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Particle Retention by the Renal Glomerular Capillaries in the Generalized Shwartzman Reaction.* (30397)

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During late pregnancy, the Syrian hamster (*Mesocricetus auratus*) regularly develops the generalized Shwartzman reaction (GSR) in response to a single intraperitoneal injection of colchicine(1,2). At 24 hours, the reaction is characterized by extensive fibrin thrombosis of the renal glomerular capillaries and renal cortical necrosis. When a suspension of carbon particles is administered intravenously from 4 to 6 hours after colchicine, at a time when renal histologic changes are minimal or absent, there is striking accumulation of carbon particles in the glomerular tuft (Fig. 1). Three possible mechanisms of particle retention by the glomerular capillaries may be considered: i) Stasis resulting from vasodilatation. This has been postulated to account for the similar phenomenon of particle retention observed during the development of the GSR in the rabbit(3); ii) Increased endothelial permeability. Endothelial "leaks" are responsible for particle retention by postcapillary venules during inflammation(4); or iii) Adherence, either to an altered endothelium or to a previously-deposited sticky material. The early appearance of fibrinoid in the glomerular capillaries during the development of the GSR in the rabbit has been demonstrated by electron microscopy (5).

The present study was undertaken to determine which of these 3 mechanisms, vasodynamic, endothelial permeability or adherence, is responsible for entrapment of carbon particles in the glomerular capillaries during the development of the GSR.

Materials and methods. On the 14th day of pregnancy (16 day gestation period), 6 Syrian hamsters were given a single injection of colchicine (300 mg/kg body weight, i.p.). After 2, 4 or 6 hours, 2 hamsters at each time were anesthetized with ether and 2 ml of a 1% carbon particle suspension (Pelikan special biological ink, C11/1431a, particle size 200-300 Å) was slowly injected into the lingual vein. The hamsters rapidly recovered from the anesthesia. Between 1 and 1½ hours later, they were anesthetized with pentobarbital sodium, and small portions of the kidney were fixed in 1% osmium tetroxide and embedded in Vestopal-W(6). Sections cut at 0.5 μ-1 μ were mounted on glass slides, stained with toluidine blue and examined by phase contrast microscopy. Photographs were taken at a magnification of 400 on 35 mm Kodak High Contrast Copy Film. In addition, portions of the kidney were fixed in

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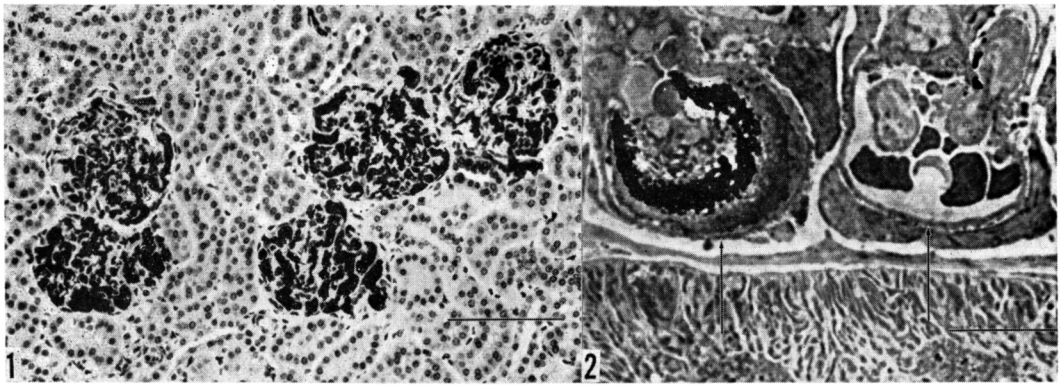

FIG. 1. Renal cortex of pregnant Syrian hamster, 7 hr after administration of colchicine and 1 hr after carbon particle infusion. Intense blackening of glomeruli is due to trapped carbon particles. Histology is otherwise normal (5 μ; H & E stain; transmitted light microscopy; scale, 100 μ, $\times$ 150).

FIG. 2. Portion of a glomerulus and adjacent tubule of pregnant Syrian hamster, 5½ hr after administration of colchicine and 1½ hr after carbon particle infusion. Arrows indicate the basement membrane of 2 adjacent glomerular capillary loops. In the capillary on the left, there is a deposit of a dark amorphous material on the basement membrane. Black carbon particles are applied to the lumenal surface of this material. Capillary on the right contains no amorphous material. Within its lumen are several erythrocytes and nucleated cells, including a phagocyte with ingested carbon particles. Cytoplasm of glomerular epithelial cells extends along lower surface of basement membrane. Bowman's capsule and the elongated mitochondria of the underlying tubular epithelial cells are prominent in lower third of field (½-1 μ; toluidine blue stain; phase contrast microscopy; scale, 10 μ, $\times$ 1400).

10% neutral buffered formalin for conventional histologic preparation. Sections were cut at 5 μ, stained with either hematoxylin and eosin (H & E) or phosphotungstic acid hematoxylin (PTAH) and examined microscopically in transmitted light.

Results. There were only a few scattered minute clumps of carbon in the kidneys both of control animals and of the 2 hamsters which received the carbon particle infusion 2 hours after colchicine. In marked contrast, there was universal intense glomerular blackening in the hamsters which had been given the carbon infusion either 4 or 6 hours after colchicine (Fig. 1). Apart from the accumulation of ink, there were no significant pathologic changes in conventional histologic sections. Fibrin was not observed, although its presence might have been obscured by the carbon. However, in another series of pregnant hamsters which received no carbon particles and which were sacrificed from 4 to 8 hours after the same dose of colchicine, trace amounts of characteristically stained fibrin were occasionally present in the glomerular capillaries.

Examination of the toluidine-blue-stained thin sections by phase contrast microscopy revealed an amorphous material applied to the lining of the glomerular capillaries. Generous quantities of carbon were attached to the lumenal surface of this material (Fig. 2). In most cases, the affected capillary appeared patent although in a few instances the material occupied the entire lumen. Capillaries which were not lined with this material contained no carbon particles.

Discussion. The constant association of trapped carbon particles with deposits of an amorphous material in the glomerular capillaries implicates this latter material as the trapping agent. Since, in the rabbit, "fibrinoid" appears in the glomerular capillaries relatively early in the development of the GSR(5), it is reasonable to assume that the amorphous material present during equivalent stages of the GSR in the hamster is a similar substance. The usual failure of this material to display the typical PTAH staining properties of fibrin may reflect its incomplete polymerization; its final identification must await electron microscopy or immunofluorescence study.

That the presence of an amorphous ma-

terial, presumably "fibrinoid," is necessary for the accumulation of carbon particles in the glomerular capillaries during the development of the GSR clearly indicates that particle retention is the primary result of adherence rather than altered capillary permeability or vasodynamic changes.

By outlining the usually inconspicuous early "fibrinoid" deposits, carbon particle retention in the glomerular tuft is a useful parameter of the initial stages of "fibrinoid" formation in the GSR. Separate evaluation of the mechanisms of particle retention at other sites will be necessary since differences in vascular architecture and function may result in variations in the method of particle capture.

Summary. During the development of the generalized Shwartzman reaction elicited by colchicine in the pregnant Syrian hamster, intravenously administered carbon particles are trapped in the renal glomeruli. The carbon particles are attached to underlying deposits of an amorphous material within the glomerular capillaries. It is concluded that this material is responsible for the capture of circulating carbon particles.

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Effect of Host Weight Loss on Friend Leukemia Virus Infections in Swiss, DBA/2, and BALB/c Mice.* (30398)

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To evaluate potential antiviral agents properly, particularly those used against oncogenic viruses, it is important to consider all possible factors which may influence the results of experiments with these agents. A primary criterion for evaluation of these drugs is to determine the inhibition of the virus-induced tumor. The effect of host weight loss on such a neoplasm could therefore be of considerable importance, especially when nonlethal drug toxicity can result in decreased food consumption and subsequent host weight loss or failure of the host to gain weight. Weight loss induced by caloric restriction has been shown to cause inhibition of growth of many experimentally induced and spontaneous tumors(1).

Among the known oncogenic viruses, the leukemia virus of Friend (FLV) has been used recently for several drug evaluation studies(2,3,4). One advantage of using this virus in chemotherapy experiments is that it induces a marked, reproducible splenomegaly in Swiss, DBA/2, and BALB/c mice following a latent period of less than one week(5,6). Because of this early onset of overt disease symptoms and the repeated use of the virus in chemotherapy experiments, FLV was chosen for the present studies of host weight loss effects.

This report presents quantitative studies on the effects of caloric restriction and resultant host weight change on the development of splenomegaly induced by FLV. In addition, the effect of host weight change on the amount of virus detectable in the spleens and plasma of FLV-infected mice has been studied. The anti-FLV activity of 2 compounds, porfiromycin and 1-methyl-1-nitrosourea, was evaluated using the conclusions drawn from these studies.

Materials and methods. DBA/2 and

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