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Interpretation of Diodrast Clearances in Man.*

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A series of diodrast (D) plasma clearances has been carried out on 11 normal human subjects, with plasma iodine (I) levels varying from 0.3 to 55 mg per 100 cc; simultaneous inulin clearances were determined in some cases. Data on distribution of D betwen cells and plasma are also given.

1. *Diodrast in cells.* The statement of Smith[1] that D is absent from the cells of drawn human blood is confirmed. However, at equilibrium after intravenous administration of D the ratio

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

averages 0.32. It must be emphasized that here, as with the dog (0.62), the cell/plasma D distribution ratio was obtained after *in vivo* equilibration had been attained. The cell content of D in man is thus about half that in the dog for a given plasma level, after cells and plasma have come into equilibrium *in vivo*.

2. *Diodrast contribution to urine by cells.* Magnitude of contribution of D to urine by cells during a renal passage will be determined by, (a) cell content of D and, (b) rapidity with which D passes from cells into plasma on D depletion of the latter. On the first of these points alone, cell contribution of D in man would be about half of that in the dog. Information on the second point has been obtained by observing the cell/plasma D ratio on a falling plasma D level following an equilibration period of a constant plasma D level, *i. e.,* by following the ratio after cessation of sustaining infusion. Such observations on the dog show a constant ratio, *i. e.,* D diffuses from cells into plasma rapidly enough, as plasma D falls, to maintain a constant distribution. With man, on the contrary, the ratio rises rapidly as plasma level falls following cessation of sustaining infusion; it may go from the equilibrium value of 0.32 to as high as 1.20. This means that D cannot pass rapidly enough from human cells into depleted plasma to keep pace with this rate of fall of plasma

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

D. The conclusion is therefore justified that the cell contribution of D in man is less than half that in the dog, *i. e.*, on the average less than 6%.

3. *Completeness of extraction of diodrast from renal vein plasma.* In the absence of direct observations on human renal vein plasma our only information here is indirect. Our data so far available suggest that D plasma clearance begins to be self-depressed at lower plasma D levels in the dog than in man, which suggests that human kidneys extract D more efficiently than do dog kidneys.

4. *Relation between diodrast plasma clearance and renal plasma flow RPF.* Since the cell contribution of D is shown to be less in man than in the dog and since the above paragraph suggests that renal extraction of D may be more nearly complete in man than in the dog, it may well be that D plasma clearance in man is a reasonably good measure of RPF. A final answer must await more adequate information on the extraction in man. Since cell contribution of D in man is shown to be small, D plasma clearance (at D plasma levels below that at which clearance begins to be self-depressed) will be less than RPF unless D is almost completely extracted. If extraction is complete in man, D plasma clearance cannot exceed RPF by more than 6%.

Values of D plasma clearance over a wide range of plasma iodine (I) levels but in the absence of inulin are shown in Fig. 1; there is no self-depression of clearance up to plasma I levels of 15 mg %. The average D plasma clearance, at D plasma levels below that at which clearance begins to be depressed, in cc/min/1.73 M^2 is 497 (58

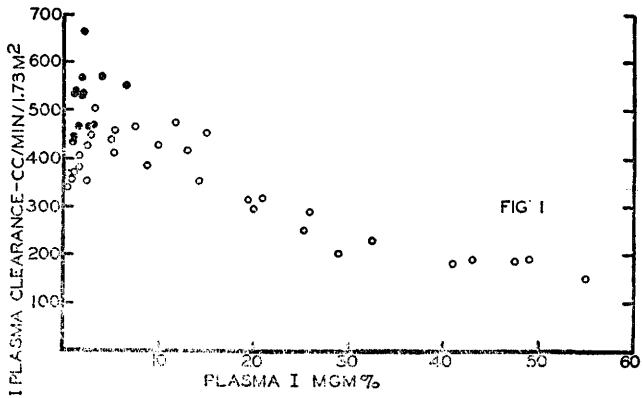

FIG. 1.

Effect of varying plasma I level on plasma I (or D) clearance. Each solid circle designates the mean of 3 or more consecutive clearance periods at a constant plasma level. Open circles designate individual clearance periods obtained on falling plasma D levels after a single injection. No inulin.

clearance periods on 11 subjects), which is considerably lower than Smith's latest figure of 737 and close to Chesley and Chesley's[2] figure of 518. The point might be raised that Smith's higher figure is due to the inulin present in his experiments. However, our average of D clearances obtained simultaneously with inulin clearances is 438 cc/min/1.73 M^2, which shows that the higher value of Smith cannot be ascribed to any action of inulin. Self-depression of D clearance does not begin until plasma I is raised to about 15 mg %, whereas Smith finds D clearance only 65% of normal at this plasma level.

Rate of tubular excretion of D is plotted against D plasma level in Fig. 2. Maximum rate of tubular excretion (Tm) averages

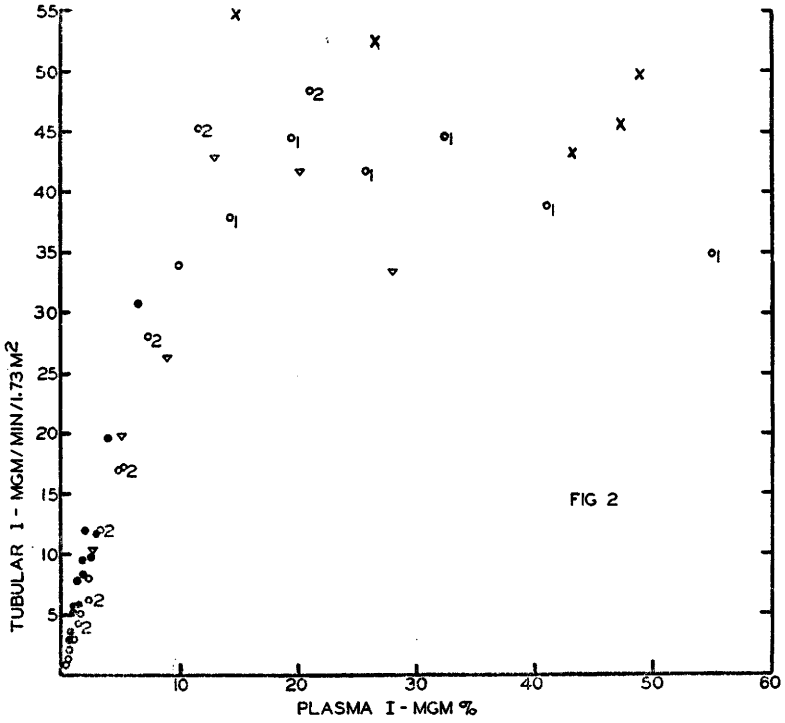

FIG. 2.

Effect of varying plasma level on rate of tubular excretion of diodrast iodine. Rate of tubular excretion is almost directly proportional to plasma level up to somewhere between 10 and 15 mg I per 100 cc plasma, where it breaks rather sharply, Tm being reached at between 15 and 20 mg I per 100 cc plasma. Solid circles designate means of 3 or more consecutive periods at a constant plasma level. ○ individual periods on a falling plasma level after a single injection with subject TF, ○1 same for another experiment on same subject, ○2 same for another experiment on same subject; △ same on subject JE; × same on subject P.

[2] Chesley, L. C., and Chesley, E. R., *Am. J. Physiol.*, 1939, **127**, 731.

44 mg I/min/1.73 M^2 on 3 normal subjects; it is reached at a plasma level between 15 and 20 mg I per 100 cc and is unaffected by presence of inulin. This value is somewhat lower than Smith's latest figure of 57. The fall in Tm seen in Fig. 2 at the highest plasma I levels was obtained in experiments where a single large dose of D (35 to 60 cc) was given within 10 minutes and urine collections begun 5 minutes later. This transitory fall in Tm is presumably due to a renal vasoconstriction or to transitory tubular disturbance and is not seen when plasma D is maintained at a high constant level for some time before beginning urine collections, *i. e.*, in the latter case Tm at 50 mg % plasma I is not lower than at 20 mg %.

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Serum Albumin Regeneration Following Intravenous Amino-Acids (Hydrolyzed Casein) in Hypoproteinemia Produced by Severe Hemorrhage.*

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Acute hypoproteinemia was produced in fasting dogs by a single severe hemorrhage; the details have been described elsewhere.[1] One hour later injections were started, intravenously, which lasted 3 hours.[2] No symptoms were produced by this treatment. The solution injected consisted of 10% each of a mixture of amino-acids and dextrose. The dose varied with the weight of the dog, *i. e.*, 3.5 g per kilo of each (amino-acids and dextrose). The amino-acid mixture was obtained from casein by enzymic digestion.† As shown by preliminary observations it contained all of the essential amino-acids in that it required no additions in order to maintain nitrogen balance in dogs. It was not as completely digested as the acid hydrolysate of casein which was used in our previous experiments.[2] Thus, only 70% of its nitrogen could be accounted for an amino-acid nitrogen; the rest probably occurred as dipeptides.

In control experiments[1] it was observed that no change in the

* Aided by a grant from the Louis B. Beaumont Fund.

1 Elman, R., *Am. J. Physiol.*, Jan., 1940.

† Product 92-Z kindly furnished by the Mead Johnson & Company, Evansville, Ind.

2 Elman, R., PROC. SOC. EXP. BIOL. AND MED., 1937, **36**, 867.