hours following the single intravenous injection of 10,000 Oxford units. When PAHA was infused to maintain a plasma concentration of 30 to 50 mgm/100 cc, the end point at which the plasma concentration of penicillin was less than the lower limit of our test (0.02 unit/cc) was extended to 3.5 hours. Penicillin ceased to be excreted in the urine in determinable quantities within 7.5 hours during the control experiments but was still being excreted in small amounts at the end of 9.5 to over 12 hours when PAHA was administered continuously over this period of time. In these experiments, also, PAHA decreased the renal clearance and the recovery of penicillin in the urine as in earlier experiments.

Forty-eight-hour experiments were performed during which both penicillin and PAHA were infused continuously. As a result of these tests we found that, if the plasma level of PAHA was maintained at 20 to 30 mgm/100 cc, we could maintain a plasma penicillin level of 0.08 to 0.1 unit/cc when the penicillin was infused at a rate of 15 units/minute. On the other hand, when PAHA was not administered the penicillin level in the plasma was 0.02 units/cc or less. Also, by raising or lowering the plasma concentration of PAHA we could concomitantly raise or lower the penicillin content in plasma even though the penicillin was infused at a constant rate during the whole of the experiments. As the plasma concentration of penicillin was caused to rise by the intravenous infusion of PAHA there was a progressive decrease in renal clearance and urinary excretion of the antibiotic substance.

There appeared to be no pathological findings attributable to the PAHA-penicillin therapy in any of the 48-hour experiments. Toxicological studies have shown PAHA to be remarkably non-toxic to mice, rabbits and dogs; so much so that the physical characteristics of the high concentrations (20 to 40 per cent.) of the sodium p-aminohippurate solutions found necessary for intravenous toxicity studies were probably the principal causes of deaths which occurred at an LD50 dose of 5,300 mgm/kg administered intravenously to mice.

The detailed accounts of these experiments will be published elsewhere. These results indicate that with the aid of PAHA one may attain and maintain materially higher concentrations of penicillin in plasma than is practicable without the use of excessive amounts of penicillin. The ease and economy with which this can be accomplished experimentally suggest that the combined intravenous administration of penicillin and PAHA may offer sufficient therapeutic advantages to make its clinical trial indicated.

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SCIENTIFIC APPARATUS AND LABORATORY METHODS

A METHOD OF OBTAINING RENAL VENOUS BLOOD IN UNANESTHETIZED PERSONS WITH OBSERVATIONS ON THE EXTRACTION OF OXYGEN AND SODIUM PARA-AMINO HIPPURATE[1]

THE present concepts of human renal physiology are based upon somewhat unstable tenets because of the difficulty in obtaining blood from persons immediately before and after its passage through the kidney. The widely used clearance techniques for determining renal blood flow are based upon the assumption that the test substance used is completely removed from the blood during one circulation through the kidney. Arterial blood may be obtained with relative ease from a peripheral vessel, because its composition is the same throughout the body, but obtaining venous blood as it leaves the kidney has presented the major problem. In animals explantation of the kidney has enabled investigators to obtain renal venous blood for extraction studies. To our knowledge human renal venous blood has only been obtained during operative procedures on the kidney.[2] The method described here has enabled us to obtain blood directly from the renal vein in the unanesthetized resting subject. A similar technique is being successfully utilized by Dr. S. E. Bradley at the Boston University School of Medicine.

The method is essentially a modification of the technique of right auricular catheterization, introduced by Forssmann in 1929,[3] and recently extensively utilized by Cournand and his colleagues.[4] A long (100 cm) No. 8 or 9 radioopaque ureteral catheter[5] with an angulated tip is passed into the venous system through the antecubital vein. A slow drip of physiologic saline

[1] From the Medical Service of the Grady Hospital and the Department of Medicine, Emory University School of Medicine, Atlanta, Georgia. The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Emory University School of Medicine.

[2] S. Weiss, F. Parker, Jr., and G. P. Robb, *Ann. Int. Med.*, 6: 1599, 1933.

[3] W. Forssmann, *Klin. Wchschr.*, 8: 2085, 1929.

[4] A. Cournand, R. L. Riley, S. E. Bradley, E. S. Breed, R. P. Noble, H. D. Lauson, M. I. Gregersen and D. W. Richards, *Surgery*, 13: 964, 1943.

[5] Obtained from the United States Catheter and Instrument Co., Glens Falls, N. Y.

solution is maintained through the lumen of the catheter during the entire procedure. Under fluoroscopic control the catheter is manipulated up the

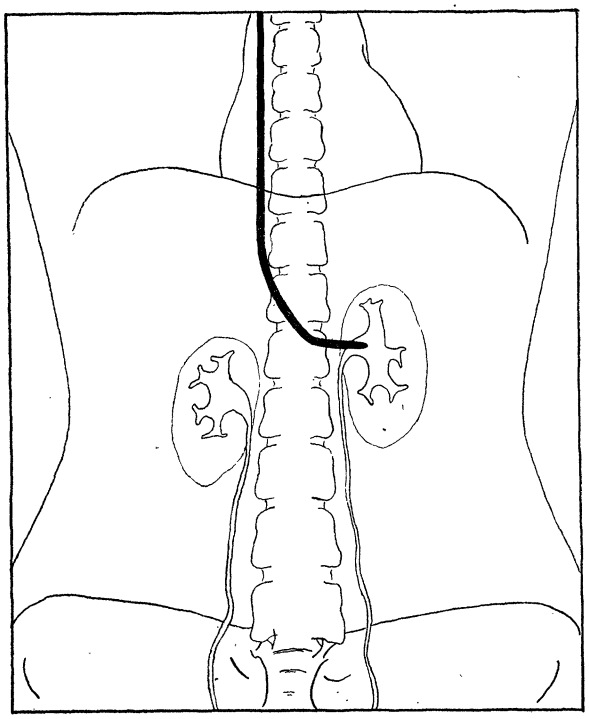

FIG. 1

venous system, through the right auricle and into the inferior vena cava. At the level of the renal pedicle the tip of the catheter is seen to pass laterally into the renal vein. When the catheter is in place the appearance is as shown in Fig. 1. Care must be taken that the catheter has not entered the hepatic vein.[6]

[6] J. V. Warren and E. S. Brannon, *Proc. Soc. Exp. Biol. and Med.*, 55, 144, 1944.

It is entirely possible that the vein entered may not be the renal vein, but one of the smaller veins in that locality. There are several methods of determining that one actually has entered the renal vein. By fluoroscopy the catheter is seen to be in position, as shown in Fig. 1, and to move as the kidney moves with respiration. The injection of diodrast or similar substance producing a pyelogram may be used to study the positions of the catheter. Samples of blood withdrawn from the renal vein have a relatively high oxygen content in contrast to venous blood from other sources, indicative of the low arteriovenous oxygen difference in the renal circulation. The most definite proof is the comparison of arterial and venous blood after the injection of one of the substances almost completely extracted by the kidney. We have used sodium para-amino hippurate[7] in low plasma concentration.

After the catheter is in the renal vein, and with the subject relaxed, simultaneous samples of blood may be withdrawn from the catheter and the femoral artery. In the cases reported here, after obtaining a sample for blank analysis, sodium para-amino hippurate was injected and 8 to 10 minutes later additional samples withdrawn for clearance studies. The catheter was then quickly withdrawn to the right auricle and a sample of mixed venous blood and expired air obtained simultaneously. This enables one to calculate the cardiac output utilizing the Fick principle. The concentration of sodium para-amino hippurate was determined by a modification[8] of the method of Bratton and Marshall[9] for sulfonamides. Subjects not receiving sulfonamides were used and it was found that much care was necessary in the use of procaine be-

TABLE 1

SUMMARY OF OBSERVATIONS ON EXTRACTION OF OXYGEN AND SODIUM P-AMINO HIPPURATE

Subject	Arterial O_2 content	Mixed venous O_2 cont.	Renal venous O_2 cont.	Cardiac A-V difference	Renal A-V difference	Cardiac index	Sodium p-amino hippurate		
							Arterial	Venous	Extraction
	Volumes O_2 per cent.			Volumes O_2 per cent.		Liters per min. per sq. meter	Mgm per cent.		Per cent.
B. S.	19.2	15.7	17.1	3.5	2.1	3.8	1.36	0.13	90
J. Y.	7.9	...	5.3	...	2.6	...	...	...	...
L. M.	20.7	14.6	18.2	6.1	2.5	2.3	0.21	0.00	100
B. J.	19.6	14.9	17.2	4.7	2.4	2.4	2.04	2.04	0
J. M.	9.1	5.4	6.8	3.7	2.3	3.8	1.68	0.21	88
A. B.	...	...	...	...	...	...	0.67	0.00	100
F. K.	6.5	3.1	3.7	3.4	2.8	3.7	1.39	0.18	87
J. W.	13.8	9.7	...	4.1	...	3.1	.95	0.11	88
H. B.	12.5	8.3	10.2	4.2	2.3	3.1	2.49	0.36	85
				...	...	...	1.56	0.24	86
M. G.	15.2	9.7	13.3	5.5	1.9	2.4	0.96	0.10	90

[7] Obtained through the courtesy of Dr. John Henderson, Sharp and Dohme, Philadelphia, Pa.

[8] H. W. Smith, Personal communication.

[9] A. C. Bratton and E. K. Marshall, Jr., *Jour. Biol. Chem.*, 128: 537, 1939.

cause these substances interfere in the analysis for hippurate.

Table 1 contains the results of studies on ten persons by these methods. The observations reported here were all made on subjects apparently free from renal disease. Several had considerable anemia, as reflected in the oxygen content of the arterial blood. The renal arteriovenous oxygen difference in the 8 cases in which it was determined varied from 1.9 to 2.8 volumes per cent. In contrast the difference in oxygen content of the mixed venous and arterial blood varied from 3.4 to 6.1 volumes per cent. The cardiac index in these subjects ranged from 2.3 to 3.8. With arterial plasma hippurate levels below 2.49 mgm per cent., the extraction by the kidney varied from 85 to 100 per cent. except for one case, when it was zero.

In all the cases reported here, in which oxygen studies were carried out, a low renal arteriovenous oxygen difference has been found. This was first noted in animals by Claude Bernard[10] in 1858. More recently Van Slyke *et al.*,[11] and Mason, Blalock and Harrison[12] have obtained similar values in animals with explanted kidneys. Weiss, Parker and Robb[2] have reported studies on renal venous and arterial blood from patients under spinal anesthesia during a surgical procedure for suspension of the kidney. The renal arterio-venous oxygen difference in three such subjects was 1.29, 2.87 and 2.96 volumes per cent., while in a patient with malignant nephrosclerosis the arterial and venous oxygen contents were 11.17 and 11.32 volumes per cent., respectively. Our results are of the same order of magnitude, but have been obtained under more physiologic circumstances. Other chemical studies are now in progress.

The use of diodrast clearance by the kidney to determine renal plasma flow is based on the assumption that at low plasma levels diodrast is completely extracted during a single circulation through the kidney.[13] The only direct evidence available at present is that from studies on animals with explanted kidneys. In such animals White[14] obtained an average extraction of 74 per cent. of the arterial content. Later Corcoran, Smith and Page,[15] using slightly lower plasma levels of diodrast, reported a value of 87 per cent. Recently it has been demonstrated that the clearance of sodium para-amino hippurate is identical with that of diodrast under normal conditions.[16] This substance has the advantage of a simple and accurate method of determination, plus the theoretical advantage of less diffusion into the red blood cells. We have used this material instead of diodrast, and our value of 88 per cent. extraction fits well with the other observations. Since renal vein blood contains not only the venous outflow from the active excretory renal tissue, but that of surrounding supporting tissue in addition, one would not expect to find absolutely complete removal of diodrast or hippurate from the blood leaving the kidney.

The value obtained in Case B. J. is of interest. Most likely it indicates failure to enter the renal vein, but the oxygen difference is low. White[14] and Corcoran *et al.*,[15] both report anomalously low extraction values on isolated occasions. They suggest that, while these results may represent technical errors, they may indicate changing tubular activity.

SUMMARY

Catheterization of the renal vein offers a safe and relatively simple method of obtaining blood as it leaves the kidney in the resting unanesthetized human subject.

In preliminary observation on 8 subjects the renal arteriovenous oxygen difference varied from 1.9 to 2.8 volumes per cent., averaging 2.3 volumes per cent. Sodium para-amino hippurate, at low plasma levels, was 88 per cent. extracted during a single circulation through the kidney.

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