THE EFFECTS OF ADRENALECTOMY ON NON-DIETARY CIRRHOSIS IN RATS*

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In discussing this subject certain views based on earlier experiments[1] were modified before the effects of adrenalectomy on egg-yolk cirrhosis were dealt with.

Previously it was thought that a renal lesion was essential to the development of egg-yolk cirrhosis and that histamine liberation might be directly involved in its pathogenesis. Neither view had been substantiated. Repeated intravenous administration of egg yolk alone to 17 rats for periods of 18 - 130 days caused cirrhosis in 15, and a potent histamine liberator, 48/80,† failed to cause hepatic fibrosis in any of 8 animals given this substance intraperitoneally for periods of 16 - 57 days.

Contrary to original expectation, egg-yolk cirrhosis had also been proved a self-limiting lesion, and animals apparently developed a tolerance to egg yolk. In 15 animals, observed for periods of 50 - 145 days, regularly repeated injections failed to produce any increase of the fibrosis or signs of portal hypertension. In addition, it had been possible to prevent or reduce the cirrhosis by giving either cortisone (5 - 10 mg.) or 'phenergan' (5 mg.) whenever egg-yolk injections were made. These findings related, however, to only 3 animals.

This non-dietary cirrhosis was furthermore not specific to egg-yolk, and an essentially similar lesion had followed repeated intravenous injections of chick-embryo extract (7 of 8 animals), egg white (3 animals) and horse serum (1 of 2 animals). The common factor in these experiments is the injection of large amounts of foreign proteins, and though this is not related to current ideas on the pathogenesis of human cirrhosis, it has experimental precedent in the work of Wells[3] and of Longcope.[2]

The modifications in this cirrhosis following bilateral adrenalectomy were then described. The adrenals were removed in two stages, and the animals maintained on 1% salt water after the second adrenalectomy. The second gland was removed usually 1 - 3 weeks after the first in 11 controls, to whom no egg yolk was given, and after an interval of 23 - 33 days in 12 experimental animals. Liver biopsies were taken at the time of the second adrenalectomy in control and experimental groups, and repeated at intervals of 7, 14, 21, 35 and 68 days in some of the controls. In all control animals, bilateral adrenalectomy caused some weight loss and hepatic atrophy was present in 4 that died, but in no control was evidence of hepatic fibrosis found in postmortem or biopsy material.

Unilateral adrenalectomy in the group of 12 experimental animals did not influence the development or progression of the cirrhosis: however, in every case bilateral adrenalectomy produced significant effects which appeared to show some correlation with the severity of the existing hepatic changes. In the early stages when changes were mild and confined to eosinophile infiltration and regenerative activity, as in 4 of the experimental group, the animals survived 25 - 122 days, gained weight, and developed Laennec-type cirrhosis in the usual way. This cirrhosis was not significantly more marked than in rats with intact adrenals, but in 1 of the 4, ascites appeared and re-accumulated despite repeated withdrawals of fluid. It was admitted that incomplete adrenalectomy could be responsible for the long survival of this group of 4 animals, and evidence of this was subsequently obtained microscopically in the long-term survivor which developed ascites.

The remaining 8 animals survived the second adrenalectomy and the continued egg-yolk injections for only 7 - 9 days. Death was preceded by precipitous weight loss and refusal of food and water. In these 8 rats, liver biopsy at the time of second adrenalectomy showed isolated liver-cell necrosis and minimal fibrosis, but at postmortem a remarkable transformation in the microscopical appearances in this short survival period of a few days after bilateral adrenalectomy was found. Fibrous bands were increased in width and number, liver-cell necrosis was widespread (but unaccompanied by fatty change and never of focal coagulative or so-called massive type), liver-cell nuclei were large and hyperchromatic, and this feature, together with increased mitotic activity, gave to the hepatic tissues an appearance of anaplasia. Eosinophile infiltration in the portal tracts was intense, sinusoid congestion pronounced, and Kupffer cells apparently engaged in tremendous phagocytic activity in a manner not previously seen in experiments with egg yolk.

The differences before and after bilateral adrenalectomy are as great as can be imagined, and yet, with the exception of two features, the intense Kupffer-cell activity and the more widespread liver-cell necrosis, all the changes are simply an intense exaggeration of those seen in animals with intact adrenals. Clearly, further experiments are needed to show whether bilateral adrenalectomy alone is responsible for these changes or whether, as in these experiments, egg-yolk injections must be continued for the changes to occur.

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† Kindly supplied by Dr. A. C. White of Burroughs Wellcome & Co., London.

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