

from 1 cc to 7 cc per kg. One animal received a single intravenous injection of 100 cc of extract and showed no changes.

Bilaterally adrenalectomized dogs which are treated with adequate daily dosage of the adrenal cortical extract do not differ in their behavior, or in the blood concentration of the substances mentioned, from normal animals. Weight is maintained, appetite, pulse rate at rest, and rectal temperature is normal, and the body skin and hair are kept in fairly good condition.

When the bilaterally adrenalectomized animal, in a good state of nutrition, with well-healed wounds and without infection, is deprived of adequate injections of cortical extract, either abruptly or by gradual reduction of dosage to less than 1/6 cc per kg daily, the first significant change we have observed is a rise in blood non-protein nitrogen and urea. This is coincident with or may precede by a few hours the refusal of food, and definitely precedes the drop in respiratory metabolism which is also a constant observation. Changes in blood creatinine do not occur until the animal is very ill. The serum potassium concentration rises steadily during the period of insufficiency. The secretion of urine diminishes markedly and there is a suppression of urinary nitrogen and urea. The chloride and inorganic phosphate excretion is suppressed when the animal begins to refuse food and if the insufficiency is allowed to go to the point where urinary secretion is very low or almost suppressed there is a diminution of creatin and creatinine excretion as well as that of injected phenol sulphonephthalein. In the earlier stages of insufficiency, however, suppression of total nitrogen and of urea nitrogen occur before the excretion of creatinine and creatin lessens. No microscopic changes are found in the urine, but small amounts of albumin are quite regularly present during insufficiency. Marked and rapid loss of weight occurs where there is diarrhea or vomiting. The muscular weakness, lowering of body temperature, characteristic gait, and psychic symptoms of dogs in advanced insufficiency have been adequately described by various writers. Lowering of the systolic blood pressure does not usually occur until after the nitrogen retention has become well established. In animals which subsequently recover, following injection of adequate amounts of extract, the oxygen consumption may drop at the time of maximum insufficiency to 20-25 per cent. below the normal value at which time the R.Q. also has fallen to 0.72-0.71. Injection of extract is then followed by a diuresis which may last for 48-96 hours and is accompanied by increased excretion of urinary nitrogen and urea, and of chlorides. At the same time the animal gains rapidly in weight and his appetite returns. The

respiratory metabolism usually returns slowly and the R.Q. more rapidly to their original levels. These changes precede or approximately parallel the return of the blood non-protein nitrogen and urine excretion nitrogen to their previous values. The fall in serum potassium concentration parallels that of the non-protein nitrogen. The delay in return to normal of this blood non-protein nitrogen and urea appears to be more marked following each subsequent period of adrenal insufficiency, a phenomenon which we have also noted in clinical studies on Addison's disease to be reported later.

We are now utilizing the early change in blood non-protein nitrogen and urea as a means of biological assay of the strength of different lots of cortical extract in adrenalectomized dogs. Studies of the effect of the extract and of its deprivation upon kidney function and upon anatomical renal damage are also in progress.

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