shown to be resistant to enormous doses of infective hookworm larvae while on an adequate diet, quickly lost their resistance and developed rather heavy infestations when given 500 larvae each after ten or twenty weeks on the deficient diet. Two of them when transferred to the good diet while still harboring large numbers of worms expelled them in a short time.

A second experiment with two dogs, which were estimated to be about two years old, was carried out in a somewhat different way. These two dogs were brought into the laboratory as pregnant females and were kept on the good diet about two months before the puppies were born and while they were being nursed. During this period, they were treated and later found to be negative to hookworms by repeated examination. While still on the good diet, they were each given 500 infective hookworm larvae by mouth. Both remained negative to repeated examinations for a period of six weeks, which indicated that they were very resistant to the hookworm. At this time, they were put on the poor diet and given repeated doses of 500 larvae at intervals of two weeks, the first dose being given two weeks after they had been placed on the deficient diet. After prepatent periods of 19 and 17 days, respectively, or after 33 and 31 days on the poor diet, they became positive. The egg counts increased with each subsequent infection until the number of eggs given off per day was about 700,000 for one dog and 900,000 for the other. At this time, 90 days after they had been placed on the deficient diet, they were transferred to the good diet. The doses of larvae at the two-week intervals were continued as before. But in spite of these constant doses of larvae, the egg counts in both dogs came steadily down until they reached a low level. In each case numbers of worms were lost after the egg counts had been greatly reduced. These two dogs are of especial interest since they show first the rapid breaking of the resistance in old dogs on the poor diet, and then a cure and a regaining of the resistance when they were placed on the good diet in spite of continued doses of infective larvae.

In the experiments outlined above, a definite correlation is demonstrated between deficiency in diet in dogs and susceptibility to infection with the dog hookworm, *Ancylostoma caninum*. The undernourished condition is characterized by lowered resistance to infection, increased rate of development of the worms and increased egg production per worm. When the dogs that had acquired an infestation while on the deficient diet were transferred to the good diet their recovery of resistance was indicated by a reduced egg production of the worms present, a spontaneous loss of worms and a resistance to further infection. It seems possible from this and other evidence that a similar relation may exist between the human hookworms and their hosts. We suspect that it will be found that heavy infestations are more easily built up in people on poor diets, and that not only the effects of the worms on the hosts may be reduced, but also the worms themselves may be partially or wholly eliminated by improvement in diet alone.

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FURTHER STUDIES ON THE ADRENAL CORTICAL HORMONE[1]

THE work herewith reported was done upon dogs with the adrenal cortical hormone prepared according to the method of Swingle and Pfiffner.[2] The material does not contain adrenalin in excess of 1 to 1,500,000. A series of bilaterally adrenalectomized dogs maintained in good health for considerable periods with the cortical hormone were then injected with gradually decreasing doses of extract (subcutaneous, one dose each day), the dose being changed at five-day intervals. One dog was maintained for a period of five days on 1/6 cc per kg weight per day, the others on 1/4 cc per kg weight per day without symptoms of insufficiency. We regard 1/4 cc therefore as the minimal maintenance dose for a single injection per day in dogs weighing 10 to 15 kg.

Extensive experiments have been made on the blood concentration and urinary excretion of various inorganic substances and of the nitrogenous compounds, following the injection of cortical extract into normal dogs, and into adrenalectomized animals. In the normal dogs we have been entirely unable to detect characteristic changes in the blood constituents which we have followed. Carbon dioxide content and capacity (alkaline reserve), oxygen capacity, nonprotein and urea nitrogen, creatinine, sugar, calcium, potassium and magnesium, cholesterol, lactic acid, plasma chlorides, hematocrit and plasma proteins, examined in arterial blood samples are not altered in any definite or quantitative manner. The determinations have been made at hourly intervals following injection, up to five hours and at the end of twenty-four and forty-eight hours. Stress should be laid, we believe, on the fact that we have used trained animals at rest, strictly in fasting condition. There was no change in the respiratory metabolism (oxygen consumption, or R.Q.) in a normal animal so injected within five hours or at the end of twenty-four hours. The amount of extract injected has varied

[1] Aided in part by a grant from the Josiah Macy, Jr., Foundation of New York.

[2] W. W. Swingle and J. J. Pfiffner, *Anat. Record*, xliv, 225, 1929; *Am. Jour. Physiol*, Vol. 96, 1931.

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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