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G. M. KELLERMAN

Department of Medicine,
University of Sydney.
Jan. 2.

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Lesions in the Hypertensive Rat Kidney produced by Hydralazine

THE use of hydralazine (1-hydrazinophthalazine) for the control of human hypertension was followed by the recognition of serious and undesirable side-effects. The similarity of some of these effects to disseminated lupus erythematosus led to the investigation of the influence on the normal dog of toxic doses of this drug[1,2]. These experiments failed to provide satisfactory evidence for the production in the dog of an experimental model of disseminated lupus erythematosus.

To reproduce more closely the conditions under which the desired changes are found clinically, increasingly large amounts of hydralazine have been given by single daily intramuscular injection to rats previously subjected to a regime shown to cause systemic hypertension. The regime comprised left nephrectomy, the subcutaneous implantation of 100 mgm. of slowly absorbed deoxycortone acetate, and the substitution for drinking water of 1 per cent sodium chloride. The development of hypertension was suppressed by the hydralazine injections, each injection being followed by an abrupt fall in blood pressure succeeded by a linear rise continuing throughout the following 24 hr.

In these circumstances the intact kidneys of the treated animals were found to contain a surprisingly large number of focal glomerular lesions. The lesions were usually confined to one segment of the glomerular tuft, and varied from focal necrosis, with aneurysmal capillary dilatation, to segmental replacement fibrosis; they were not accompanied by arterial or arteriolar changes.

In control animals subjected to the same hypertensive regime and injected daily with an inert fluid the tubular effects of deoxycortone were recognized but were accompanied only by glomerular enlargement and seldom by the characteristic glomerular lesion seen when larger amounts of deoxycortone are more rapidly absorbed. Similar deoxycortone effects were also present in the hydralazine-treated animals.

Hydralazine may therefore influence the integrity of the rat glomerulus under certain carefully defined conditions. The effect is indirect, and is observed neither in the normal animal nor in the animal from which one kidney has been removed but which has received no deoxycortone. The glomerular damage clearly cannot be satisfactorily explained in terms of sustained hypertension, nor is it likely to be a result of the gradual rise in blood pressure which is the sequel of the acute hypotension following each daily injection of hydralazine. It is, however, possible that the damage may be directly related to the daily hypotensive episode.

The production of these lesions in the rat glomerulus is considered to be of importance, partly because their recognition provides the first satisfactory evidence of a damaging effect of hydralazine upon the kidney in experimental hypertension, and partly because of the suggestion that episodic hypotension may be the immediate causative agent. In addition, the experiment provides some evidence for the suggestion that glomerular lesions due to deoxycortone can be distinguished from those due to variations in blood pressure, and thus that the glomerular effects of deoxycortone are not necessarily due to hypertension.

D. L. GARDNER

Department of Pathology,
University of Edinburgh,
Teviot Place,
Edinburgh.

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Determination of Transaminase Activity of Serum Protein Fractions separated by Paper Electrophoresis

THE electrophoretic mobility of glutamic–oxalacetic acid transaminase in blood serum has been found to be between those for α_2- and β-globulins[1]. In our experiments[2] the glutamic–oxalacetic acid transaminase was associated mainly with α_2-globulins. This communication deals with this transaminase and glutamic–pyruvic acid transaminase and their relations to serum protein fractions.

Blood sera of six patients with characteristic activities of both enzymes were studied. 0·2-ml. samples of sera were electrophoretically separated on Whatman No. 1 filter paper strip (14 cm. × 35 cm.) in 5 hr. Barbital buffer of pH 8·6, ionic strength 0·1, was used with a voltage of 350 V. and a current of 0·5–0·8 m.amp. per cm. The marginal sections (3 cm.) were stained for proteins with bromthymol blue. The middle section of paper was cut into corresponding protein fractions and tested for their transaminase activity. The method for simultaneous determination of glutamic–oxalacetic acid and glutamic–pyruvic acid transaminases with an incubation mixture containing glutamate, oxalacetate and pyruvate was used. The action of enzymes was followed by determining the formation of L-aspartic acid and L-alanine, which have been estimated by the ninhydrin method after electrophoretic separation from aliquots of the incubation mixture[3]. In other experiments the middle section was, first of all, cut longitudinally into two identical parts and these were afterwards divided into strips containing the single protein fractions. One part of these strips was incubated with α-ketoglutaric and L-aspartic acid (both kindly supplied by the California Foundation for Biochemical Research, Los Angeles) and the other one with α-ketoglutaric acid and L-alanine. The activities of the glutamic–oxalacetic acid and glutamic–pyruvic acid transaminases in single protein fractions were assayed by hydrazone methods[4,5].

The distribution of transaminases on blood serum protein fractions is presented in Table 1.

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