospital for research purposes, and unless the cost of the extract can be reduced many patients must eventually die owing to lack of money to buy the extract. (2) The potency of the extract is said to vary very considerably and the methods of standardization are not at all easy, but it is to be hoped that improvements in this respect will soon take place.

All the intensive work on the preparation of the extract and its effect on patients did not explain what the function of the cortex was, and it is to Robert Loeb⁽⁷⁾ that we owe a new conception of one at least of its functions. Loeb had been estimating the balance of bases, and acid radicles in various conditions, and made a complete examination of the blood of three patients with Addison's disease.

TABLE II.

BLOOD CONTENT of Na, K and Cl in HEALTH and ADDISON'S DISEASE (Loeb.).

NORMALS.				ADDISON'S DISEASE.	
Mgm. per 100 c.c.				Mgm. per 100 c.c.	
Sodium	...	...	325-350	{	248 Case 1
					246 „ 2
					300 „ 3
Potassium	...	...	18.7	{	27.6 „ 1
					33.9 „ 2
Chlorine	...	...	372	{	248 „ 1
					258 „ 2

The figures in Case I showed that the sodium was 100 mgm. or 28% below the normal figure; the chlorine was 124 mgm. or 33% below the normal while the potassium was about 9 mgm. or 50% higher than the normal. The question at once arose whether the decrease of the sodium and chlorine or the increase in the potassium was the more important factor. It was already known that the blood volume was concentrated and the increase of potassium might have been due solely to this change, or might be responsible for the symptoms. Loeb and Atchley⁽⁸⁾ solved the problem in two ways, (1) by experiments on animals which could be repeated with adequate controls, and (2) by the administration of sodium chloride to patients with Addison's disease. They experimented on dogs and estimated the intake and output in the urine of sodium, chlorine, potassium, urea, calcium, and when the excretion was fairly constant one adrenal was excised, and its effect noted for a period of 7 days, and finally the second adrenal was removed and the urine collected for a further period of five days and on the day of death. No significant change was noted after the removal of the first gland, but in the five-day period after the excision of the second adrenal the excretion of sodium rose from 23.9 mgm. to 61.8 mgm. per day, and to 56.8 mgm. on the last day, although no food was eaten that day; the chlorine rose from 24.1 mgm. to 48.6 mgm. as the average excretion of the five-day period, and 46.2 mgm. on the last day of life. The potassium excretion decreased slightly from an average of 166.5 mgm. to 157.5 mgm. in the last five days, and fell to 74.1 mgm. on the last day of life. These important experiments show that both sodium and chlorine are lost from the body when the control of the adrenal cortex is removed, and either might be the important factor. The value of the sodium can be demonstrated by giving other salts of sodium, like sodium citrate or sodium bicarbonate to adrenalectomized animals, and this enables them to live much longer than usual.

The importance of the sodium has also been demonstrated by Darrow & Yannett⁽⁹⁾ in an ingenious way. They injected 1,000 c.c. of an isotonic glucose solution into the peritoneal cavity of a healthy dog. During the next five hours little absorption of the fluid occurred but sodium salts were excreted into the peritoneal fluid. If this fluid is removed about 35% of the total sodium of the body is present in the fluid; the blood volume is concentrated, and the hæmoglobin, serum protein and potassium are all increased in amount. The blood pressure falls

and the animals develop "shock" after small losses of blood. If the same procedure is repeated the next day (Harrop⁽¹⁰⁾) the condition of the animals is typical of those dying after adrenalectomy.

It is therefore accepted that one of the chief functions of the adrenal cortex is to maintain the control of sodium at a constant level, and that if the cortex fails in its activity sodium, and with it chlorine, will be excreted in the urine, and the other changes like the concentration of the blood and the increase in the potassium content of the blood will then occur.

Loeb and his co-workers⁽¹¹⁾ completed their observations by trying the effects of large doses of sodium chloride on three patients with Addison's disease. The clinical condition was much improved after the addition of sodium chloride to the diet, although the blood pressure did not rise. The principle of the treatment is made clear by the following diagram.

FIG. 11.

- A. Reservoir containing sodium.
- B. Hole in reservoir through which sodium is escaping.
- C. Normal level of sodium in the reservoir.
- D. Level of sodium in Addison's Disease.
- E. Pipe Introducing sodium.

The level of the reservoir can be maintained at the effective level, either by adding sodium or by closing the hole by means of cortical extract.

No one will deny that the ideal treatment is to give sufficient cortical extract to prevent the loss of sodium but until the extract is both more potent and cheaper it is necessary to give as much sodium as the patients can take, in order to reduce the amount of cortical extract to the minimum.

In the last two years five patients with Addison's disease have been admitted to St. Bartholomew's Hospital—one died three days after admission, but the other four cases have been treated with salt by Dr. Hinds Howell, Lord Horder, Dr. Chandler, and Professor Witts, whom I have to thank for permission to see their cases and quote their results.

I. Dr. Hinds Howell's⁽⁸⁾ patient presented all the classical symptoms of Addison's disease and was so weak that he could not sit up in bed; the blood-pressure varied from 60/40 to 80/50. The blood sodium was 298 mgm. per 100 c.c. and the hæmoglobin 81%. He was given 2.5 g. of salt in milk four times a day (3.8 g. of sodium) and the clinical condition improved in a remarkable fashion. I chanced to see him an hour after he had had his second dose and the ward sister told me that he had suddenly sat up in bed, which he had never been

able to do before. His condition continued to improve and he eventually went out of hospital, although the blood-pressure and pigmentation were unaltered. The blood findings are very interesting. The sodium had hardly changed after fourteen days of salt treatment, but the hæmoglobin, had decreased from 80% to 65% although iron was being given in full doses. On the twenty-fourth day the blood sodium had risen to 315 mgm. per 100 c.c. and the hæmoglobin to 74%. It is probable that the decrease in the hæmoglobin was due to an increase in the blood volume which masked an increase in the sodium. The after-history is a sad one. The patient kept very well for about three months and then developed a febrile illness and died in two or three days. It was most unfortunate that no effort was made to send him back to hospital.

II. The patient was a man, aged 28, who also showed the classical symptoms, with intense pigmentation, but the blood pressure was 94/56. He complained of weakness but was able to be up and about. The blood sodium was 312 mgm. per 100 c.c. and rose after salt to 333 mgm. per 100 c.c. The patient was certainly stronger but he was very dissatisfied that he was not given any cortical extract, as he had been told this would be given in hospital. Since his discharge from hospital he has been treated by at least two consulting physicians and given a daily injection of cortical extract at a cost of from 10/- to 20/- a day. He died about a year afterwards, at a time when the sodium chloride intake had been reduced as the patient was tired of the salt.

III. The third case, that of a woman, aged 33, was not quite typical. She was a farm worker; pigmentation had begun six months before admission and was very marked. She had become too weak to do her work on the farm but was still capable of walking about. The blood-pressure was never lower than 96/62 and was on occasion 120/80. The blood sodium was 336 mgm. per 100 c.c. when she was taking an ordinary diet. The therapeutic effect of giving additional salt was good, but in order to try and prove the diagnosis a salt-free diet was given. This method has been suggested by Loeb⁽¹¹⁾ in cases in which the diagnosis is in doubt. It should only be undertaken if the patient is under careful supervision and if facilities for giving intravenous saline and cortical extract are available, since the symptoms may become very alarming after one, two or three days of a salt-poor diet. In this case the patient felt very weak indeed, but the blood sodium did not decrease below 326 mgm. per 100 c.c. so that the diagnosis was not proven. She left hospital taking 10 g. of salt a day and feeling definitely better, but two months later she developed dyspnoea with severe vomiting and died a week later. In this case also no attempt was made to send the patient up to hospital again.

IV. The fourth patient, a woman aged 43, who is under the care of Professor Witts, has all the typical symptoms, but the pigmentation is not marked. Blood pressure 100/70.

TABLE III.

DATE.		SODIUM. mg. per 100 c.c.		BLOOD UREA. mg. per 100 c.c.		HÆMOGLOBIN %
19/2	...	285	...	92	...	110
27/2	...	327	...	37	...	88
2/3	...	325	...	63	—	—
20/4	...	341	...	60	—	—
28/4	...	335	...	76	—	—
27/5	...	320	...	—	—	—
7/7	...	325	...	30	—	—

Treatment. Sodium chloride, 0.5 g.; sodium bicarbonate, 0.5 g.; six times a day=5.6 g. of sodium daily.

The immediate response was good, but she did not gain much strength and was distressed on the slightest exertion. She was then given 10 c.c. of a cortical extract daily in addition to the salt. This was followed by a striking improvement in strength and vivacity, and a further increase in the sodium of the blood to 341 mgm. per 100 c.c. When the cortical extract was replaced by a liver extract for four days without her knowledge she became languid and tired, but recovered quickly when the cortical extract was given. After leaving hospital she continued to gain strength and has walked $1\frac{1}{2}$ miles in the day. She has had one severe relapse and been in hospital, during which she required 310 c.c. of extract in five days, but has otherwise kept well. The cost of the extract for 10 months has been £142.

These results with sodium chloride alone are admittedly unsatisfactory and certain lessons can be learnt from the failure. Two patients developed some acute illness and died within 2 or 3 days. Both of them lived at a little distance from hospital and neither was sent back to hospital by their own doctor. It is important to impress on both the patients and their own doctors that any illness will render the adrenal deficiency greater just as experience has shown that any illness however trivial may cause a diabetic condition to become worse unless larger amounts of insulin are injected. One patient tired of the amount of salt which was given him and decreased it. The results reported by Levy Simpson⁽¹³⁾ and Allott⁽¹⁴⁾ at a meeting of the Therapeutic Section of the Royal Society of Medicine are similar and show that while sodium chloride is of great value in aiding the patients it cannot replace a potent extract if the condition is severe or complicated by an acute infection.

Recent work has shown that the sodium chloride is not the best form in which to give the sodium. Too much emphasis was at first laid on sodium chloride and 10 g. a day was given in divided doses, either in milk or in cachet form, and larger amounts were given intravenously for the treatment of acute conditions. Harrop, Soffer, Nicholson and Strauss⁽¹⁵⁾ have kept dogs alive for 150 days on a mixture of sodium chloride and sodium bicarbonate, and Kendal⁽¹⁶⁾ has kept two dogs alive for 80 and 100 days on a mixture of sodium chloride and sodium acetate without any cortical extract. It is important to remember that it is the sodium factor which is essential although a sufficiency of chlorine must be given. Sodium chloride actually supplies the greatest amount of sodium of any sodium salt (Table IV), 3.8 g. out of a 10 g. dose, but it is certainly advisable to mix it with sodium bicarbonate and sodium citrate—15 grams of this mixture supplies 4.5 gm. of sodium and in addition is more palatable. In acute illness 600 c.c. of 5% NaCl will supply 11.4 g. of sodium and this amount can be repeated once or twice in the day.

TABLE IV.

10 g. of		g. of Sodium
Sodium Chloride		= 3.8
Sodium Bicarbonate		= 2.7
Sodium Citrate	CH ₂ COONa COH COONa CH ₂ COONa	) = 2.6
Sodium Lactate	CH ₃ CHOH COONa	
		= 2.0

In the last year another discovery has been made by Wilder and Kendal⁽¹⁷⁾ which is most unexpected. They have shown that a curious relation exists between the amount of sodium and potassium. Thus, if the intake and output of sodium and potassium of a patient with Addison's disease is stabilised, great changes can be made in the sodium output by altering the potassium intake. An increase of potassium from 1 g. to 4 g. will cause a decrease of the sodium in the blood from 315 mgm. to 300 mgm. in the course of five days, and an increase of the sodium output from 220 mgm. to 440 mgm. a day. The balance can be redressed by giving cortical extract. Kendal's work shows that the potassium must never be given as a medicine, and that the potassium in the diet must be reduced to as small an amount as is consistent with keeping the diet palatable. Potassium is present in all vegetables and potatoes and these play an important part in rendering the diet palatable and in supplying vitamins. It has been suggested that the vegetables should be boiled and then carefully strained. If this process is performed three times, the amount of potassium will be negligible but so will the value of the vegetables. It would be better to give adequate amounts of vitamins A, B, C and D in condensed form, together with as small an amount of fruit juice and vegetable as will render the diet tolerable for the patient. It is hoped that the new discoveries will reduce the amount of cortical extract which is necessary to maintain the health of the patient.

This survey of the pathology and principles of treatment of Addison's disease shows how great the advance in knowledge has been, and holds out great hope for the future of these patients. The next and most important advance should be the preparation of an extract which is potent, easily standardized and above all things cheap.

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