cluded that gel filtration offers an extremely useful tool for assessing the degree of heterogeneity of these or similar products.

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Renal Artery Response to Epinephrine.* (28739)

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Significant changes in the I^{131} radiorenogram occurred in both hypertensive patients and normal control subjects in association with signs and symptoms of apprehension. With relief of the subject's anxiety the renogram changes were no longer present. These renogram effects were considered secondary to an acute decrease in renal blood flow which was probably induced by a neurohumoral mechanism(1). This series of experiments was performed in an attempt to clarify the origin of this response.

Methods. Group A. Sixteen normal mongrel dogs weighing 12 to 14 kg were anesthetized with pentobarbital and standard control radiorenograms utilizing I^{131} Ortho-iodohippuric acid performed as previously reported(2). Seventy to 85 μg per kilogram of epinephrine (Parke, Davis and Co. ampoule #88, which does not contain any nor-epinephrine) were injected into the jugular vein and in one minute another renogram was recorded. A third renogram was recorded 30 minutes later.

This same procedure was followed in 3 dogs utilizing doses of epinephrine ranging from 7 to 75 μg per kilogram.

Group B. Thirteen dogs were anesthetized as above, and a #7 polyethylene catheter was placed in the aorta just above the origin of the renal arteries *via* a femoral artery cutdown. A control angiogram of the renal arteries and lower aorta was run with 12 ml of 75% hypaque injected at 200 lb pressure with an automatic injector. Serial films were obtained using a Schonander automatic film changer. The sequence of films varied from one per second to 6 per second for different periods. Seventy-five to 85 μg per kilogram of epinephrine were injected into the jugular vein and a repeat angiogram was run one minute later. Utilizing a similar technique, cineradiographic studies of the renal arteries and lower aorta were made in 10 dogs both before and after adrenaline injection.

Results. Group A. Epinephrine injection of 75 to 85 μg per kilogram was uniformly associated with a change in the radiorenogram consisting of a slowed ascent of the vascular (OA) and secretory (AB) and slowed descent of the excretory (BC) components. This is illustrated in Fig. 1. The smaller epinephrine doses caused less apparent but still significant changes in the reno-

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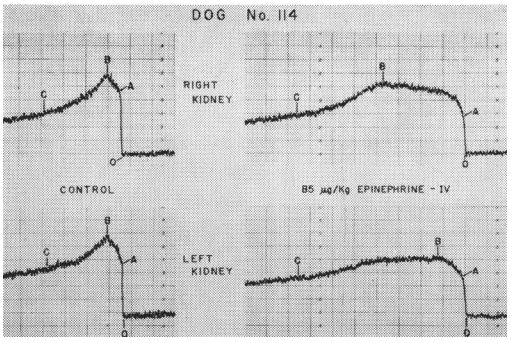

FIG. 1. A normal dog's control renogram compared with a renogram recorded one minute after intravenous injection of epinephrine. The renogram is read from right to left and the distance between vertical lines represents 3¾ min. OA represents vascular, AB secretory and BC excretory portion of the renogram.

gram. Renograms recorded 30 minutes after completion of the hormone injection were noted to return to their control pattern.

Group B. (Fig. 2 and 3). In 12 experiments there was constriction of the renal arteries just proximal to and usually including their first major bifurcation. In 3 of these 12, the area of constriction extended to within about one centimeter of the renal artery origin. That portion of the renal artery proximal to the constriction was dilated as compared with the control pictures. The vessels distal to the constricted area were also smaller in size, and a nephrogram which was uniformly noted in the control angiograms either did not appear in the post-

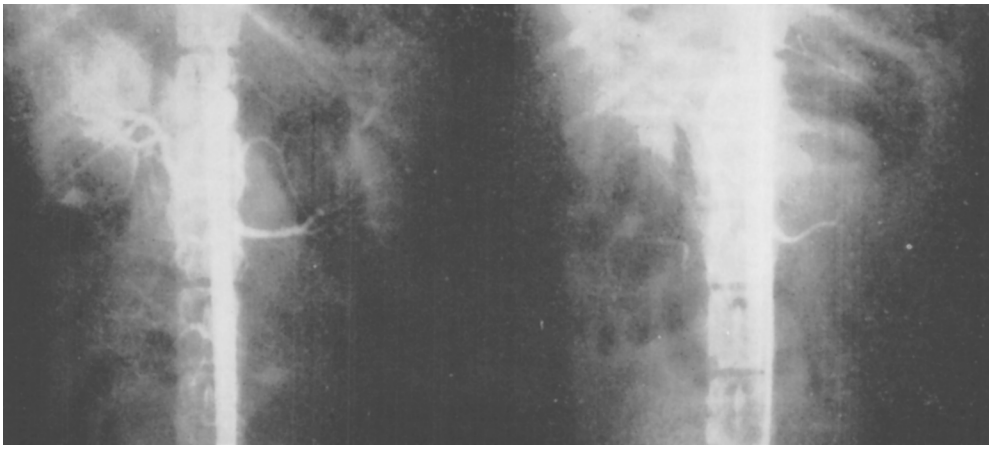

FIG. 2. A normal dog's control angiogram on the left and the one minute postepinephrine angiogram on the right. Both recorded one second after injection of the contrast agent.

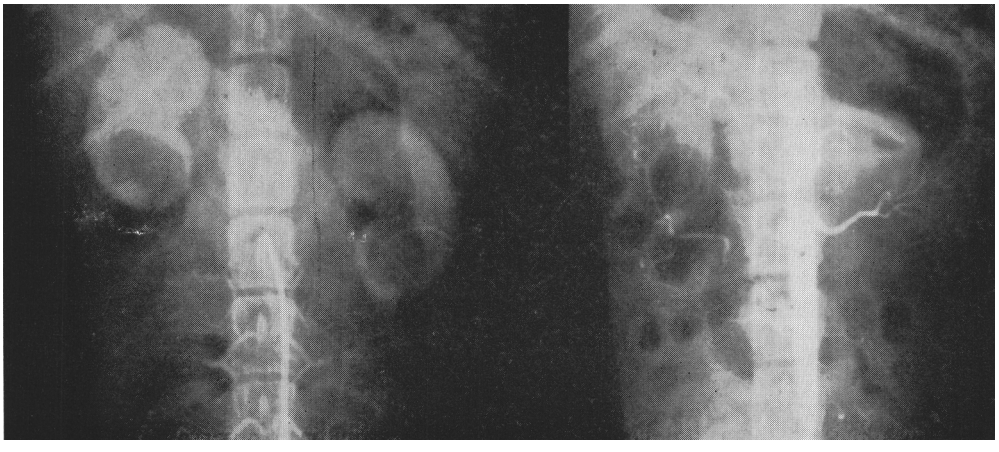

FIG. 3. Same animal as in Fig. 2 except at 2 seconds after injection of contrast agent.

adrenaline series or if it did it was delayed and very faint in appearance. In the controls the contrast material entered the aorta and filled the iliac vessels within one second of the injection. In the post-epinephrine series the contrast column remained at a level of about 3 to 5 cm below the origin of the renal arteries. The lower aorta and iliac vessels did not opacify during the period of post-epinephrine observation. In one dog the contrast material never passed beyond the first centimeter of the renal arteries.

The cine studies revealed similar effects of adrenaline already noted during the angiographic studies. In addition, the post-adrenaline cine revealed an up and down motion of the contrast column synchronized with diastole and systole respectively. During the period of observation the lower level of the column advanced only to about one-half of the distance between the origin of the renal arteries and the origin of the iliac arteries. This was in marked contrast with the control studies where the column proceeded into the iliac and femoral vessels in one second and the abdominal aorta was free of any contrast material within 3 seconds.

With smaller adrenaline doses the arterial constriction occurred but to a lesser degree. Findings similar to these were reported while this paper was in preparation(3).

In the post-adrenaline state injection of the contrast material was usually associated with a generalized increase in the dog's muscle tone, which at times was associated with convulsive-like activity of the extremities. This rigidity usually lasted for several minutes following the test, but in one-third of the animals a flaccid paralysis of the hind legs persisted.

Discussion. The radiorenogram changes associated with apprehension in human subjects were simulated in the Group A dogs who received pharmacologic doses of epinephrine. The probable vascular origin of these radiorenogram changes was confirmed by the experiments in Group B, where, in all instances epinephrine injection was associated with intense segmental constriction of the renal arteries, usually in the zone proximal to the first major bifurcation, but also noted to occur within one to one and one-half centimeters of the aorta in 4 dogs. We could not visualize the lower aorta for constriction because so little contrast material passed into this area during the period of observation. It is possible that the delayed passage of the contrast material through the lower aorta reflects increased vascular resistance in the more distal arteries.

We have not detected any significant gross histologic change in the muscle layers of the dogs' renal arteries which might correlate with this zonal response to epinephrine. However, measurement of phosphorylase activity in these vessel walls indicate there is increased activity in the zones where intense constriction appears in response to epinephrine. If confirmed, these findings could explain this response on a metabolic basis since epinephrine stimulates phosphorylase which initiates glycogenolysis by catalyzing the conversion of glycogen to glucose-1-phosphate. Continuing investigation of the mechanism of this renal artery response as well as a search for other similar segmental vessel response areas is in progress. Identification of such specific reactive segments in strategic zones of the vasculature may afford us a better understanding of how the immediate diversion of blood flow from one body area to another occurs in response to the demands of acute stresses of exercise and disease.

Of great interest to us in this connection was the initial observation which prompted these experiments, namely, that apparent apprehension in humans caused radiorenogram changes consistent with interference of renal arterial blood flow. In an attempt to verify this observation we recorded the humans' radiorenograms during periods of controlled conditioned reaction to pain. These experiments demonstrated that normal humans, in association with fear or anticipation of pain, did have renogram changes similar in all respects to the human and animal groups mentioned above.

These combined observations suggest that some individuals subject to specific daily

stimuli may place an unusual stress on certain organs, such as the kidney, because of the interference with its normal blood supply. A continuing series of such reactions over prolonged periods may not only interfere with the organ's function, but could also adversely affect the vessel segment which is reactive to the repetitive stimulation. A clearer understanding of the stimuli which provoke this response, the specific area where the response occurs, and the cellular factors providing the energy for the response may afford us valuable etiologic information for diseases such as essential hypertension and specific diseases of vessels.

Conclusions. (1) Pharmacologic doses of intravenous epinephrine in dogs caused a significant decrease in the vascular phase and a slower ascent to peak concentration of the I^{131} radiorenogram. These changes are essentially the same as noted to occur in humans who suffered with acute apprehension during the test procedure. (2) These same doses of epinephrine caused an intense constriction of the renal arteries proximal to or at the first major bifurcation as visualized with angiography and cineradiography. In one-fourth of the dogs the renal artery constriction was noted to occur within one to one and one-half centimeters of their aortic origin. The renal arteries proximal to the constricted zone were dilated.

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Stimulation of Phosphogluconate Pathway in Rat Brain Mince by Ethanol. (28740)

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Certain cerebral effects of ethanol would be understandable on the basis of impaired intracellular energy metabolism. If this were the case, glucose metabolism might be expected to be deranged since free glucose is the predominant energy source in the central nervous system(1). Indeed, ethanol does depress glucose oxidation in stimulated cortical preparations(2,3) and it has generally been considered that the Embden-Meyerhof glycolytic pathway represents the predominant catabolic route in this tissue(4-6). However, the fact that enzymes of the phosphogluconote pathway are present in adult brain(7-10) suggests that this latter pathway may, under certain conditions, also assume importance. The difficulty in demonstrating operation of this pathway seemed to be due to failure to maintain adequate levels of NADP* in the cerebral preparations. Glutathione reductase is specific for NADPH and is present in brain(11) and it has been shown that GSSG stimulated oxidation of C-1 of glucose without affecting that of C-6(12). Moreover, cerebral tissues contain a potent system which, upon disruption of cell structures, liberates nicotinamide from its nucleotides. Therefore NAD and NADP were included in our preparations at physiological concentrations and nicotinamide was added to inhibit

* The following abbreviations are used: NADP and NADPH, oxidized and reduced forms, respectively, of nicotinamide adenine dinucleotide phosphate (formerly triphosphopyridine nucleotide); NAD and NADH, oxidized and reduced forms, respectively, of nicotinamide adenine dinucleotide (formerly diphosphopyridine nucleotide); GSSG, oxidized glutathione; ATP, adenosine triphosphate.