incidental (*e.g.* thrombinolytic or "progressive" antithrombic) effects.

Summary. The data, as a whole, clearly indicate that the crystalline polypeptide tested has a weak inhibitory action on blood-clotting systems. There is good evidence for an antifibrinolytic as well as for antiprothrombic and antithrombic effects. A co-factor seems to be necessary, at least for the last, and it can be supplied in crude plasma albumin. The similarities to the actions of (small quantities of) heparin[4] are striking and the minor discrepancies may be due to such experimental variables as impurity of the albumin, inadequate amounts of inhibitor, and other experimental conditions. In contrast to the "immediate" character of typical heparin effects,[4] there is, in the present experiments, a definite suggestion of a *time-factor* required for the full development of the antithrombic and other inhibitory effects. This may very well explain part of the difficulty encountered in demonstrating more convincingly the first-phase inhibition by the crystalline polypeptide.

These experiments are preliminary and require confirmation with larger amounts of polypeptide and extended study of the question as to optimal conditions for the inhibitory effects. Nevertheless, they are highly suggestive and fit in with a new blood-clotting theory,[5] which revolves around the dominant role of serum-tryptase and its inhibitors in natural blood-coagulation systems.

[5] Ferguson, J. H., *Science*, in press.

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A Simple Method for Determining Effective Renal Blood Flow and Tubular Excretory Mass in Man.*

PIERO P. FOÀ† AND NAOMI L. FOÀ. (Introduced by H. B. Lewis.)

From the Department of Neurosurgery, University of Michigan School of Medicine, Ann Arbor, Mich.

Quantitative methods for the determination of the tubular excretory mass and the rate of blood flow through the active renal tissue by diodrast clearance have been developed by Smith and his associates[1] and have been used in recent years almost entirely for the purpose of research. We have suggested recently[2-4] that the determination of the effective renal blood flow in patients with arterial hypertension might furnish not only interesting data on the pathogenesis of the disease, but also information of considerable value for the prognosis and selection of patients to be submitted to surgical treatment.

To confirm this possibility it became necessary to find a simple method suitable for the routine clinical study of a large number of patients. The methods of Smith and his associates are not practical as they require continuous intravenous infusion, inlying catheter, the full attention of a physician and a technician for several hours, and a large number of chemical determinations.

To our knowledge, Findley and White[5] made the only attempt to simplify the determination of effective renal blood flow, by the use of a single subcutaneous injection of diodrast. They measured effective renal

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† Research Fellow.

[1] Smith, H. W., Goldring, W., and Chasis, H., *J. Clin. Invest.*, 1938, **17**, 263.

[2] Foà, P. P., Woods, W. W., Peet, M. M., and Foà, N. L., *Arch. Int. Med.*, 1942, **69**, 822.

[3] Foà, P. P., Woods, W. W., Peet, M. M., and Foà, N. L., *Arch. Int. Med.*, in press.

[4] Foà, M. M., Woods, W. W., Peet, M. M., and Foà, N. L., *Univ. Hosp. Bull.*, Ann Arbor, 1942, **8**, 9.

[5] Findley, T., and White, H. L., PROC. SOC. EXP. BIOL. AND MED., 1940, **45**, 623.

blood flow in 3 hypertensive subjects by 3 consecutive clearance periods. The determinations were not repeated on different days, or controlled by the determination of the ratio of effective renal blood flow to tubular excretory mass. Normal individuals have not been studied. Since the blood flow in hypertensive patients varies widely from case to case, there is no definite standard to which the low values obtained by Findley and White can be compared. Furthermore, the results may have been influenced by the local anesthetic which they used at the site of injection. After subcutaneous injection of diodrast, the concentration of this substance in the plasma is a result, not only of its excretion by the kidney, but also of its absorption from the subcutaneous tissue. For this reason, the concentration of diodrast iodine in the plasma may not remain constant or (it may not) decrease at a uniform rate, and it becomes necessary to determine it in several samples of blood taken during the clearance period.

The following procedure has given very satisfactory results and avoids the disadvantages of continuous intravenous infusion, catheterization, and collection of a large number of specimens. The experiment requires about the same length of time as a urea clearance test.

Procedure. a. Determination of effective renal blood flow: During the hour preceding the experiment, the patient drinks approximately 2000 cc of water to promote diuresis. The test begins with the collection of a specimen of urine, U_0, and of 30 cc of blood, B_0, from the cubital vein. U_0 and B_0 are used as blanks in the chemical determinations. 5 cc of 35% diodrast are then injected intravenously. After 15 min, the patient is asked to empty his bladder completely, the time is exactly recorded and the urine discarded. Ten min later, 30 cc of blood (B_1) are collected and the time recorded. A second sample of blood (B_2) is taken 10 min after B_1 and finally the urine is accurately collected 10 min later. This specimen of urine is usually between 200 and 500 cc and, in these conditions, a normal bladder can be emptied satisfactorily without catheterization. When greater accuracy is desired, especially if the flow of urine is below 8-10 cc/min or if the patient cannot urinate freely, it is advisable to use a catheter and to wash the bladder once or twice with 20 cc of saline.

b. Determination of tubular excretory mass: The patient drinks another 500 cc of water and about 30 min later, 30 cc of 35% diodrast are slowly injected intravenously. Within a minute or two after the injection, the bladder is emptied with care and the urine discarded. Approximately 5 and 15 min thereafter, specimens of blood (B_3 and B_4) are taken from the cubital vein and about 5 min after the collection of B_4, the urine is accurately collected.

This schedule can be modified, but it is necessary that the time of each collection of blood and urine be recorded exactly. When the patient is sufficiently coöperative and when each collection of urine can be timed at will, only one sample of blood need be taken during each urine collection period—this blood must be collected *exactly* at the *mid-point* of the urine period.

The diodrast is determined as iodine following the method of Alpert.[6] The computation of the diodrast clearance is based on the usual formula: $C_D = UV/P$, where C_D = diodrast clearance; U = concentration of diodrast iodine in the urine; V = volume of urine in cc per minute; and P = concentration of diodrast iodine in the plasma at the mid-point of the urine collection. If only one sample of blood is taken at the mid-point, P is equal to the concentration of diodrast iodine in this sample. If 2 samples of blood are taken, the concentration of iodine in the plasma is plotted against time and the desired concentration read on the curve at the time corresponding to the mid-point of the period of urine collection. The diodrast plasma clearance is equal to the effective renal plasma flow. A hematocrit determination permits the conversion of this value to blood flow. The tubular excretory mass is computed according to Smith *et al.*, again from the concentration of diodrast iodine in the blood at the mid-point of urine collection. The filtration rate, necessary for

[6] Alpert, L. K., *Bull. Johns Hopkins Hosp.*, 1941, **68**, 522.

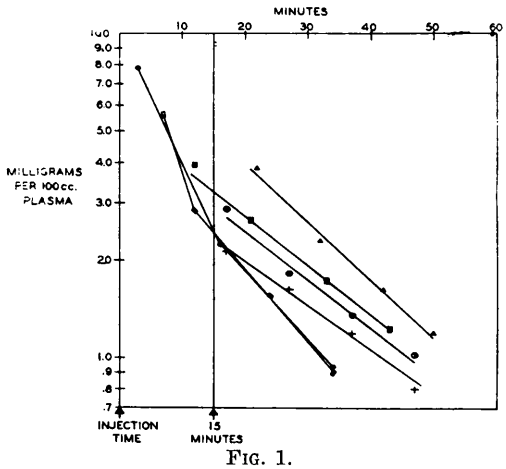

FIG. 1.
Concentration of Iodine in the Plasma After Intravenous Injection of 5 cc of Diodrast.

the computation of Diodrast Tm, is obtained by simultaneous determination of the inulin clearance by the method of Alving and Miller.[7]

As shown in Fig. 1, the concentration of diodrast iodine in the plasma, following a single intravenous injection of 5 cc of 35% diodrast, falls sharply for about 15 min. This period probably corresponds to the time necessary for the diodrast to diffuse into the extracellular fluid. Following this period of equilibration the concentration of iodine in the plasma decreases slowly and in a straight line from 2-4 mg to 0.7-1.5 mg per 100 cc of plasma in about 30 min. The concentration at the mid-point of the urine collection period therefore represents the mean concentration of iodine during the whole period and can be used for the computation of the diodrast clearance for that period. The diodrast clearance, at these concentrations of diodrast in the plasma, is equal to the effective plasma flow.

For the determination of tubular excretory mass, the concentration of diodrast iodine should be maintained above approximately 15 mg of iodine per 100 cc of plasma. This is obtained by a single intravenous injection of 30 cc of 35% diodrast. Following this injection, the concentration of iodine in the plasma falls from approximately 23-40 mg to approximately 14-18 mg per 100 cc of plasma, remaining sufficiently high throughout the whole clearance period to allow the

[7] Alving, A. S., and Miller, B. F., *Arch. Int. Med.*, 1940, **66**, 306.

TABLE I.
Effective Renal Blood Flow and Tubular Excretory Mass in Eleven Normal Subjects.

	Subject age, sex	Blood pressure	Diodrast plasma clearance, C_D cc/min	Effective renal blood flow, cc blood/min	Tubular excretory mass Tm_D, mg I_2/min	C_D/Tm_D	Inulin clearance during determination of Tm_D, cc plasma/min
1.	62 M	165/125	424	785	34	12.6	94
		150/94	465	832	31	14.8	169
		*125/90	514	900	38	15.4	53
		170/105	461	842	—	—	—
2.	30 M	110/80	465	786	45	10.1	95
		120/80	513	871	47	10.9	116
3.	26 M	122/68	467	800	—	—	—
		—	548	915	40	13.6	124
4.	29 M	110/75	717	1245	39	18.5	100
5.	30 M	110/60	695	1262	47	14.9	144
6.	37 M	122/81	518	849	25	23.4	68
Avg of 6 males		120/78	566	987	39	15.9	108
7.	23 F	105/65	754	1134	—	—	—
		95/50	694	1061	39	17.6	145
8.	58 F	160/90	534	791	31	17.9	103
		* —	552	817	—	—	—
9.	27 F	105/62	485	794	41	11.9	105
10.	45 F	105/70	440	710	30	14.8	142
11.	40 F	128/80	651	1017	25	26.1	101
Avg of 5 females		119/72	568	885	33	17.6	119
Total avg		120/75	566	940	36	16.7	113

*Under ether anesthesia.

determination of the tubular excretory mass.

If greater accuracy is desired, the calculation should take "delay time" into account.‡ Two samples of blood should be collected during the clearance period and the plasma concentration taken 150 sec before the midpoint of the urine period. This was done in five of our subjects and the difference between the value given in the table and the corrected value averaged 7.78% (5.66 to 9.9%). This difference has very little clinical significance, and becomes negligible when the rate of urine flow is 15-20 cc/min or more.

Results. Effective renal blood flow and tubular excretory mass were determined in 11 normal subjects (6 males and 5 females). In 5 subjects the determinations were repeated after an interval of a few days. As shown in Table I, the values obtained are well within the normal range as determined by Smith's method[1,2] and the determination can be repeated in the same patient with good agreement.

Summary. A simple method for the determination of effective renal blood flow and tubular excretory mass in human subjects is described. Continuous intravenous infusion and catheterization are avoided. The method is suitable for routine clinical use.

‡ for the significance of "delay time" see Smith *et al.*[1]

The diodrast used in this study was generously supplied by the Winthrop Chemical Co.

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Effect of Testosterone Therapy on Concentration of Potassium in Serum.*

ALLAN M. BUTLER, NATHAN B. TALBOT, AND E. A. MACLACHLAN. (Introduced by A. B. Hastings.)

From the Department of Pediatrics, Harvard Medical School, and The Children's Medical Service of The Massachusetts General Hospital, Boston, Mass.

In his pioneer investigations on perfusion fluids, Ringer observed that while the addition of potassium was not essential for the maintenance of the frog or turtle heart beat, a concentration of approximately 4 milliequivalents per liter was one of the requisites of a solution providing optimal contractions. For the mammalian heart Locke designated the optimal potassium concentration of perfusion fluids at approximately 5.5 meq. per liter.

The observation that potassium salts relieved the paralysis of so-called familial periodic paralysis[1-6] and the more recent observation that a fall in serum potassium concentration was associated with the attacks of paralysis suggested a correlation between muscle weakness and serum potassium concentration.[2-6] During such attacks bradycardia, hypotension, arrhythmia and cardiac dilatation have been observed. However, though a fall in the serum potassium concentration occurs with such attacks, the specific concentration at which paralysis appears varies greatly. A somewhat similar concomitant decrease in serum potassium and in muscle strength has been observed following the administration of desoxycorticosterone acetate[7-13] and the skeletal mus-

* This investigation was aided by a grant from the Commonwealth Fund, New York City.

1 Mitchell, J. K., Flenner, S., and Edsall, D. L., *Trans. Assn. Am. Physicians*, 1901, **16**, 268.

2 Aitken, R. S., Allott, E. N., Castleden, L. I. M., and Walker, M., *Clin. Sc.*, 1937, **3**, 47.

3 Allott, E. N., and McArdle, B., *Clin. Sc.*, 1938, **3**, 230.

4 Ferrebee, J. W., Atchley, D. W., and Loeb, R. F., *J. Clin. Invest.*, 1938, **17**, 504.

5 Gannon, G. D., Austin, J. H., Blithe, W. D., and Reid, C. G., *Am. J. Med. Sc.*, 1939, **197**, 326.

6 Talbott, J. H., *Medicine*, 1941, **20**, 85.

7 Ferrebee, J. W., Ragan, C., Atchley, D. W., and Loeb, R. F., *J. A. M. A.*, 1939, **113**, 1725.

8 Thorn, G. W., Howard, R. P., and Emerson, K., Jr., *J. Clin. Invest.*, 1939, **18**, 449.