THE SIGNIFICANCE OF THE DIFFERENCE IN SYSTEMIC ARTERIAL AND VENOUS PLASMA CONCENTRATIONS IN RENAL CLEARANCE METHODS

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Diodrast clearance values reported in the literature have been calculated partly on constant and partly on rising or falling plasma concentrations. However, we have observed unexpectedly low clearance values on rapidly falling concentration, and as far as we know this phenomenon has not been reported before.

Published values of the diodrast clearance in normal subjects differ with the different techniques applied, and these differences may be explained in part, on the basis of our observations. By analyzing White, Findley and Edwards' (1) results we see that in the subjects where continuous infusion was applied, the average diodrast clearance was 517 ml./min., while in the subjects where falling plasma concentration after a single injection was used, the value was 410 ml./min. One of us, (Hilden [2], by application of an intravenous single injection, obtained an average clearance of 411 ml./min., whereas by subcutaneous injection, which gives a far more slowly falling plasma concentration, obtained a clearance of 613 ml./min. Goldring, Chasis, Ranges and Smith (3), who used continuous infusion, indicate the normal value to be 688 ml./min. Josephson (4) recently stated that he finds lower diodrast clearance values on the basis of spontaneously falling plasma concentrations than after a single intramuscular diodrast injection.

A few instances will be given first of the above phenomenon. Figure 1a shows the diodrast clearance at different plasma concentrations estimated on rising and falling concentration. Values calculated on falling plasma concentration at about 10 mgm. per cent cease to increase and in fact begin to decline. In comparison it may be seen that the values calculated on rising concentration at the same low level range from about 700 to about 1000 ml./min. The question of why the values vary so much during rising concentration will be discussed later. Similar results are plotted in Figure 1b. From the moment the concentration begins to fall spontaneously the clearance declines at an increasing rate the lower the concentration. Here, too, the values are essentially higher when calculated on rising concentration. In Figure 1c the diodrast clearance values calculated on a falling curve have been compared with the diodrast clearance estimated on constant blood concentration; a marked difference is noted again. Figure 1d illustrates an experiment, in which a spontaneous fall in the plasma concentration was elicited over one hour and a half, and when the plasma concentration had fallen to 8 mgm. per cent, diodrast was infused intravenously, and the plasma concentration increased. The diodrast clearance increased from about 400 ml./min. to about 600 ml./min. at the same plasma concentration. Figure 1e shows an experiment beginning with an intravenous infusion of diodrast, which brought about a rapid rise in the plasma concentration. Then the infusion was discontinued with the result that the plasma concentration began to fall spontaneously. The diodrast clearances calculated on the rising curve were found to exceed those on the falling curve. The turn occurred at the moment the infusion was discontinued.

A total of 16 experiments were performed. Low clearance values on falling plasma concentration were unquestionable in 12 and in the remaining four the phenomenon was questionable or not present. The reason why the phenomenon may occasionally fail to occur will be mentioned later.

We shall now discuss the possibilities which we have considered in trying to explain the phenomenon.

a. In the above experiments *no* correction was made for delay time; by delay time we mean the time it takes for the urine to pass through the kidneys and the urinary tract from the moment of production until it has reached the bladder. The urine dsicharged from the bladder at a given point

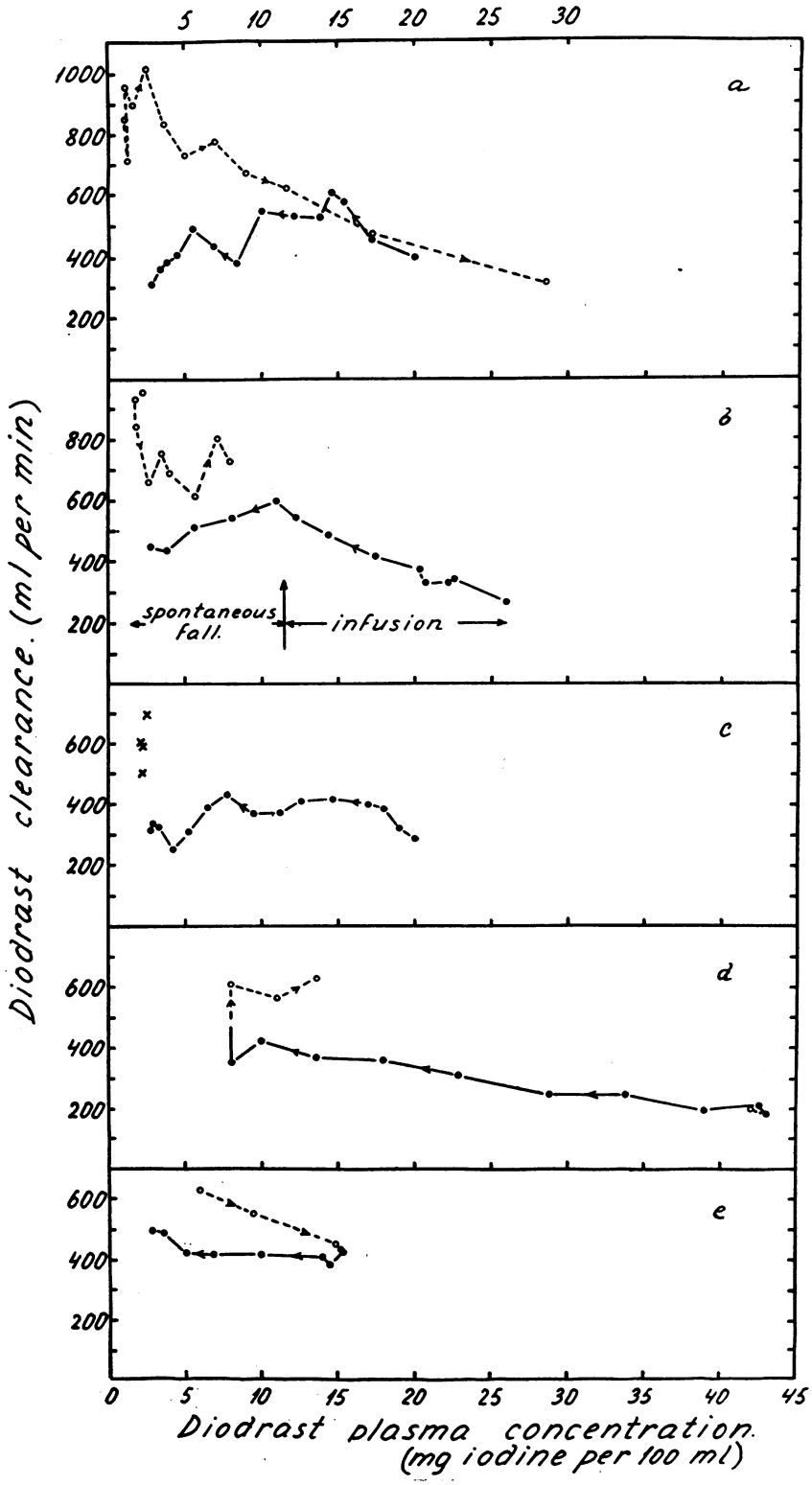


FIG. 1 (a through e). DIODRAST CLEARANCE VALUES CALCULATED ON FALLING AND RISING PLASMA CONCENTRATIONS

Solid dots represent falling, and open circles rising concentrations.

of time is thus produced in the kidneys some five to 15 minutes previously (depending on, among other things, the urine volume). When working with rapidly varying plasma concentrations there may, accordingly, be a great difference between the concentration during which the urine is actually produced and that used in the clearance period. Clearance values determined on falling plasma concentration therefore will be calculated too high. Consequently, omitting correction for delay time cannot alone explain our observations.

b. If diodrast is deposited in the renal tissue for some time before being excreted the diodrast clearance will likewise be calculated too high, because at the high concentrations the excretion will lag somewhat behind the plasma curve.

c. Furthermore, the possibility might be conceived that, at rapidly falling plasma concentration, the erythrocytes were not able to give off their contents of diodrast during the rapid passage through the kidneys. This would result in a shift in favor of the erythrocytes of the normal equilibrium between the diodrast concentrations in blood cells and plasma. The erythrocytes might be conceived to give off diodrast to the plasma after the blood sample had been taken, and the diodrast concentration in plasma accordingly be analyzed as higher than it had been when the blood passed through the kidneys. To elucidate this fact, we compared the diodrast concentrations in blood plasma centrifuged off immediately after withdrawal of blood, and plasma which had been left standing with erythrocytes for an hour after withdrawal. This analysis showed that no diodrast is given off from the blood cells, and that accordingly no such process can explain the phenomenon.

d. Differences in the binding of diodrast to the plasma protein substances, at falling and rising plasma concentration, might likewise be conceived to be responsible for a difference in the plasma extraction of diodrast in the kidneys. This seems rather unlikely, however, since the dissociation of the diodrast-protein complex is known to take place very quickly; the blood is, at least at plasma concentrations below that at which the clearance is self-depressed, almost completely cleared of diodrast by a single passage through the kidneys.

Thus, none of the four possibilities mentioned above appear to explain the low diodrast clearance values calculated on falling plasma concentrations. However, we believe we have found an explanation in another possibility; the diodrast concentration in arterial blood may differ considerably from that in venous blood, when the plasma concentration is changing quickly.

e. The distribution of diodrast in the circulation, *while the concentration falls,* must be supposed to occur in the following way: the renal venous blood, which is almost or completely free of diodrast, is led to the right half of the heart, where it is mixed with diodrast-containing venous blood from the extrarenal part of the organism. The concentration in the mixture will be identical with that in the arterial blood. It appears, therefore, that the diodrast concentration in arterial blood must be lower than that in the venous blood from the arm generally applied for analysis. Since the clearance (UV/P) ought to be calculated on the basis of the concentration of arterial blood from which diodrast is actually excreted by the kidneys, then the clearance values will be calculated too low when the venous blood concentration is used in the formula.

To this hypothesis the objection might be raised that the above difference between the concentrations in arterial and venous blood always must be present, since the renal venous blood in normal individuals always must represent an afflux poor in diodrast to the heart. If one, however, maintains a *constant* diodrast plasma concentration by continuous infusion, the concentrations in arterial and in mixed venous blood will be identical; the concentration is maintained by supplying diodrast to the venous blood at a rate equal to that at which it is being excreted through the kidneys.

During rising plasma concentration the arterial blood concentration should accordingly be higher than the peripheral venous blood, because the mixed venous blood is being fortified at a rate greater than the rate of excretion. The mixed venous blood (and the arterial blood) will have, therefore, a higher concentration than peripheral venous blood. The arteriovenous difference will depend mainly on the relative rates of loss and infusion.

On the basis of these considerations we have determined the relative concentrations in arterial and venous blood under conditions of rising, falling and constant diodrast concentration.

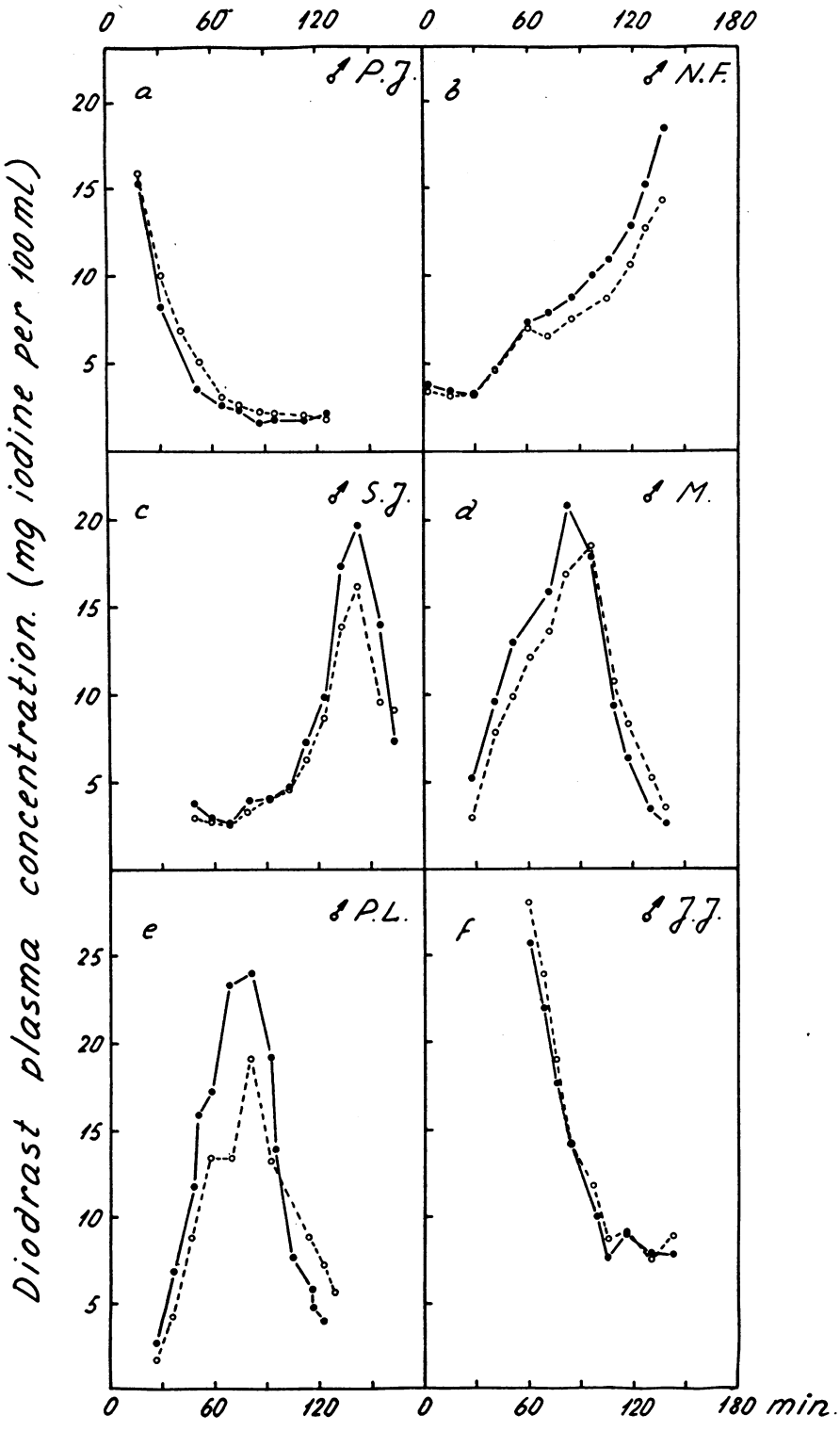


FIG. 2 (a through f). DIODRAST PLASMA CONCENTRATIONS IN ARTERIAL AND VENOUS BLOOD ON RISING AND FALLING PLASMA CONCENTRATIONS

Solid dots represent concentrations in arterial, and open circles concentrations in venous blood.

TABLE I

Experimental results from subjects P. L. and M. (male)

	Urine collection period	Urine volume +100 ml. water	Urine volume	Delay time	Inulin					Diodrast								
					Plasma		Urine	Clearance*		Plasma				Urine	Clearance*			
					Arterial	Venous		Arterial	Venous	Arterial†	Venous†	Arterial‡	Venous‡		Arterial†	Venous†	Arterial‡	Venous‡
	min.	*ml.*	*ml./min.*	*min.*	*mgm./ 100 ml.*	*mgm./ 100 ml.*	*mgm./ 100 ml.*	*ml./min.*	*ml./min.*	*mgm. iodine/ 100 ml.*	*mgm. iodine/ 100 ml.*	*mgm. iodine/ 100 ml.*	*mgm. iodine/ 100 ml.*	*mgm. iodine/ 100 ml.*	*ml./min.*	*ml./min.*	*ml./min.*	*ml./min.*
Subject P. L. (male)	9:50	115	1.5	8.0	16.6	14.4	132	93	107	5.7	3.5	2.5	1.8	233	478	779	1085	1510
	12:40	122	1.7	8.0	30.0	25.0	282	91	109	13.0	8.1	8.0	4.7	434	322	517	522	890
	9:40	124	2.5	7.0	38.8	33.4	335	111	129	17.2	12.0	16.2	10.7	441	329	472	348	528
	10:10	139	3.8	6.0	45.8	36.4	305	91	115	21.6	14.8	19.1	13.0	366	232	338	262	385
	12:10	162	5.1	5.0	47.2	38.8	420	119	144	23.5	17.8	23.2	16.5	447	253	334	257	361
	13:00	153	4.1	6.0	38.0	38.4	373	116	114	19.0	14.5	21.0	17.8	425	263	344	238	281
	10:20	137	3.6	6.0	28.4	30.8	272	127	117	8.3	11.2	11.5	12.7	381	608	451	439	398
	13:00	140	3.1	6.0	23.6	25.4	283	120	112	6.0	8.7	6.9	9.8	310	557	384	483	340
	6:15	112	1.9	7.0	19.6	21.6	126	115	105	3.8	6.8	4.8	8.2	132	623	348	493	288
Subject M. (male)	11:40	123	2.0	7.0	37.4	32.6	400	113	129	9.0	6.9	6.5	4.5	503	589	771	817	1180
	20:00	150	2.5	7.0	40.2	37.0	745	139	151	12.8	10.6	11.3	9.0	980	574	694	651	816
	11:20	131	2.7	7.0	44.4	41.0	548	143	155	16.1	13.5	14.5	12.2	770	552	660	613	729
	14:10	135	2.5	7.0	50.2	46.0	708	135	147	21.0	17.0	18.2	14.8	1050	477	589	550	676
	10:40	130	2.8	7.0	50.6	53.0	427	103	98					600	—	—	—	—
	11:10	134	3.0	7.0	40.4	45.0	640	190	171	10.1	12.8	13.0	16.5	830	§775(986)	§612(779)	§602(766)	§474(603)
	9:20	115	1.6	8.0	33.0	37.8	377	141	123	6.6	8.6	8.6	11.4	505	943	724	725	546
	12:30	130	2.4	7.0	27.6	32.0	378	142	123	4.0	6.0	5.2	7.5	450	1171	780	899	624
	7:10	117	2.4	7.0	24.4	27.0	241	161	146	2.8	3.8	3.2	5.1	200	1165	859	1020	640

* Inulin and diodrast clearances calculated using both the arterial and venous plasma concentrations.
† Uncorrected for delay time.
‡ Corrected for delay time.
§ Since in Subject M. the inulin and urea clearances in period 6 are high in relation to the mean value for all periods, while the same clearances in period 5 are correspondingly lower, there must have been an error in bladder emptying in period 5. Accordingly, the diodrast clearances in period 6 have been corrected in proportion to the mean inulin clearance; the calculated values are in parentheses, and the corrected values are marked with §. In period 5, the diodrast clearances have not been calculated, because the diodrast plasma concentration varied too much for an accurate estimation of the mean value (Figure 2d).

TECHNIQUE

Venous and arterial blood samples were taken every ten minutes. Blood was collected from a retention cannula in the median cubital vein, brachial artery or femoral artery. Clotting was prevented in the venous cannula by constant, slow infusion of a dilute heparin-saline solution.

Urine was collected by catheter and the bladder was washed twice with 50 ml. of water plus air after each discharge.

Diodrast was analyzed by Bak, Brun and Raaschou's (5) modification of White and Rolf's (6, 7) method. Inulin was analyzed by Brun's (8) modification of Corcoran and Page's (9) and Miller, Alving and Rubin's (10) method.

Procedure of experiments. The subjects used in this study showed no evidence of cardiovascular-renal disease and were afebrile.

The experiments were carried out in three different ways. Generally, a rather rapid rise in the plasma concentration was first obtained by the intravenous infusion of diodrast solution. The infusion was discontinued when the concentration had reached a sufficiently high level, and the concentration was left to fall spontaneously. In other subjects a large intravenous single injection brought about a high diodrast concentration which was allowed to fall spontaneously.

RESULTS OF EXPERIMENTS

Six experiments were made with simultaneous determination of the diodrast level in arterial and venous blood on rising and falling concentration. Figure 2 illustrates the blood curves plotted for all six experiments. Table I shows the results from two of the experiments (P. L. and M.) in a more detailed form.

During falling plasma concentration the diodrast level is higher in venous blood than in simultaneous arterial blood, whereas the reverse is the case during rising plasma concentration.

Table II shows the average percentage differences between diodrast and inulin concentrations in arterial and venous blood (expressed in per cent of the arterial blood concentration) during spontaneously falling concentrations. In the case of diodrast the differences have been calculated only for the concentrations below the self-depression limit. With regard to diodrast the average difference for all six experiments was 29 per cent. This figure corresponds approximately to what might be expected from theoretical calculations. The arteriovenous difference in concentration will depend partly on the diodrast extraction in the kidneys and partly on the ratio between the "renal"

TABLE II

Comparison of diodrast and inulin concentration differencs (in per cent) in arterial and systemic venous blood during spontaneously falling concentrations

Subject	Diodrast	Inulin
	per cent	*per cent*
H. A. (male)	28	5.8
P. J. (male)	26	7.0
M. (male)	31.3	8.0
A. (male)	10.9	
P. L. (male)	52.0	8.7
Average	28.7	7.4

The values are obtained using the following formula:

$$\frac{P_{D_V} - P_{D_A}}{P_{D_A}} \cdot 100 \qquad \frac{P_{IN_V} - P_{IN_A}}{P_{IN_A}} \cdot 100$$

in which P_{D_A} and P_{IN_A} are the arterial plasma concentrations of diodrast and inulin and P_{D_V} and P_{IN_V} are the venous plasma concentrations of diodrast and inulin.

and the "extrarenal" minute volume. Starting from a level below the self-depression limit, where the renal venous blood is almost completely cleared of diodrast, and supposing that one-fifth of the minute volume of the heart passes through the kidneys, we may set up the following equation from which the ratio of arterial concentration to venous blood concentration may be calculated:

$$V \times P_{D_A} = 1/5V \times 0 + 4/5V \times P_{D_V}$$
$$P_{D_V} = 5/4V \times P_{D_A}.$$

P_{D_A} and P_{D_V} are the diodrast concentrations in arterial and venous blood, and V the cardiac output.

In the case of inulin, the renal venous blood will be cleared of only about one-fifth of the quantity present in the arterial blood. Hence the equation for inulin is as follows:

$$V \times P_{IN_A} = 1/25V \times 0 + 24/25V \times P_{IN_V}$$
$$P_{IN_V} = 24/25V \times P_{IN_A}$$

where P_{IN_A} and P_{IN_V} indicate the inulin concentrations in arterial and venous blood.

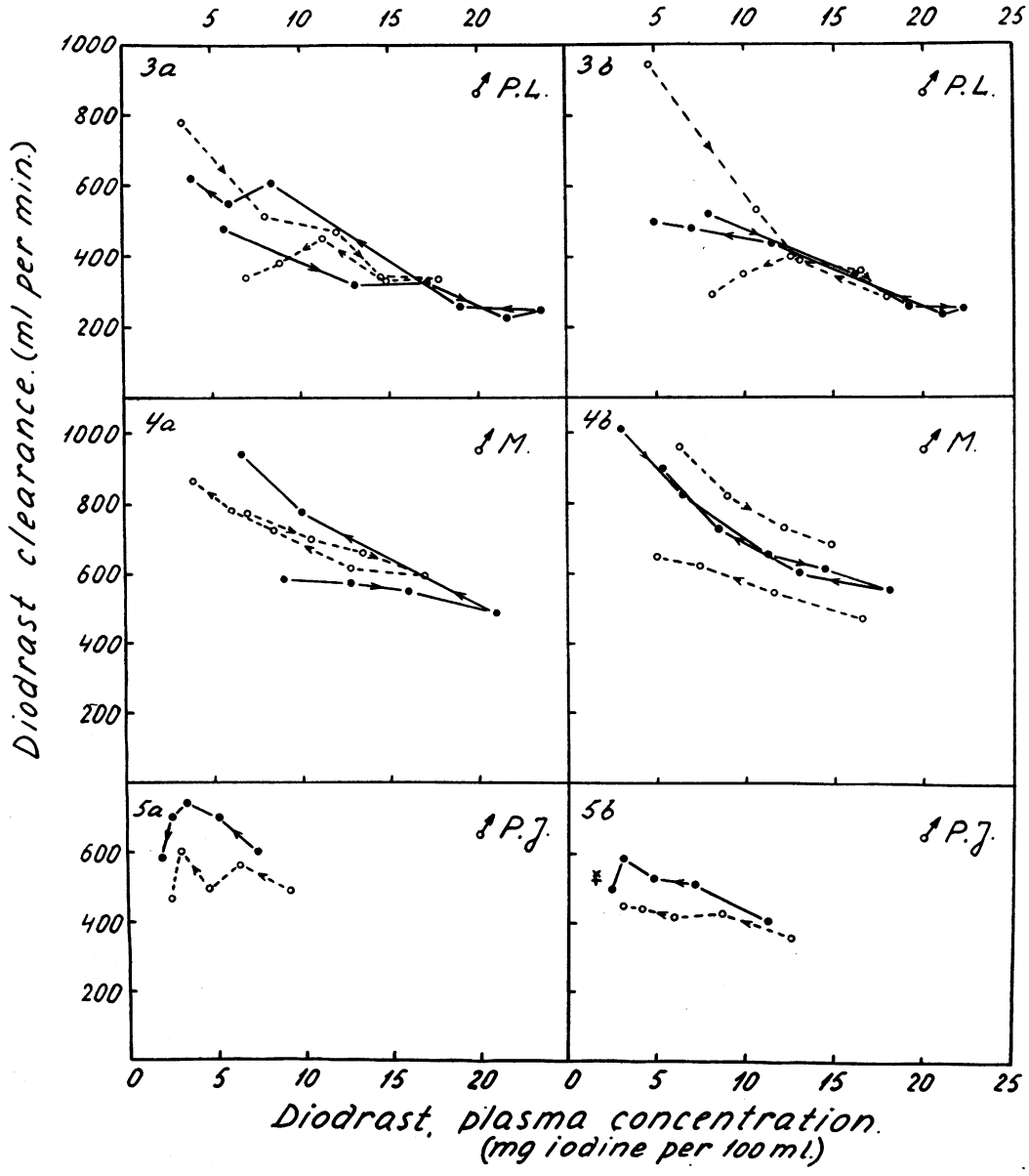
In the case of inulin, too, the difference found (7.4 per cent Table II) corresponds fairly closely to what might have been expected.

These calculations are approximate, of course, because we do not know the exact ratio between the cardiac output and the renal blood flow. Moreover, we cannot *a priori* be certain that the deposition of diodrast is uniform in all tissues. On the contrary, investigations by Lengemann (11) seem to show that the largest amounts of diodrast are deposited in liver and skin. The blood from the median cubital vein is cutaneous venous blood and

it may be particularly rich in diodrast on falling plasma concentration.

During rising plasma concentration the level in the arterial blood is, as mentioned above, higher than in the corresponding venous blood, partly because a certain amount of diodrast is deposited in the tissues and partly because of the variations in the distribution of diodrast in the blood. The rate of infusion is the factor determining the arteriovenous concentration difference.

We shall now report the results arrived at by calculating the diodrast clearance on the basis of arterial blood concentration and venous blood concentration, respectively. The diodrast clearance



FIGS. 3–5. DIODRAST CLEARANCE VALUES CALCULATED ON THE BASIS OF ARTERIAL AND VENOUS PLASMA CONCENTRATIONS

Figs. 3a, 4a, and 5a show uncorrected clearance values, and Figs. 3b, 4b, and 5b show clearance values which are corrected for delay time. Solid dots represent arterial, and open circles venous plasma concentrations.

values refer partly to Table I (P. L. and M.), and partly to Figures 3, 4 and 5 (P. L., M., and P. J.).

By using the arterial and venous concentrations and without allowing for delay time we arrive at the results indicated in Figures 3a, 4a, and 5a.

In Figure 3a (P. L.), the "venous clearance" values are seen to be high on rising and low on falling blood concentration, while the "arterial clearances" are low on rising and high on falling blood concentration. On the other hand, it appears that the "venous clearance" (Figure 4a) may be identical on rising and falling blood concentrations, whereas the "arterial clearance" is low on rising and high on falling blood concentration. Finally, it appears from Figure 5a that the "arterial clearance" values are higher during spontaneously falling blood concentration than the "venous clearance." That the diodrast clearance has been calculated on the basis of concentrations above the self-depression limit is naturally of no importance in these subjects, where it was the question of comparing the "arterial" and the "venous" clearance values calculated on simultaneous plasma concentrations, and not of estimating the absolute clearance values.

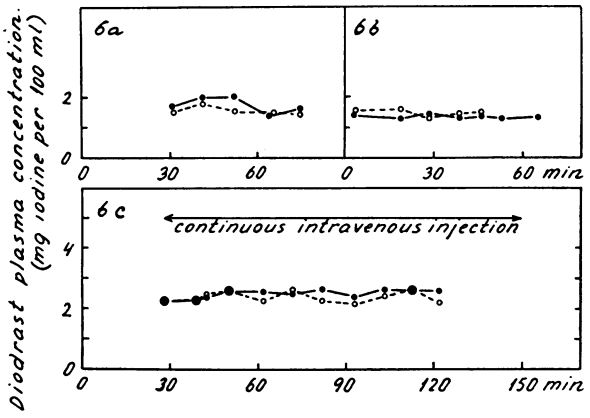


FIG. 6 (a through c). DIODRAST PLASMA CONCENTRATION IN ARTERIAL AND VENOUS BLOOD DURING A CONSTANT INTRAVENOUS INFUSION

Solid dots represent concentrations in arterial, and open circles concentrations in venous blood.

However, we feel that allowance should be made for delay time in the calculation of the diodrast clearance. In a subsequent article (12) we will publish the results of experiments dealing with delay time in normal individuals for different urine volumes. In the present article it will only be pointed out that the delay time must be supposed to be longer than it was previously thought to be (three minutes), (Goldring, Chasis, Ranges and Smith [3]). For urine volumes like those dealt with in our experiments (1½ to 5 ml. per min.) the delay time is between five and eight minutes.

With allowance for these facts we have calculated the diodrast clearance values indicated in Figures 3b, 4b and 5b, as well as in Tables I and II, which show that the "arterial clearance" values are identical during rising and falling blood concentrations, whereas the "venous clearance" values are low on falling and high on rising blood concentration. It appears from Figure 5b that, after correction for delay time, the "arterial diodrast clearance" values calculated during falling blood concentration are found to be comparable with the diodrast clearance calculated on the basis of a constant plasma concentration curve.

Finally some experiments were made in order to investigate the arterial and the venous plasma concentrations of diodrast using the constant intravenous infusion method. The arterial and the venous plasma concentrations are seen to differ very little (Figure 6). The clearance values calculated on the basis of the arterial plasma concentration were practically identical with those calculated on the venous plasma concentration.

DISCUSSION

It appears from the results of the above experiments that the "venous diodrast clearance" values calculated during rapidly falling or rising plasma concentrations are either too low or too high. The "arterial diodrast clearance," on the other hand, presents identical and correct values under the same experimental conditions *provided that allowance is made for delay time.*

We may, therefore, for the present conclude that the cause has been found for the error in the diodrast clearance, when it is calculated using venous blood analyses and falling plasma concentration; the error is due to the difference between the diodrast concentrations in arterial and venous blood.

Foa and Foa (13) calculated the diodrast clearance on the basis of a falling plasma concentration

curve and venous blood analyses, a procedure which, according to the above observations, we cannot recommend. That these writers found the average normal value to be as high as 566 ml./min. is no doubt due to the fact that they made no allowance for delay time. This may in some measure eliminate the error made in diodrast clearance calculation based on rapidly rising and falling plasma concentrations, and may offer an explanation of the fact that in some cases we did not observe low clearance values on falling concentrations.

It has previously been mentioned that strikingly high and irregular diodrast clearance values may be observed within the first part of an infusion period (*vide* Figures 1a and 1b), as well as at a later stage of the experiment, whenever there is a great increase in the infusion rate. This may be owing in part to the fact that the tissues are not saturated with diodrast, and consequently, the percentage difference between the diodrast concentrations in arterial and venous blood is large. The plasma concentrations, therefore, used in the clearance calculation are far too low when venous blood analyses are used. Another cause may be the fact that at the beginning of some of our experiments the infusion was irregular, so that sudden and relatively great changes might have occurred in the diodrast concentration in arterial blood without these fluctuations necessarily being reflected to the same extent in the venous blood. Finally the possibility cannot be omitted that actual variations in the renal plasma flow underlie these high and irregular clearance values.

CONCLUSIONS

1. Diodrast clearance values obtained during rapidly falling plasma concentration are erroneously low. This error is due to the fact that significant differences in diodrast concentrations between arterial and systemic venous blood occur during rapidly rising and falling plasma concentrations. Therefore the customary use of peripheral plasma concentration in calculations of the diodrast clearance can lead to large errors.

2. If arterial plasma concentration is used and if correction is made for delay time the diodrast clearance is independent of rate of change in the plasma concentration.

3. If a constant intravenous infusion is used, the clearance calculation using venous plasma concentration is permissible.

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