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Experimental Studies with Cortisone

By **C. Cavallero, G. Sala and C. B. Ballabio**

The authors have studied the effects of cortisone and some other steroids in the rat from the morphological and the biochemical point of view.

The treatment of adult male rats with 1-5 mg of cortisone daily for 70-20 days respectively, has constantly determined a strong decrease of body weight which occurred independently of the food intake. A diminution of weight was ascertained in the thymus, spleen and adrenals, while the weight of the liver was increased.

The biochemical examination of the liver revealed an increase of the glycogen and fat content and a decrease of water and total nitrogen; in the kidney a decrease of alkaline phosphatase was found; the calcium, phosphorus and nitrogen of the bone were unmodified as well as the calcium level of the serum.

The histological examination confirmed the increase of glycogen and of fat in the liver; in the bone marrow it was possible to demonstrate a disappearance of eosinophils and an increase of the adipose tissue; in the bone tissue a reduction of chondrogenesis and osteogenesis and a thinning of the junction cartilages were noted; characteristic changes were evident in the brown fat tissue of the interscapular gland.

The most striking findings were the atrophy of the cortex of the thymus, together with an atrophy of the white and red pulp of the spleen and an involvement of the perifollicular accumulations of plasma cells; hypotrophic changes were also evident in the derma and epidermis with strong decrease in number of mast cells; in the kidney, renal glomeruli were atrophied and tubular epithelia showed nephrotic changes.

In the endocrine glands there was found: a compensatory atrophy of the adrenal cortex with loss of steroids, an involvement of the seminal epithelium of the testicles, an occasional hyperfunction of the pancreatic islets, cytological alterations in the hypophysis and no changes in the parathyroid glands.

It was further demonstrated histochemically that there occurred a reduction of acid mucopolysaccharides and of alkaline phosphatase in the organs examined.

The disappearance of eosinophils and the diminution of lymphocytes with relative neutrophilia was noticed in the peripheral blood.

When dealing with pathological features, it was seen that cortisone had an inhibitory effect on the following processes: healing of experimental wounds in the rabbit, formation of local granulomata in rats infected with *Coccidioides immitis*, development of granulomatous panarteritis lesions in the rat by «endocrine kidney», and lastly para-articular formalin reaction of the rat. Control experiments with DCA, 21-acetoxypregnenolone, DCA + ascorbic acid, testosterone and progesterone have proved that these substances do not have similar effects.

In all these experiments cortisone caused an evident modification of the newly formed connective tissue; in contrast to the other steroids, it inhibited the fibroblasts, the fibrils and the ground substance. It diminished the fibrocytic proliferation, the genesis of blood vessels and leucocytic exudation, determining a delay of the necrotic hemorrhagic processes as well as of the cicatrical sclerosis. When cortisone was given to CCl_4 -intoxicated rats, it prevented, in part, the liver fibrosis and accelerated the spontaneous regression normally observed when the administration of the drug was suspended. Cortisone diminished the reactivity and sensitivity to tuberculin in guinea pigs infected with virulent or attenuated germs, while DCA increased the degree of the reaction.

Concerning the resistance to the infections, it was seen that spontaneous infections often followed a long term treatment with cortisone. In the granulomatous infection of the rat by *Coccidioides immitis* a frequent diffusion of the fungus was noticed. In the pneumococcus infection of the mice, cortisone and ACTH considerably increased the mortality rate, while ACE and DCA did not modify the course of the infection.

In order to study the influence of cortisone on metabolic processes, experiments were performed to ascertain the effect of the hormone on carbohydrate metabolism, both in normal and in alloxan or depancreatized diabetic rats. Cortisone did not provoke diabetes in normal animals but it caused only a renal glycosuria; on the contrary it aggravated the alloxan and pancreatectomy diabetes. In all animals the hormone did not modify the sensitivity to insulin but it increased the hyperglycemic response to adrenalin, with an increase of hepatic but no alteration of the muscular glycogen. Similar experiments with DCA have

shown that this steroid has in many ways an antagonistic action to cortisone.

Cortisone caused a constant increase of the arterial blood pressure and cardiac rate in normal rats while the plasma and blood volumes were not affected.