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The Radiorenogram in Experimental Hypertension. (28253)

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Taplin and co-workers(1) discovered that an intravenous injection of radioactive iodopyracet (Diodrast-I^{131}) produced a characteristic pattern of radioactivity over the renal areas (radioisotope renogram). The value of the radioisotope renogram in detecting hypertension due to unilateral renal disease was soon recognized. Utilization of radioactive sodium iodohippurate (o-iodhippurate-I^{131}) (2) eliminated many of the technical difficulties associated with the use of radioactive iodopyracet and established the renogram in many centers as a clinical test of differential renal function.

However, despite the voluminous literature devoted to the radioisotope renogram in human hypertension, there is no published report of its characteristics in the experimental animal with renal hypertension. The present study was designed to utilize the radioisotope renogram in experimental renal hypertension.

Method. Twenty-one female dogs each had a right nephrectomy; 30 to 119 days later the left renal artery of each animal was constricted. A polyvinyl sponge clamp with an internal diameter approximately 85% of the external diameter of the renal artery was placed on the main trunk of the artery(3).

The blood pressure of each animal was measured by means of a 20-gauge needle placed directly in the femoral artery and was recorded on a Sanborn recorder *via* a 10-lb strain gauge. Multiple blood-pressure readings were recorded after each surgical procedure. The dogs were checked periodically for 9 months after the onset of hypertension.

Blood-urea concentrations were determined at frequent intervals.

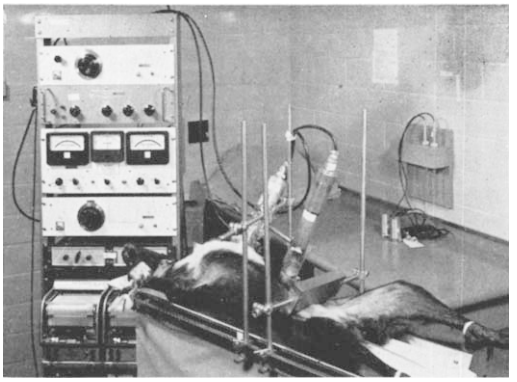

FIG. 1. Method for performing renographic study. Animal is supine on worktable with scintillation counters aimed at heart and left kidney. All dogs in anesthetized group were catheterized at beginning of each experiment.

A minimum of one radioisotope renogram was made on each dog before application of the arterial constriction and after the onset of hypertension. Several dogs had serial renograms taken; 9 animals had renograms taken shortly after application of the arterial constriction and again several weeks later.

The dog was placed supine on a worktable and 2 scintillation counters, one aimed at the heart and the other at the left kidney, were used (Fig. 1). The amount of radioactivity was recorded continuously for about 1 hour after intravenous injection of o-iodohippurate-I^{131} (Hippuran-I^{131})* (Fig. 2). The amount injected per dog was 1 microcurie per kilogram of body weight. Ten of the dogs were studied while they were awake and 11 while under pentobarbital anesthesia. A more reliable tracing could be obtained with the an-

* Supplied by Abbott Laboratories, Oak Ridge, Tenn.

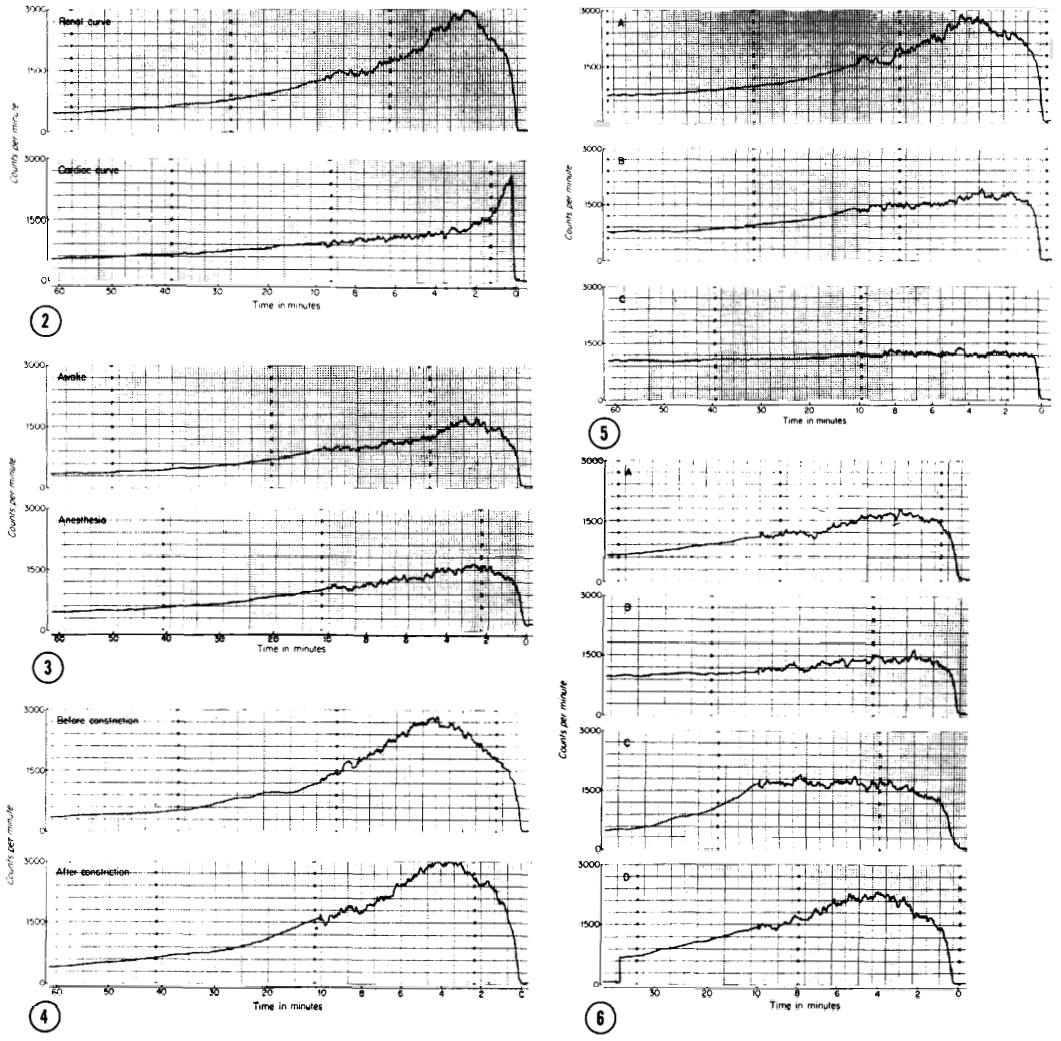

FIG. 2. Normal renogram and cardiac curve. Tracings show o-iodohippurate-I^{131} renographic results obtained over left kidney (top) and over heart (lower) of a normal animal 3 wk after right nephrectomy. During first 10 minutes chart rate was increased to permit recording of early, rapidly changing components of the curve. Note initial rise reaching a peak, followed by steady decline in radioactivity. These changes in the curves are attributed to initial distribution of o-iodohippurate-I^{131} in blood, interstitial fluid, and kidney; to accumulation of radioactivity within renal collecting system; and to disappearance of o-iodohippurate-I^{131} from blood and kidney and its excretion *via* renal outflow tract(4).

FIG. 3. Effect of anesthesia on renogram. Renograms from same animal obtained consecutively with dog awake and then under anesthesia. After renogram was obtained while dog was awake, dog was anesthetized with pentobarbital while in same position and a second injection of iodohippurate was given for second renogram. Differences between tracings are negligible except for increase in background activity.

FIG. 4. Renogram of animal with hypertension. Tracings from animal (dog 14) that had hypertension without uremic syndrome. Tracings are similar and retain similarity when done 1 hr or 3 mo after constriction of artery. Normal (control) tracing (top) was taken 1 day before constricting artery, the other, 59 days later. Blood pressure was 152/68 before constriction, and 235/144 after.

FIG. 5. Renogram of animal with hypertension. This animal (dog 16) died after constriction of renal artery. Normal (control) blood pressure was 139/62, and just before death it was 170/123. Note normal tracing (A) taken after constriction of renal artery 1 hr previously, followed 7 days later by tracing (B) in which peak is lower and terminal slope less rapid, and finally tracing (C) taken 20 days after constriction, in which curve shows no uptake

TABLE I. Renographic Indices in Normal Unilaterally Nephrectomized Dogs Before and After Constriction of the Renal Artery.

Group	Urograms	Index* b/a	c/a	d/a
Before constriction of renal artery (controls)	40	1.65 ± .04†	.97 ± .03	.61 ± .03
After constriction				
Hypertension without uremic syndrome	20	1.58 ± .04	.87 ± .04	.52 ± .03
Hypertension with uremic syndrome	5	1.12 ± .19	1.10 ± .20	1.07 ± .24

* Based on renogram. a = height of initial steep rise in radioactivity; b = height of peak of radioactivity; c = height of curve at 10 min; and d = height of curve at 30 min.
† Number after ± is standard error of mean.

esthetized dog, but the dogs were divided into these 2 categories to evaluate any changes due to anesthesia. No differences in the characteristics of the renogram were noted between these 2 categories (Fig. 3).

Two photomultiplier tubes (¾-inch Dumont Type K 1382) were used for the renograms; each tube was attached to a ½ by ½ inch NaI (Tl) crystal with a preamplifier. Recordings were made on a rectilinear recording milliammeter (Rectiriter, model 301). The chart rate was ¾ inch per minute for the first 10 minutes with a probable error in the recording of 2.0%, and 12 inches per hour for the next 50 minutes with a probable error of 0.5%.

The renograms were compared with renograms from normal animals by visual inspection and by the use of indices as defined in Table I. Normal (control) values were determined from 40 renograms made on animals during the control period after right nephrectomy.

Results. Animals were considered to be hypertensive if either the systolic blood pressure rose 40 mm of mercury or diastolic pressure rose 20 mm above normal control values (Table II). On this basis, all 21 animals became hypertensive. Five died (hypertension with uremic syndrome) and 15 of the 16 that lived had hypertension without uremic syndrome. The other animal that lived presented characteristics of both groups and is discussed separately.

Hypertension without uremic syndrome. In 15 dogs with hypertension the only abnormal finding was a definite elevation of blood pressure. Blood-urea concentrations ranged from 20 to 62 mg per 100 ml (Table II); they all had been normal prior to constriction of the renal artery. The radioisotope renograms were unchanged (Fig. 4) and renographic indices were not significantly different from those of the normal (control) animals (Table I).

Hypertension with uremic syndrome. Five hypertensive animals died; in each the concentration of blood urea was markedly increased and definite changes in the radioisotope renogram were seen (Fig. 5 and Table III). Characteristic of this group, the peak of the renographic curve was greatly reduced and the final slope of the curve decreased less rapidly after arterial constriction. These changes were considered to represent reduced renal uptake and reduced clearance of o-iodohippurate.

Renographic studies were performed on 3 animals in this group within one hour after constriction of the renal artery, and it is noteworthy that all 3 tracings were normal.

The charactersitic findings in the animals that died consisted of increased blood pressure, retention of urea, rectal bleeding, weight

of radioactivity by kidney and little or no clearance from blood. Blood urea measured 217 mg/100 ml on day of death.

FIG. 6. Abnormal renogram in an animal (dog 21) which survived. Tracing (A) taken 3 days before constriction, is normal; tracing (B) taken 13 days after constriction, similar to terminal tracing in Fig. 5, is abnormal; tracing (C) taken 37 days later demonstrates delayed excretion with definite uptake of media; tracing (D) taken 74 days after operation is again normal.

TABLE II. Blood Pressure and Values for Blood Urea.

Dog	Avg blood pressure, mm Hg: In control period	Avg blood pressure, mm Hg: After onset of hypertension	Blood urea, mg/100 ml, after onset of hypertension: Range	Blood urea, mg/100 ml, after onset of hypertension: Avg
Hypertension without uremic syndrome				
1	129/60	167/91	35-44	40
2	139/59	180/90	35-42	39
3	158/73	183/97	45-62	52
4	149/78	184/106	22-38	30
5	123/55	188/114	25-51	37
6	148/77	195/111	28-29	29
7	141/76	211/139	24-34	28
8	167/83	212/109	23-32	29
9	164/75	218/138	24-41	33
10	158/79	219/123	27-40	35
11	187/90	222/118	20-31	27
12	170/83	235/136	25-49	40
13	166/81	235/142	40	40
14	152/68	235/144	29-40	33
15	183/84	248/140	30-40	34
Hypertension with uremic syndrome				
16	139/62	170/123	42-217	129
17	162/85	220/148	43-592	202
18	151/77	220/165	311-323	317
19	186/94	223/130	53- 75	66
20	191/94	248/145	43-194	99
Hypertension of indeterminate type				
21	161/91	223/123	24-84	41

TABLE III. Comparison of Differences of Renographic Indices* in 5 Dogs Before Constriction of Renal Artery and After Onset of Hypertension With Uremic Syndrome.

	Index† b/a	Index† c/a	Index† d/a
Mean difference	.47	.24	.58
Standard error of mean	±.16	±.06	±.08

* All differences highly significant.
† As defined in Table I.

loss, anorexia, blindness, convulsions, and rapid deterioration during a period of 1 or 2 weeks.

Hypertension of indeterminate type. One of the 16 dogs that lived (dog 21) does not fit clearly into either hypertensive group. The blood pressure rose from 161/91 to 223/123, and concentration of blood urea reached 84 mg per 100 ml after arterial constriction. The animal lost weight, bled from the rectum, and showed evidence of rapid deterioration. Glucose in water was infused to maintain adequate hydration, and after a few days the concentration of blood urea returned to normal. The animal began to eat and recovered rapidly; the blood pressure, however, remained elevated. This animal demonstrated definite signs of the uremic syndrome and is considered to represent the only recovery in this group. The renogram (Fig. 6), taken at the time the concentration of blood urea was elevated, exhibits a definite reduction of renal function, but subsequently the function returned to normal.

Discussion. Two types of experimentally induced renal hypertension, previously described by Goldblatt and co-workers(5,6), were noted in this study. One type was that in which the renographic findings were within normal limits (hypertension without uremic syndrome). The other type was that in which definite changes were visible in the radioisotope renogram (hypertension with uremic syndrome). The blood pressure in both groups was elevated by about the same degree.

Although the term "ischemic hypertension" has gained common clinical use, objective experimental evidence to support this view is limited. Results of studies have shown repeatedly that it is possible for experimental renal hypertension to exist with normal renal blood flow(7). The present study has demonstrated that normal renographic results with o-iodohippurate-I^{131} are possible in the presence of experimental renal hypertension.

Summary. Renographic studies with o-iodohippurate-I^{131} were performed on 21 dogs before and after the onset of hypertension experimentally induced by constricting the renal artery. Sixteen of the dogs tolerated the constriction of the artery and showed no changes in the renographic findings. Five animals died from severe renal damage following surgical procedures; renograms of these 5 animals demonstrated reduced renal function.

The radioisotope renogram may not show any abnormality in the presence of experimental renal hypertension.

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Carcinogenic Effect of Egg White, Egg Yolk and Lipids in Mice.* (28254)

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It has been demonstrated that mice maintained on a Rockland rat diet supplemented with hard boiled hens' eggs develop a high incidence of malignancies(1,2). The mice eat preferably the egg yolk, but as they also consume part of the egg white, it is impossible to determine which of the 2 is carcinogenic. We have therefore carried out experiments with mice of 2 inbred strains, the "A" and the "T. M." This report concerns results obtained with the T.M. strain of mice. This strain, considered cancer resistant, was developed locally by Dr. Carmen Casas, and in 15 years of inbreeding the mice have rarely developed malignancies.

Methods. Two series of experiments were carried out. In both, the mice were divided into 4 groups and placed at the age of 4 weeks on the following diets. Group 1, the control, was maintained on the Rockland rat diet only, with no supplement. For the other 3 groups the Rockland rat diet was supplemented with hard boiled egg white (Group 2), with raw egg yolk (Group 3) or with cholesterol and lard (Group 4). One egg white, one egg yolk or 50 to 100 mg of cholesterol and 1 g of lard were given daily per cage of 10 to 12 mice. As some sugar was added to the cholesterol and lard in order to induce the mice to eat it, it was also added to the egg white and egg yolk. The egg white was boiled after removal, intact, of the egg yolk. For this an opening was made at the large extremity of the egg, the egg yolk carefully separated from the egg white and removed. The shell containing the egg white was then placed upright in a boiling water bath, avoiding penetration of water into the shell.

In one series of experiments males and females were caged separately, while in the other series the mice of the 4 groups were bred and their offspring maintained on the same diets. Each group in this series was made up, consequently, of mice of 3 to 4 generations. The mice of each generation were bred only twice; males and females were then caged separately. Some of the offspring of the mice of the 3rd and 4th generations of Groups 3 and 4 were changed to the control diet at the age of 4 to 6 weeks. They were also bred twice, but their offspring were not used in the present experiments.

All the mice of both series of experiments were autopsied after death and their affected organs fixed with Bouin's fluid, sectioned and stained for microscopic studies.

Results. The results are summarized in Tables I and II. The average life span of the control mice (Group 1) of the first series of experiments, in which the mice were virgins, was the same as in the second series of experiments in which the animals were bred. Yet the incidence of malignancies was higher in the latter than in the former. Lung adenocarcinomas, the most frequent malignancies of the control mice, were usually small tumors as compared with those found in the animals of Groups 2 and 3. Moreover, in the latter, on the diets supplemented with hard boiled egg white and raw egg yolk, respectively, lung malignancies appeared at a relatively earlier

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