Many recent publications incriminate some alteration in the renal circulatory bed as a primary factor in the production and/or maintenance of most states of acute renal insufficiency (1-13). On the one hand, measurements of renal blood flow made by use of the Fick principle either at the onset of the injury or subsequent to an ensuing anuric or oliguric period have shown a significant renal ischemia associated with surgical and hemorrhagic shock, abortion, incompatible blood transfusions, heavy metal poisoning, hemoglobin infusions, and carbon tetrachloride poisoning (1-11). The accuracy of some of these measurements is open to question because of the almost negligible renal extraction of the test substance involved and the difficulties of urine collection during severe oliguria. However, this body of data has been interpreted as indicating that an initial renal ischemia is primarily responsible for the development of renal insufficiency and ultimately anuria produced by all insults not directly nephrotoxic; and that renal ischemia probably is present throughout the period of anuria whatever the initial cause. On the other hand, Trueta Raspall (12), using the results of rabbit experiments, has proposed that the important vascular abnormality is an intrarenal “juxtamedullary shunting” of blood presumably with a normal over-all flow. The continuation of this “shunting” throughout the period of renal inadequacy is implied.

Since the “shunt” hypothesis has been widely challenged and the other not yet entirely documented, consideration of these concepts raises certain related questions: 1) Do intrarenal shunts in the intact subject ever play any part in the development or continuation of renal insufficiency states? 2) Does an initial renal ischemia persist to become a major contributor to the continuation of renal insufficiency or to the commonly associated anuria? With the development of a gas diffusion method for measuring renal blood flow which does not require urine for analysis (14) and with the application of newer arteriographic techniques, more direct and more satisfactory answers can now be given to these questions.

In the absence of readily available clinical material, two abnormal conditions which might simulate those leading to acute anuria in humans were created in dogs: bichloride of mercury poisoning and an incompatible blood transfusion reaction. Then at the time of anticipated maximal urinary suppression, the renal circulatory behavior and tubular function were studied by correlating measurements of renal blood flow, intrarenal distribution of flow, renal para-ami-no-hippurate (PAH) extraction, and renal arteriovenous oxygen differences with urinary and post mortem renal morphological changes.

METHODS

The two methods of producing renal or urinary tract abnormalities were: administration of human blood by transfusion, and mercuric chloride poisoning. To simulate human incompatible blood transfusion reaction, the administration of human blood rather than dog blood was resorted to. This was done despite the heterologous nature of the infusion because homologous transfusions in the dog given without regard to blood types have never been noted to cause renal damage. Mercuric chloride was chosen in light of its known ability to cause human anuria. The dosages to be given were decided as follows: the volume of human blood used was that calculated as being equivalent to transfusing 500 ml. of whole blood into an average adult human, and the amount of mercury given

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1 This work was supported in part by the National Heart Institute of the U. S. Public Health Service (H 405) and in part by a University of Pennsylvania Faculty Research Grant.

2 Research Fellow of the American Heart Association during the tenure of this study.
was that found to cause the greatest renal damage without consistently killing or excessively "shocking" the dog before the studies could be done.

In all, 21 dogs were used. Ten were given 7.5 ml. per Kg. of human blood intravenously 48 to 72 hours previous to the study, while two were given the same dose two and one-half weeks previous to the study and the dose repeated three days previous to the study. Blood of all types secured from a hospital blood bank was used 10 to 15 days after its donation. Control studies were done on all dogs given human blood. Eight dogs were given 15 mg. per Kg. and one, 30 mg. per Kg. of mercuric chloride by the intramuscular route.

In preparation for the renal studies, all animals were lightly anesthetized by an intravenous injection of equal parts of Pentobarbital Sodium and Dial-Urethane, 0.3 to 0.4 ml. per Kg. A No. 8, curved tip, woven venous catheter was then passed under fluoroscopic guidance from the external jugular vein deep into the renal vein (usually the left), so that the tip lay within the shadow of the renal parenchyma. The left renal vein was used because of previous anatomical studies in dogs which showed the segment of renal vein from the renal parenchyma to the spermatic vein on the left to be consistently longer than the entirety of the right renal vein. Thus, the possibility was minimized of including in the sample, blood other than renal venous blood.

Renal venous blood was then collected through a manifold system (15). Arterial blood was obtained via a plastic catheter passed through the femoral artery into the aorta, the tip lying superior to the renal artery. This catheter was also connected to a manifold system.

Renal blood flow was measured by the gas diffusion method utilizing nitrous oxide. This principle and this specific method have both been described elsewhere in detail (14, 15). Flow is expressed in ml. per 100 Gm. of renal tissue per minute.

Intrarenal distribution of flow was determined by injecting (in approximately one second) 20 ml. of 70 per cent Iodopyracet into the arterial catheter and taking seven successive radiographs of the kidneys usually 1, 2, 3, 4, 10, 20, and 30 seconds after the injection.

Mean arterial blood pressure was measured by a mercury manometer connected with the arterial catheter-manifold system. Renal resistance was calculated in mm. Hg per ml. per 100 Gm. per min. from the renal flow and the mean arterial pressure. No correction for venous pressure was employed.

Simultaneous arterial and venous samples for oxygen content were drawn into oiled, heparinized 10 ml. syringes and were analyzed manometrically after the method of Van Slyke and Neill (16). The results were corrected for renal arteriovenous hematocrit differences, the largest correction being 3 per cent of the oxygen content. Oxygen consumption was calculated in ml. per 100 Gm. of renal tissue per minute. The hematocrits were determined by centrifugation of samples placed in Wintrobe tubes and spun for 30 minutes at 4000 rpm. in a General Electric size 2 centrifuge.

PAH measurements were done on whole blood. The reason for the use of whole blood determinations, as well as the details of the method involved with the following exception, have been described elsewhere (17). Trichloracetic acid (3 per cent in final solution) was used for protein precipitation in place of cadmium sulfate, since its use resulted in more consistent and essentially complete PAH recoveries. As compared with 85 to 90 per cent renal plasma PAH extraction (E_{PAH}), whole blood extractions were found to be somewhat lower (74 ± 8 per cent), presumably due to slower diffusion of PAH from the red cells.

Blood urea nitrogen was determined in one animal. The amount of urine, if present, was measured, specific gravity determined, and the urine was examined microscopically and tested for albumin.

After the animals were sacrificed, the kidneys were weighed and the weight expressed in Gm. per Kg. of dog weight. The kidneys were then examined both grossly and microscopically.

RESULTS

1. Human blood (Table I)

During the initial administration of blood at a rate of approximately 3 ml. per minute, a fall in blood pressure invariably occurred after 10 to 35 ml. This hypotension varied markedly in degree and duration. In animals being given a first infusion, mean systemic pressure falls of 40 to 100 mm. of mercury were observed for periods from 15 minutes to an hour. This phenomenon could be repeated once or twice, but thereafter, the systemic pressure stabilized or tended to rise when the infusion was continued. In the two dogs given a second infusion, the fall in pressure was 60 to 90 mm. of mercury and this was sustained for three hours in one, and over five hours in the other. Unfortunately, renal hemodynamics were not evaluated at this time.

Three of the dogs, including the one which had the longest period of hypotension after a second blood infusion, died before the subacute renal circulatory changes could be determined. Six which were given only a first infusion of blood, showed no evidence of renal abnormality when studied by the techniques described herein at the prescribed 48 to 72-hour period. A complete recapitulation of the data on these animals is therefore excluded from the present report, leaving only the results in the three in which a definite renal effect was demonstrated. These three animals were designated
T able I

The effects of the intravenous administration of human blood on the renal circulation, tubular function, urinary volume and composition, and renal morphology of the dog

<table>
<thead>
<tr>
<th>Experimental state</th>
<th>Urine</th>
<th>Post mortem kidneys (5.8-9.0 Gm./Kg.)*</th>
<th>Renal arteriography</th>
<th>Mean arterial blood pressure (100-140)</th>
<th>Renal blood flow (290-400)†</th>
<th>Renal resistance (0.25-0.48)‡</th>
<th>Oxygen consumption (5-9)§</th>
<th>Whole blood PAH extraction (66-82%)¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control A</td>
<td>Normal</td>
<td>1 ml./min.</td>
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<td>—</td>
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<td>—</td>
<td>—</td>
<td>115, 323, 0.35, 6.6, 86</td>
</tr>
<tr>
<td>A</td>
<td>7½ ml./Kg.</td>
<td>A+ blood 0.25 ml./min. 48 hrs. before study</td>
<td>Sp. gr. 1.008 Vessels hyperemic, slightly pale, not swollen, 7.3 Gm./Kg. “transfusion nephrosis” Normal 42 110 305 0.36 5.9 57</td>
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<tr>
<td>Control B</td>
<td>Normal approx. 1 ml./min.</td>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>135, 380, 0.36, 7.2, 78</td>
</tr>
<tr>
<td>B</td>
<td>7½ ml./Kg.</td>
<td>AB+ blood 0.2 ml./min. 72 hrs. before study</td>
<td>Sp. gr. 1.010 Pale, slightly edematous 9.0 Gm./Kg. “transfusion nephrosis” Slightly prolonged dye shadow. Enlarged kidneys 49 135 295 0.46 5.6 3</td>
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<tr>
<td>Control C</td>
<td>Normal approx. 1 ml./min.</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>45, 125, 380, 0.33, 6.5, 75</td>
</tr>
<tr>
<td>C</td>
<td>7½ ml./Kg.</td>
<td>Anuria 2½ weeks 72 hrs. before study BUN—40</td>
<td>Pale, edematous Prolonged dye shadow. Enlarged kidneys 43 110 150 0.73 4.8 0</td>
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</tbody>
</table>

* Normal limits in 15 animals.
† Normal limits in 11 animals.
‡ Calculated from normal limits for B.P. and R.B.F.
§ Normal limits in 11 animals.
¶ 74% ± 8% (2 S.D.) in 12 animals.

as IA, IB, and IC; the latter being the surviving dog given a second blood transfusion. The results were as follows:

Urine. Dogs IA and IB were passing 0.25 ml. and 0.2 ml. of urine per minute, respectively. The urinary specific gravity was 1.008 to 1.010 with slight proteinuria. Dog IC was anuric.

Circulatory bed. In dogs IA and IB, renal blood flow and renal resistance were within normal limits, the flow being slight (5 and 22 per cent), but not significantly less than the control values. Dog IC had a renal blood flow of approximately 40 per cent of normal with an elevated renal vascular resistance. The intrarenal distribution of flow was normal in all, although the prolonged parenchymal dye shadow suggested reduced total flow. Compare the renal arteriogram from a normal dog (Figure 1) with that of dog IC (Figure 2).

Renal function. Renal whole blood PAH extraction (EPAH) fell from 86 to 57 per cent in dog IA, 78 to 3 per cent in dog IB, and 73 to 0 per cent in dog IC. The oxygen consumption remained within normal or borderline normal limits in all three animals. However, the results represented a decrease from the control values in each case. The blood urea nitrogen in dog IC was elevated.
to 40 mg. per cent. Unfortunately, this measurement was not made in the other two animals.

Post mortem examination. The tubular degeneration and necrosis associated with hemoglobin casts in the tubular lumina which have been described as characteristic of “mismatched transfusion nephrosis” were present to a moderate degree in dog IA and in large degree in dogs IB
FIG. 2. RENAL ARTERIOGRAM OF DOG IC SEVENTY-TWO HOURS AFTER THE ADMINISTRATION OF HUMAN BLOOD

The renal vessels are normally visualized at two seconds and the dye appears equally distributed throughout the cortex at ten seconds. The right kidney, partially obscured by the rib cage, is reproduced poorly in the photograph. The left appears somewhat enlarged.

and IC. The picture seemed to represent a conglomeration of patchy changes rather than involvement of any one anatomical part of the nephron. Degenerative swelling, renal edema, and inflammatory reaction were much more in evidence in dog IC.
II. *Mercury bichloride poisoning* (Table II).

Nine animals were given mercury bichloride; five died from the extrarenal effects before studies were made. The surviving four all showed to a varying extent: dehydration, weakness, lethargy, and bloody diarrhea. The following renal data were obtained in these animals:

**Urine.** Dogs IIA and IID were passing relatively normal amounts of urine (0.5 to 1.0 ml. per min.) 60 and 54 hours, respectively, after the mercurial injection. Dog IIC was anuric 72 hours after the injection. Dog IIB, while showing little decrease in urinary volume after 48 hours, had become severely oliguric after 12 hours. All dogs passing urine had hyposthenuria with albumin and casts.

**Circulatory bed.** The renal blood flow was normal in the two dogs showing little or no urinary

<table>
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<tr>
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<th>Urine</th>
<th>Post mortem kidneys (5.8-9.0 Gm./Kg.)*</th>
<th>Renal arteriography</th>
<th>Mean arterial blood pressure H’crit</th>
<th>Renal blood flow (200-400)†</th>
<th>Renal resistance (0.25-0.48)‡</th>
<th>Oxygen consumption (5-9)§</th>
<th>Whole blood PAH extraction (66-82%)‖</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
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<tr>
<td>15 mg./Kg. (IM)---HgCl₂ 60 hrs. before study</td>
<td>Sp. gr. 1.014</td>
<td>Oliguria minimal 0.4 ml./min.</td>
<td>Grossly normal No microscopic 7.1 Gm./Kg.</td>
<td>— 125 355 0.37 — —</td>
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<td><strong>B1</strong></td>
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<tr>
<td>30 mg./Kg. (IM)---HgCl₂ 48 hrs. before study</td>
<td>Sp. gr. 1.011</td>
<td>++ albumin and casts</td>
<td>— 44 115 265 0.43 7.1 57</td>
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<td><strong>B2</strong></td>
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<tr>
<td>Same dog at 120 hrs.</td>
<td>Extreme oliguria (occ. drop) ++ + + + albumin and casts</td>
<td>Gross-slight swelling &amp; pallor Micro-mod. tubular deg. &amp; necrosis 8.4 Gm./Kg.</td>
<td>Normal distribution Prolonged cortical dye shadow</td>
<td>65 120 170 0.70 3.4 15</td>
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<td><strong>C</strong></td>
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<tr>
<td>15 mg./Kg. (IM)---HgCl₂ 72 hrs. before study</td>
<td>Anuric</td>
<td>Grossly normal Micro-marked tubular destruction deg. and necrosis 7.3 Gm./Kg.</td>
<td>Normal</td>
<td>36 73 155 0.47 1.0 5</td>
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<tr>
<td><strong>D</strong></td>
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<tr>
<td>15 mg./Kg. (IM)---HgCl₂ 54 hrs. before study</td>
<td>Sp. gr. 1.007</td>
<td>0.5 ml./min. ++ + + + albumin and casts</td>
<td>Grossly normal Micro-similar to Dog C</td>
<td>— 51 118 400 0.30 2.0 4</td>
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</tbody>
</table>

* Normal limits in 15 animals.
† Normal limits in 11 animals.
‡ Calculated from normal limits for B.P. and R.B.F.
§ Normal limits in 11 animals.
‖ 74% ± 8% (2 S.D.) in 12 animals.
volume change and was only slightly subnormal in
dog IIB when first studied. However, at the time
when urinary volume was essentially nil in dog IIB
and in dog IIC, renal blood flow was only appro-
imately 40 to 50 per cent of normal. Intrarenal
distribution of blood flow, as determined by ar-
teriography, was normal in all cases studied. The
calculated renal resistance was within top normal
limits in all studies except in the case of the second
study on dog IIB. Here with a blood flow ap-
proximately 50 per cent normal (170 ml. per 100
Gm. per min.) and an associated mean pressure of
120 mm. Hg, the calculated mean resistance was
50 per cent above normal. The hematocrit, how-
ever, had increased from 44 to 65. Only anuric
dog IIC had a mean pressure at shock levels 73
mm. Hg.

**Tubular function.** Both oxygen consumption
and PAH extraction were markedly reduced in
the three dogs so studied except the first study on
IIB where clearly abnormal values were not dem-
onstrated. This reduction occurred in roughly
parallel fashion, $E_{\text{PAH}}$ varying from 5 to 20 per
cent normal and oxygen consumption from 20 to 65
per cent normal.

**Post mortem examination.** The kidneys showed
widespread tubular degeneration and necrosis with
scattered, minute deposits of calcium. The proxoi-
mal convoluted tubules were most involved. In
many areas only tubular outlines remained recogni-
able and the tubular lumen was obliterated. The
severity of the morphological changes was
well-correlated with the degree of reduction in
PAH extraction and oxygen consumption, but
not with the urine volume.

**DISCUSSION**

These studies show that mercury bichloride in
the dosage employed here will consistently produce
severe renal tubular damage in the dog, and that
initial transfusions of human blood will occasion-
ally do so. They also suggest that appropriately
timed second transfusions are much more likely to
produce renal damage than the first, a view sup-
ported by other data (17, 18). Although the mi-
croscopic morphology indicated a difference in lo-
cation and intensity of the damage caused by blood
as opposed to that caused by mercury (in agree-
ment with Oliver’s hypothesis [1]), all affected
animals from both groups had developed a similar
functional impairment in regard to PAH extrac-
tion and inability either to make urine or to con-
centrate it. The very low renal oxygen consump-
tion found after mercury poisoning can be at-
tributed to the widespread tubular necrosis and
marked degeneration of the non-necrotic epi-
thelium, while the nearly normal values found fol-
lowing the human blood infusions can be attribut-
ted to a less massive necrobiosis and to a promi-
ient increase in the number of leukocytes in the
interstitial tissues.

These studies also show that at a time two or three
days after the initial injury, marked renal circu-
latory derangements are not necessarily a con-
comitant of the tubular damage produced either
by mercury or by human blood. In fact, a marked
circulatory derangement was found only in two
out of four animals given mercury and in only one
out of three developing tubular impairment from
human blood. When present, the circulatory ab-
normality was a reduction of renal blood flow to
approximately one-half normal or less without
any suggestion of alteration in the corticomedullary
flow pattern. Indeed, no evidence of functioning
intrarenal shunts was found in any of the animals.

The reductions in renal blood flow were not
nearly so great as those reported by Bull, Joekes,
and Lowe (6) in human anurics just before or
after the anuric period. Their data, obtained by
using the Fick method, indicated renal blood flows
of from 0 to 20 per cent of normal.

The immediate factors responsible for the oc-
currence of renal ischemia in the two animals de-
veloping it after bichloride of mercury injections
appeared to be dehydration and “shock level”
blood pressure in dog IIC and severe dehydration
with extreme hemoconcentration in dog IIB. Re-
nal edema, which has been implicated as a cause of
renal ischemia and anuria (19–21), was minimal
in the dogs given mercury, but its presence was
more obvious in the dogs given blood, particularly
in dog I. In this dog, severe renal edema was
noted and was the only obvious factor on which
blame could be laid for the presence of renal
ischemia.

Finally, the studies show that in regard to the
two experimental abnormalities produced herein,
the urinary finding of extreme oliguria or actual
anuria can be much better correlated with the
presence of renal circulatory impairment than with the presence or extent of tubular damage. The three dogs (IC, IIB, IIC) making little or no urine, were the same ones found to have moderately severe renal ischemia, while all the remaining dogs had a fair to good urinary minute volume and an essentially normal renal circulation. On the other hand, the demonstrated abnormalities in tubular function and morphology were almost identical in dogs IB and IC given human blood and also, in dogs IIB and IIC given mercury; yet the urinary minute volume in the former of each group was only moderately decreased, whereas it was nil in the latter of each group. Some years ago, it was stated (22) that the development of anuria following mercury bichloride poisoning was the result of complete loss of tubular impermeability with resultant glomerular filtrate-blood iso-osmotic equilibration. The presence of an essentially normal urinary volume (and renal circulation) in dog IID, having histological evidence of tubular necrosis quite as marked (see Figure 3) as that found in anuric dog IIC, suggests that filtrate-blood iso-

![Figure 3](image-url)

**FIG. 3. PHOTOMICROGRAPH OF KIDNEY OF DOG IID GIVEN MERCURY BICHLORIDE FORTY-EIGHT HOURS PREVIOUSLY (H & E STAIN)**

There is widespread tubular necrosis involving proximal tubules most severely. Note complete loss of structure with obliteration of lumina in some areas. Glomerular changes appear to be negligible.
renal ischemia may in turn be due, not directly to tubular damage, but to such sequelae thereof as renal edema or cast obstruction or it may result from such systemic derangements as shock or dehydration.

**SUMMARY**

1. The effects of intramuscular mercuric chloride injection and transfusions of human blood on renal tubular function, renal circulation, urinary volume and composition, and renal morphology in the dog were studied two to four days after the initial stimulus.

2. Mercuric bichloride consistently produced renal tubular damage, while human blood produced renal tubular damage occasionally after a first transfusion and in the only dog surviving a repeated transfusion.

3. Anuria was present in two out of four surviving animals having renal damage due to mercury poisoning, and one out of three having damage following human blood transfusion.

4. The renal circulation was essentially normal in all animals, save the anuric ones in which renal blood flow was reduced to 50 per cent of normal or less. As judged by renal arteriography, no functioning intrarenal shunts were present in any of the animals.

5. It is proposed that in the present experiments, the occurrence in three animals of anuria rather than moderate oliguria was mainly due to the superimposition of renal ischemia upon existing tubular damage.

**ACKNOWLEDGMENTS**

The authors wish to express their appreciation to Dr. Carl F. Schmidt for extending to them the use of the facilities of the Department of Pharmacology during the course of these studies and to Drs. C. F. Schmidt, J. K. Clark, and F. C. Wood for constructive criticisms of the manuscript.

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