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Nature of Renal Changes in Acute Choline Deficiency.

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Changes in the kidneys of acutely choline-deficient young rats, referred to as hemorrhagic degeneration of the kidneys were described by Griffith and Wade,[1] and later by Györgyi and Goldblatt,[2] Christensen,[3] Engel and Salmon[4] and others. The most careful histological study by Christensen showed the quite secondary role of hemorrhage in this syndrome, but left open the question of interdependence of tubular degeneration and vascular congestion.

Experimental. Young rats, 20 to 21 days old and weighing about 35 g, were placed in individual cages and fed water and the following diet *ad libitum:*

Basal diet:

	%
Sucrose	65
Alc. Ext. Casein	15
Salts No. 2	5
Lard	10
Gelatin	3
Corn Oil	2

with the addition of the following vitamins/kg:

Thiamin chloride	10	mg
Pyridoxine hydrochloride	10	"
Calcium pantothenate	20	"
Niacin	10	"
Para-aminobenzoic acid	20	"
Riboflavin	10	"
Inositol	50	"
Biotin	0.2	"
Vit. E	25	"
Menadione	5	"
Vit. A	20,000	units
" D	2,000	"

It was determined by observation that under our conditions the renal syndrome began to appear at about the fifth day. Thus most experiments were terminated on the seventh day since by this time all the rats would show marked renal hyperemia.

A detailed examination of the kidneys for structural changes due to this deficiency, led to the following conclusions as to the nature and sequence of these changes:

(1) Both grossly and microscopically the change observed first is venous stasis resulting in extreme cyanosis of the outer cortex.

(2) Absence of red blood cells from the lumen of the tubules is evidence of lack of hemorrhage.

(3) Epithelial degeneration and necrosis, limited to the tubules occupying the outer cortex, are secondary to the vascular disturbance.

(4) The lack of glomerular involvement, in sharp contrast to the marked tubular injury, proves interference with venous outflow rather than disturbance of arterial supply.

The outlined sequence of events of the renal syndrome is observed in reversed order in the phase of recovery, with venous stasis disappearing most rapidly, epithelial regeneration following considerably later, and hyaline casts, distended tubules and small scars forming the last residues of the disturbance. That interference with venous outflow is involved, finds support in our observations, that ligation of the renal vein in rats results in lack of damage to the glomeruli while there is marked injury to the tubular epithelium.

Experimental evidence of the priority of vascular disorder over epithelial injury is suggested by the protective effect of renal decapsulation. This operation was performed under ether anesthesia on the left side only, the right kidney serving as a control. In one group of experimental animals an incision was made on both sides but decapsulation of the kidney was performed on the left side only. The operation took place

[1] Griffith, W. H., *Biol. Symposia*, 1941, **5**, 193; Griffith, W. H., and Wade, N. J., PROC. SOC. EXP. BIOL. AND MED., 1939, **41**, 188.

[2] Györgi, P., and Goldblatt, H., *J. Exp. Med.*, 1940, **72**, 1.

[3] Christensen, K., *Arch. Path.*, 1942, **34**, 633.

[4] Engel, R. W., and Salmon, W. D., *J. Nutrition*, 1941, **22**, 109.

on the day that the rats were put on the choline-deficient diet. This operation gave protection to the decapsulated kidney in proportion to the completeness of the operation. In 19 out of 34 animals there was complete protection from the renal syndrome of acute choline deficiency on the operated side. This protection seems to be in abeyance if the operation is not performed well in advance of the acute disturbance, since if the decapsulation is not done until the fifth day, no protection is observed.

Wolbach[5] has suggested the possibility that a neurovascular mechanism might be the basis of the renal syndrome observed in acutely choline-deficient rats. There is support for such an assumption in our findings that subcutaneous administration of atropine seems to inhibit the renal syndrome. When rats were treated with 1 mg atropine sulfate daily, from the day they were started on the choline-deficient diet, prevention of the renal syndrome was observed in almost half of the cases. In these preliminary experiments, which lasted 7 days, 10 of 21 choline-deficient young rats failed to show the "hemorrhagic renal syndrome."

Summary and Conclusion. Morphological and experimental studies suggest a vascular disorder to be the primary injury observed in the kidney of the acutely choline-deficient rat.

[5] Wolbach, S. B., and Besser, O. A., *Physiol. Rev.*, 1942, **22**, 233.

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Reticulo-Endothelial Immune Serum (REIS). VI. Production of Potent Serum by Anamnestic Reaction.*

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The development of antiorgan sera has been reported in studies from our laboratories.[1] Whereas in our original work[2] we followed the method of Soviet workers,[3] some modifications in the production of REIS were introduced in the present study. It was thought that an accumulation of antibodies in the recipient host would be enhanced by a slow process of immunization rather than by the rapid method of using massive doses.[4]

In the preparation of antiguinea pig and of antirat sera, constant amounts of tissue, 400 mg of spleen plus 100 mg of bone marrow, suspended in 6 ml of saline were administered to the rabbit. Intravenous antigen injections of 0.25, 0.5, 0.5, and 0.75 ml were given at 4-day intervals, and the same amounts were given by mouth, the total being approximately 133 mg of spleen and 33 mg of bone marrow by each route within 12 days.

Complement-fixation titres illustrate the high values of antirat and antiguinea pig sera following low antigenic dosages.

The achievement and maintenance of adequate potency of the serum was one of the main objectives. Attempts were made, therefore, to provoke an increased antibody production in previously immunized animals by their anamnestic response to a renewed contact with the antigen. A single intravenous injection of the same type of antigen 30-40 days following the last injected dose was administered to rabbits.

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[1] Pomerat, C. M., *Phi Beta Pi Quart.*, 1945, **42**, 203.

[2] Pomerat, C. M., and Anigstein, L., *Tex. Rep. Biol. and Med.*, 1945, **3**, 122.

[3] Marchuk, P. D., *Am. Rev. Sov. Med.*, 1943, **1**, 113.

[4] Straus, R., Runjavac, M., Zaitlin, R., Duboff, G., and Swerdlow, H., *II. J. Immun.*, 1946, **56**, 155.