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## Interpretation of Diodrast Clearances in the Dog.\*

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If some otherwise suitable substance could be found which was completely removed from the blood on one passage through the kidneys, its blood clearance would be a measure of renal blood flow. If the substance were either (a) absent from the blood cells or (b) fixed in the cells during a passage through the kidney, its plasma clearance would be a measure of renal plasma flow (RPF). Diodrast (D) has been proposed by Smith and collaborators<sup>1, 2, 3</sup> as meeting or very nearly meeting the conditions that it is completely removed on passing active renal tissue and that it is absent from the cells. We find on trained, unanesthetized renal explant dogs, with D<sup>4</sup> and inulin<sup>5</sup> analyses of urine and of renal vein and arterial (or leg vein) whole blood, plasma and cells, that D plasma clearance departs considerably from RPF independently measured and we have established the factors which bring about this discrepancy.

1. *Diodrast in cells.* The statement of Smith<sup>1</sup> that D is absent from dog cells is based upon essentially complete recoveries from plasma of D added to drawn blood. We confirm this finding but find that after intravenous administration the ratio

$$\frac{\text{D per 100 cc arterial cell water}}{\text{D per 100 cc arterial plasma water}}$$

$$\text{D per 100 cc arterial plasma water}$$

averages 0.62, with extremes 0.48 to 0.73. The average is of 18 observations with plasma levels from 1.51 to 11.50 mg I per 100 cc; the value of the ratio is independent of plasma iodine (I) level, I being a measure of D.

2. *Diodrast contribution to urine by cells.* Even though we have shown that the cells contain a large proportion of the D, one could still use D plasma clearance as a measure of RPF (if plasma D extraction were complete) provided all the cell D stayed in the cells on

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<sup>1</sup> Smith, H. W., Goldring, W., and Chasis, H., *J. Clin. Invest.*, 1938, **27**, 263.

<sup>2</sup> Chasis, H., Ranges, H. A., Goldring, W., and Smith, H. W., *J. Clin. Invest.*, 1938, **27**, 683.

<sup>3</sup> Smith, H. W., *Physiology of the Kidney*, Univ. of Kansas Press, Lawrence, 1939.

<sup>4</sup> White, H. L., and Rolf, D., *PROC. SOC. EXP. BIOL. AND MED.*, 1940, **43**, 1.

<sup>5</sup> Coreoran, A. C., and Page, I. H., *J. Biol. Chem.*, 1939, **127**, 601.

passing the kidney. If, however, cell D moves into plasma on D depletion of the latter, then urinary D per minute will be greater than plasma contribution of D per minute and to this extent, if there were no other complicating factors, D plasma clearance would exceed RPF. We have shown that such a contribution of cell D does take place; renal vein cell D is always much lower than arterial cell D. The average ratio

$$\frac{\text{mg I per 100 cc renal vein cells}}{\text{mg I per 100 cc arterial cells}}$$

is 0.74 (average of 9 observations). However, renal vein cell D does not fall proportionally to renal vein plasma D; whereas arterial plasma D is always higher than arterial cell D, renal vein plasma D is always lower than renal vein cell D. The above observations show that D does not behave (a) as does inulin, since D is present in the cells, (b) as does creatinine, since some D moves from cells into plasma during a renal passage, with a partial approach toward diffusion equilibrium, nor (c) as does urea, since D does not come into complete diffusion equilibrium between cells and plasma during a renal passage.

3. *Completeness of extraction of diodrast from renal vein blood or plasma.* We find that renal extraction  $\frac{A \cdot RV}{A}$  of D is never complete from either plasma or cells, with arterial plasma levels from 1.52 to 7.09 mg I per 100 cc. Plasma D extraction averaged 0.73 (0.61-0.85), cell extraction 0.24 (0.10-0.39) and whole blood extraction 0.58 (0.46-0.66). Within this range of plasma levels there is only rough correlation between plasma I level and completeness of extraction; the series is being extended.

4. *Relation between diodrast plasma clearance and renal plasma flow.* Two factors, the incompleteness of D extraction and the cell contribution of D, work in opposing directions to disturb the relation between D plasma clearance and RPF; the action of the first is to make D plasma clearance lower than RPF, while the second works to make D plasma clearance higher than RPF. If the first factor alone were operative, D plasma clearance/D plasma extraction would be a measure of RPF. Since the second factor also is always operative, this expression will always give values higher than RPF. If the cell contribution of D raises D plasma clearance less than the factor of incompleteness of D extraction lowers it, D plasma clearance will be less than RPF. It is conceivable that the two factors could be just balanced, so that D plasma clearance would equal RPF; this can be determined only by simultaneous D clearance determinations and independent flow determinations.

5. *Comparison of diodrast plasma clearances with independently determined renal plasma flows.* Let  $V_p$  equal plasma fraction of hematocrit reading. Renal plasma flows were obtained by 3 methods simultaneously,

$$(a) \frac{\text{Inulin plasma clearance}}{\text{inulin plasma extraction}},$$

$$(b) \frac{\text{Inulin whole blood clearance} \times V_p}{\text{inulin whole blood extraction}},$$

$$(c) \frac{\text{D whole blood clearance} \times V_p}{\text{D whole blood extraction}}.$$

The average values in cc/min/M<sup>2</sup>, are (a) 360, (b) 370, (c) 355, while the corresponding D plasma clearance average is 310, and the average

$$\frac{\text{D plasma clearance}}{\text{D plasma extraction}}$$

is 406. The last value is higher than RPF because of the cell contribution of D; 406 is 113% of 362, the average true RPF, which means that for every 100 mg D contributed to the urine by the plasma, 13 mg are contributed by the cells. This is even more direct evidence of cell contribution of D than is the finding that renal vein cell D is lower than arterial cell D, since the latter finding might be explained by diffusion after drawing the sample. The D plasma clearance is lower than RPF because the factor of incompleteness of D extraction overbalances that of cell contribution of D. On the average, with the dog one can get RPF by multiplying D plasma clearance by 1.17, but this multiplier varies between 1.03 and 1.43. These values were obtained over a range of plasma I levels from 1.52 to 7.09 mg per 100 cc, with but little correlation between value of multiplier and of plasma I level. Average whole blood flow is 683 cc/min/M<sup>2</sup>, or 23.2% of cardiac output, taking Marshall's<sup>6</sup> value of 2940 cc/min/M<sup>2</sup> for the latter. Inulin plasma clearance averages 101 cc/min/M<sup>2</sup>. Both diodrast and inulin plasma clearances in the hypophysectomized dog are about 50% of normal.

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<sup>6</sup> Marshall, E. K., Jr., *Am. J. Physiol.*, 1926, **77**, 459.