THE BIOCHEMISTRY OF ADDISON'S DISEASE.

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Thomas Addison of Guy's Hospital first described this disease which bears his name. It is a disease found in all races throughout the world characterized by pigmentation of the skin and mucous membranes, myasthenia, subnormal temperature and blood-pressure and gastro-intestinal upset. In nearly all cases a lesion of the suprarenal gland has been found. In cases where the suprarenal has been found healthy, damage to the coeliac plexus has always been present. The majority of cases are due to tuberculosis while others are due to secondary deposits of carcinoma, hemorrhage or simple atrophy of the gland.

Until recently the disease was fatal within five years but, with the advances in hormone research, the treatment is more firmly based on reality and the outlook correspondingly improved.

That Addison's disease is primarily a defect of salt metabolism has been firmly held for many years and McCance was able to show that the symptoms and signs of experimental salt deficiency in man were strongly suggestive of Addison's disease. It is now possible in addition, in the light of modern findings in pure biochemistry, to adduce explanations for most of the changes which occur. All these changes, many of them up to now isolated facts, can be attributed to destruction of the suprarenal gland tissue.

Firstly the discoloration of the skin. This is characteristic. It is deepest on the areas exposed to light, friction and pressure and on the mucous membranes of the mouth, anus and vulva. This pigment is an excess of the normal melanin found in the skin, retina and hair. Raper has shown that melanin is formed by oxidation of the essential amino acid tyrosine by the enzyme tyrosinase present in the cells of the rete malpighii of the skin. By the action of this enzyme tyrosine is converted into dihydroxy indole and then into its carboxylic acid. This compound is red and polymerizes spontaneously into the black pigment melanin.

Tyrosine, or rather its desoxy compound, is also the precursor of adrenalin which we know is produced by the medulla of the suprarenal gland. With the destruction of this gland the production of adrenalin is reduced—thus accounting for the hypotension—and an excess of tyrosine is present in the body. This excess of tyrosine is then changed into melanin by the tyrosinase of the rete malpighii thus producing the pigmentation of Addison's disease.

Myasthenia is present in the majority of cases and has been difficult to explain. The muscular fatigue is like that found in myasthenia gravis. The contractions are, at first, of average power but fatigue soon develops. On resting the muscle power returns. This can now be correlated with the biochemical changes. The cortex of the suprarenal controls the water and salt metabolism of the body. When the gland is removed the excretion of sodium is increased and in consequence the sodium chloride and bicarbonate level of the plasma is reduced. To maintain the ionic equilibrium the plasma potassium rises to counterbalance the fall in sodium. In Addison's disease this ionic change also occurs. The serum sodium and chloride fall from the normal 350 mgm. per cent and 325 mgm. per cent respectively and the potassium rises from 20 to 25 mgm. per cent. So constant is this change that it is of diagnostic importance.

It is this ionic change which is responsible for the myasthenia. Muscle contractility and power is dependent upon the presence of calcium ions and is counter affected by potassium ions. Thus as the potassium level rises in the disease so the myasthenia increases.

Coincident with this myasthenia creatinuria occurs. Creatine is of endogenous origin and is only excreted in the urine before puberty and in women during pregnancy. In adults creatine is excreted in the form of its anhydride creatinine and this excretion per day is constant for the individual. Now the chief function of creatine is to form phosphagen which acts
as the phosphate reservoir for muscular contraction. Hence this creatinuria in Addison’s
disease is a consequence of the muscle atrophy. This creatinuria can be made use of in
measuring the progress of the disease. This is directly comparable to the ratio of creatine
to creatinine excretion.

The ionic changes in the plasma are also responsible for the well known biochemical finding
—a rise in the blood urea level. As a result of the lowered electrolyte content of the plasma
water is lost in order to maintain the osmotic equilibrium. In consequence the blood becomes
more concentrated and its volume reduced. This accounts for the readings for blood urea
estimations being increased and this may be aggravated by the gastro-intestinal disturbance
which is sometimes present.

Not only is the suprarenal associated with water and salt metabolism but it has been shown
that the gland influences the phosphorization of carbohydrate in the intestine. Through
this mechanism the suprarenal maintains the level of the blood sugar and the liver glycogen.
When the gland is destroyed therefore the absorption of carbohydrate is reduced and hypo-
glycaemia occurs. This activity of the suprarenal gland has not been well worked out yet
but that it is important is manifest during treatment. Even though the levels of blood
sodium, potassium and urea are normal there is little improvement in the patient’s well
being unless the fasting blood sugar is over 60 mgm. per cent.

So far the suprarenal gland alone has been considered but as with all endocrine disorders
more than one gland may be involved. Thus at autopsy the testes and ovaries are atrophied
and the pituitary is found to contain fewer basophil cells than normal. The disease is not
primarily one of pituitary origin however although Langdon Brown emphasized the pre-
dominance of the pituitary in endocrinology by calling it “the leader of the endocrine
orchestra.” The basophil cells are reduced owing to the absence or diminution of the supra-
renal hormone. This change in the basophil cells is associated with reduction in the basal
metabolic rate and body weight just as this occurs in Simmond’s disease which bears some
similarity to Addison’s disease and is caused by destruction of the pituitary gland.

Treatment.—It must be borne in mind that unless Addison’s disease is due to simple
atrophy of the gland we are dealing with more than just a hormone deficiency and that the
body has another pathology to deal with in addition.

The aim of treatment is to keep the blood sodium normal, to prevent the blood urea
and potassium rising and to keep the fasting blood sugar above 60 mgm. per cent.

The administration of sodium salts enormously benefits patients. About 15 grammes per
day are needed preferably administered in capsules to avoid the emetic effect. The sodium
may be given solely as the chloride, or since the chloride level of the blood automatically
increases with the sodium level, a mixture of the citrate, phosphate and bicarbonate may be
given. This is less likely to produce emesis.

For the hormone deficiency itself dried whole suprarenal gland may be given. This is
beneficial provided it is given in large enough doses since only a small percentage of the active
principle is absorbed.

Extracts of the gland are obtainable. The activity of the extracts is associated with the
lipid fraction and from this numerous ketones and alcohols have been isolated, several of
which have some activity. The most active is corticosterone which is a sterol derivative.
This compound not only controls the salt metabolism but also influences the carbohydrate
metabolism. It does not represent the full activity of the gland since more potent non-
crystalline fractions of the gland have been obtained. Corticosterone is expensive and so
it is best used for treating the crises which are such a feature of this disease. Up to 50 c.c.
given intravenously may be required every six hours. If used for maintenance up to 20 c.c.
daily may be needed and this is best given intramuscularly.

Because of its expense many attempts to synthesize corticosterone have been made. So
far these attempts have failed but a compound closely related to corticosterone has been
obtained. This is desoxycorticosterone acetate, known usually as D.O.C.A. This can be
made fairly easily but unfortunately it does not control all the manifestations of the disease.
It is given intramuscularly in oily solution and so has a more prolonged action than corti­
costerone. This precludes its use during the crises. 5 mgm. are approximately equal to
10 c.c. of cortin. If necessary 50 mgm. tablets can be implanted subcutaneously in the
abdominal wall. These exert their effect up to three months after implantation.

The simplest index of good treatment once the patient is stabilized is his weight. If this
falls then injections of the extract must be started or increased and the salt intake increased.

So far therefore the treatment of Addison’s disease with glandular extracts has not
reached the same stage as the treatment of diabetes mellitus with insulin. Much progress
has been made but our treatment is still only partially successful.

RESUSCITATION IN THE FIELD.

[The following article describes an ingenious method of applying heat in cases of shock.
The apparatus was devised by R.S.M. Saxon of 203 Field Ambulance and has the advantage
of providing a more even distribution of heat over the body surface. It should, however,
be borne in mind that over-efficiency in heat production may have a deleterious effect, as
pointed out in Item 163 of A.M.D. Bulletin, No. 22. Care must therefore be exercised in
the use of all such appliances.

It is suggested that the apparatus could be made more readily portable by soldering to
the openings of the petrol tins collars of such a size that the funnels can be slipped off for
packing.—Ed.]

The object in view when constructing the “Saxonfone” was to distribute in a more even
manner the hot air rising from the heating unit under the resuscitation bed.

The graph indicates that when the heating unit is placed under the resuscitation bed,
the temperature rise is more even. The chart shows the temperature comparisons at the
centre and ends of the stretcher.

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**Chart Showing Temperature Comparisons at Centre of Stretcher.**

**Chart Showing Temperature Comparisons at Ends of Stretcher.**