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FUNCTIONAL DISORGANIZATION OF THE KIDNEY IN DISEASE

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Evidence has accumulated in recent years [Smith, 1937; Richards, Bott & Westfall, 1938] to show that the inulin clearance is a measure of the glomerular filtration rate, and it has also been demonstrated that in health and for a given species fairly stable relations exist between the inulin, creatinine and urea clearances. Based upon these facts a reasonably simple explanation can be given of the way in which creatinine and urea are excreted. Thus in some mammals the inulin and creatinine clearances are identical, and therefore creatinine is considered to be eliminated solely by glomerular filtration. In man, however, the creatinine clearance exceeds the inulin clearance, and it would seem therefore that the tubules of the human kidney excrete some creatinine into the urine. Urea is thought to be excreted by glomerular filtration in all species but to undergo some reabsorption from the lumen of the tubules. Filtration, reabsorption and tubular excretion proceed so smoothly, however, in the intact and healthy animal that there is a tendency to forget that there must be forces regulating and controlling these processes. It is only when some chance experiment or disease produces gross departure from normal conditions and throws some function unexpectedly out of gear that we appreciate the complexity of the normal integration. Thus Shannon & Winton [see Winton, 1937] have reported that in the "isolated" kidney of the dog the creatinine clearances may no longer be equal to the inulin clearances, but substantially below them. The following observations on man describe comparable departures from the normal clearance ratios and give in addition information on the simultaneous excretion of other substances. The present work deals mostly with the secretion of urine in diabetic coma and is the logical outcome of an earlier investigation of the

same subject (including a review of the literature) by McCance & Lawrence [1935]. Both papers, however, contain records of similar phenomena from patients not in diabetic coma, and it is believed [Allott, 1938] that the abnormalities may be of relatively general occurrence.

METHOD

Inulin and creatinine were injected intravenously, and subsequently urine and blood were collected at suitable intervals for analysis. In studying normal persons the usual dose of inulin has been 50 g., and this amount was administered to the first patient (P. 5, Table III) who was in deep coma. This dose was found to raise the plasma inulin to unnecessarily and unjustifiably high levels, and thereafter 20–30 g. were administered to patients with raised blood ureas. In making these tests on patients in diabetic coma large doses of insulin and 500–1000 c.c. of saline were always administered before the inulin and creatinine, but all intravenous medication was suspended for the next 2 or 3 hr. while the specimens of urine and blood were being collected. Details of the actual procedures on normal persons and on patients may be found in previous papers by McCance & Widdowson [1937, 1938].

In order to determine as accurately as possible the glucose in diabetic urines, the small reduction due to non-sugar substances was found by removing the glucose by fermentation, and this value was deducted from the total reducing power. The correction was in all cases a very small one.

Chasis & Smith [1938] have suggested that owing to the relative insolubility of inulin it is advisable to keep the urine flow above 1 c.c./min. during tests. It should be mentioned, therefore, that although some of the specimens of urine obtained from these patients had very low minute volumes and contained high concentrations of inulin (see Tables III and IV) crystallization was never observed until the urine had cooled. Histological records are not available, since it was impossible to obtain permission for post-mortem examinations on the patients who died. This is probably a matter of little importance, however, for in these functional renal abnormalities the morbid anatomists have so far given little if any constructive help [McCance & Lawrence, 1935].

Notes on the patients

P. 1. ♀ Age 40. Suffering from diabetic coma due to the omission of insulin. Blood pressure during tests 90/50 falling to 80/50. In health 122/88.

P. 2. ♀ Age 78. Well-controlled diabetic suffering from an inoperable carcinoma of rectum and two boils. A full dose of morphia and scopolamine was given to which the patient proved abnormally sensitive but from which she recovered. Blood pressure during tests 120/64. In health 124/60.

P. 3. ♀ Age 45. Admitted in diabetic coma due to insufficient insulin. Blood pressure during tests 110/75–126/80.

P. 4. ♀ Age 66. Admitted in diabetic coma. Blood pressure during tests 114/68.

P. 5. ♀ Age 41. Untreated diabetic in deep coma. Blood pressure during tests 94/55.

RESULTS

Clearances and clearance ratios. Smith and his collaborators [1937] have found that the normal inulin clearance is of the order of 122 c.c./min. for an "ideal" man with a surface area of 1·73 sq. m. and that the corresponding creatinine clearance is about 170 c.c./min. at the plasma levels of creatinine at which we have been working. Thus the creatinine/inulin clearance ratios are of the order of 1·4. The urea clearance varies with the minute volume of the urine and at minute volumes of about 2 c.c./min. has a normal value of the order of 70 c.c./min. The urea/inulin clearance ratios therefore in normal health are a little below 0·6 [Chasis & Smith, 1938].

For the sake of comparison with the results obtained in disease, Table I shows the values obtained by our methods on a normal man, results which are in agreement with previous observations [McCance & Widdowson, 1938] and with those of Smith and his collaborators.

TABLE I. Clearances and clearance ratios in a normal man (surface area 1·94 sq. m.)

Period	Min. vol. c.c.	Clearances (c.c./min.)			Clearance ratios	
		Inulin	Creatinine	Urea	Creatinine/inulin	Urea/inulin
1	1·8	125	189	69	1·51	0·55
2	2·0	150	222	73	1·48	0·49
3	4·2	131	214	82	1·63	0·62
4	8·0	134	207	76	1·54	0·57
5	2·5	132	200	72	1·52	0·55
6	3·7	138	210	67	1·52	0·49

Two types of deviation from such normal renal function may be distinguished. (1) The common type in which the absolute clearances are greatly reduced without much change in the ratios between the clearances. One instance of wide fluctuations in the inulin clearance accompanied by normal clearance ratios has already been published [McCance & Widdowson, 1937]. Two examples from other diseases of reduced inulin clearances and relatively normal clearance ratios are given in Table II. The figures in each case are the average of three consecutive periods. Chasis & Smith [1938] have reported a series of cases of glomerulo-nephritis in which they found a tendency for the urea/inulin clearance ratios to rise as the disease advanced, but the change was a relatively

TABLE II. Clearances and clearance ratios in Addison's disease and chronic nephritis

	Clearances (c.c./min.)			Clearance ratios	
Nature of disease	Inulin	Creatinine	Urea	Creatinine/ inulin	Urea/ inulin
Addison's disease	50	74	19	1·47	0·38
Chronic interstitial nephritis	10·6	12·4	8·1	1·17	0·76

small one and their findings in no way conflict with the above generalization. (2) The type now to be described in which the ratios between the clearances are notably unusual, the absolute clearances being at the same time often but not invariably reduced. The results obtained on four patients in diabetic coma and one patient suffering from an overdose of morphia and scopolamine are given in Table III. For each patient the periods followed each other without any interval of time, and the duration of the periods was arranged according to the expected flow of urine. It will be observed that the first four patients show creatinine/inulin clearance ratios well below 1, and that these ratios are not necessarily associated with particularly low minute volumes. It is, however, by no means invariable to find creatinine/inulin clearance ratios below 1 in diabetic coma. They may be within normal limits, and in one subject (P. 5) a ratio of over 2 was found when the patient first came under observation. It is nevertheless true to say that creatinine/inulin clearance ratios below 1 are relatively common in patients who are in deep coma and dangerously ill. These low creatinine/inulin ratios were associated with very low urea/inulin clearance ratios in P. 1, 2, 4 and the later periods of P. 5. The lowest urea/inulin clearance ratios have accompanied very low minute volumes. In P. 5 the actual clearances were all very low, which should have tended, other things being equal, to a high urea/inulin ratio [Chasis & Smith, 1938]. These low ratios indicate extensive urea reabsorption, and in P. 5, periods 2 and 4, this appeared to become so extensive that there was a smaller percentage of urea in the urine than there was in the blood. It is possible that this was an artifact due to admixture of the urine passed during these periods with water used to wash out the bladder at the end of the previous periods, but there was no evidence of this at the time, and in the light of other findings recorded in this paper such extensive reabsorption must be accepted as a reasonable possibility.

The excretion of glucose. It has been known for some time [see McCance & Lawrence, 1935] that in disease the kidney may not excrete glucose even when the blood sugar is demonstrably very high. Two

TABLE III. Abnormal clearance ratios in diabetic coma (P. 1, 3, 4 and 5) and after morphia and scopolamine overdosage (P. 2)

Patient and no. of period	Duration of period minutes	Min. vol. c.c.	Plasma mg./100 c.c.			Ratio urine/blood			Clearance c.c./min.			Clearance ratios	
			Inulin	Creatinine	Urea	Inulin	Creatinine	Urea	Inulin	Creatinine	Urea	Creatinine/inulin	Urea/inulin
P. 1 1	43	0·75	190	25·8	68·2	38	18·6	4·3	28·4	13·8	3·20	0·49	0·110
2	38	0·32	180	24·3	69·2	37	21·8	2·8	11·7	6·9	0·90	0·59	0·077
3	90	0·16	150	23·0	70·5	66	31·0	2·1	10·3	4·8	0·32	0·47	0·031
4	130	0·13	115	21·3	72·5	122	52·0	2·4	15·9	6·7	0·31	0·42	0·019
P. 2 1	35	0·66	95	16·2	32·2	153	98	22·0	101	64	14·5	0·64	0·144
2	58	0·27	73	13·3	32·2	216	164	29·5	58	44	8·0	0·76	0·138
3	31	0·23	50	11·7	32·2	314	220	36·7	73	51	8·4	0·70	0·116
P. 3 1	31	1·79	91	11·7	69·9	68	51	22·5	121	91	40·3	0·75	0·33
2	35	2·20	50	9·1	70·7	43	39	14·0	93	79	30·8	0·85	0·33
P. 4 1	68	1·13	105	18·8	112	35·3	15·5	3·2	31·8	17·5	3·6	0·55	0·113
P. 5 1	26	0·26	742	87·0	98	7·4	17·2	2·30	1·90	4·5	0·58	2·3	0·31
2	47	0·15	560	79·0	99	8·2	14·7	0·97	1·23	2·2	0·15	1·8	0·12
3	78	0·07	540	74·0	102	22·2	30·2	1·45	1·47	2·1	0·10	1·5	0·07
4	153	0·09	470	70·0	108	8·3	11·1	0·42	0·78	1·0	0·04	1·4	0·05

TABLE IV. Failure of glucose excretion during diabetic coma

Patient and no. of period	Plasma (mg./100 c.c.) Inulin	Plasma (mg./100 c.c.) Glucose	Urine min. vol. c.c.	Urine (mg./100 c.c.) Inulin	Urine (mg./100 c.c.) Glucose
P. 1 1	190	840	0·75	7,240	2,600
2	180	805	0·32	6,680	2,630
3	150	740	0·16	9,900	1,480
4	115	615	0·13	14,100	30
P. 5 1	742	653	0·26	5,500	680
2	560	610	0·15	4,600	332
3	540	580	0·07	11,500	160
4	470	550	0·09	3,900	13

instances of this are given in Table IV. The fact that these kidneys were excreting so little glucose in the urine in spite of the high levels of glucose in the plasma is interesting enough, but the interest is greatly enhanced by the demonstration that these kidneys were at the same time excreting inulin relatively freely. This strongly suggests that the absence of glucose from the urine was due to reabsorption.

The excretion of electrolytes. The urine is well known to contain relatively small quantities of the chloride ion during diabetic coma. This is usually associated with a very low figure for the plasma chloride, and so long as this is so there is nothing to suggest any abnormality of kidney function. Several workers, however [see McCance & Lawrence, 1935], have recorded cases of diabetic coma in which the urine was as usual almost chloride free in spite of abnormally high plasma chlorides. Allott [1938] has made similar observations in cases of uncompensated alkalosis. This is indeed an uncommon but a well-authenticated phenomenon, and two instances of it are recorded in Table V. It is clear that

TABLE V. Excretion of electrolytes and ammonia in diabetic coma

Patient and no. of period	Serum* mg./100 c.c. Na	Serum* mg./100 c.c. K	Plasma* mg./100 c.c. Cl	Urine min. vol. c.c.	Urine (mg./100 c.c.) Na	K	Cl	NH_3	Urea
P. 1 1	420	10·7	395	0·75	61	42	160	54	295
2			394	0·32	20	20	89	44	196
3				0·16	32	31	106	63	145
4				0·13	46	54	110	86	173
P. 4 1			374	1·13			17		
2			374	1·01			12		

* Normal serum and plasma values: Na 315, K 18, Cl 360 mg./100 c.c.

with plasma sodium and chloride so abnormally high as they are in P. 1 one would have expected a high concentration of these ions in the urine, especially in the presence of an oligura. It will be recalled (see Tables III and IV) that this patient was excreting inulin freely, so it may be assumed

that the sodium chloride was passing through the glomerular membranes into the tubules. The excretion of potassium may have been normal in this patient, especially in view of the low serum value. The high rate of excretion of ammonia is to be noted relative to the almost complete failure to excrete urea. This was observed frequently by McCance & Lawrence, and it appears that this particular function of the kidney may remain unimpaired when others are greatly disorganized [McCance, 1935].

Discussion

The present studies, incomplete though they are, substantiate and extend those which have previously been made. It is clear that certain diseases may bring about gross functional disorganization of the kidney, and it is probable that these changes are unaccompanied by any constant anatomical change. A fall in glomerular filtration (inulin clearance) is readily explained in diabetic coma by the fall in blood pressure and dehydration which usually accompany it, but the other abnormalities are difficult to explain. The fall in the creatinine/inulin clearance ratios to less than 1, the extremely low urea/inulin clearance ratios and the correspondingly low urine/blood ratios for urea have been detected often enough to leave little doubt that the observations are correct. The same is also true of the differential rates of excretion of glucose and inulin and the reluctance of such kidneys to excrete sodium chloride whatever the level of these ions in the plasma. All these phenomena have been observed in the same patient (P. 1), but more usually they are not all found together. It is to be remarked that all these abnormalities tend to produce a hypotonic urine, and it is noteworthy that under the conditions in which Shannon & Winton found abnormal creatinine/inulin clearance ratios the urine was also extremely hypotonic. It is difficult to believe that with inulin passing freely or relatively freely into the urine—presumably by glomerular filtration—crystalloids are not also passing into the glomerular filtrates. The abnormality therefore in each instance is probably unrestrained reabsorption on the part of the tubules. The production of the very hypotonic urines characteristic of the fully developed condition must involve the tubule cells in more work than normal against osmotic pressure per c.c. of urine formed. The problem is to explain why all this is taking place. A possible explanation seems to be to follow the lead of Starling & Verney [1924–5] and to suppose that this excessive reabsorption is an "escape" phenomenon. In other words the kidney would always reabsorb in this way but for some restraining influence, presumably hormonal in nature. The isolated kidney, in which

Starling & Verney were interested, is cut off from its normal hormonal control, and hence the tubules reabsorb chloride ions which they would normally pass into the urine. In disease the hormones may not be secreted or, if they are, the kidney may not be responsive to them. Hence the kidney is functionally "isolated", and the tubules reabsorb not only chlorides but also glucose and urea and to some extent creatinine. An alternative explanation, at present less complete but within its own limits probably a better one, has been suggested by Shannon & Fisher's [1938] recent work. These authors have explained the well-known phenomenon of the renal "threshold" for glucose by pointing out that the glomerular filtration rate is normally very constant and by postulating that the tubules can only reabsorb a certain quantity of glucose per unit time. When glucose is delivered into the tubules by glomerular filtration at a rate faster than this, glucose appears in the urine. In the present series of observations, although the blood sugar was very high, the glomerular filtration rate was very low. Hence the total quantity of glucose delivered to the tubules per minute may not have been above the maximum which relatively normal tubules were capable of transferring back to the blood. This explanation may be extended to cover the present observations on chlorides but not the abnormal creatinine/inulin clearance ratios, nor would it seem to explain all the observations which have been made on the excretion of chlorides either experimentally or in disease.

Summary

1. Kidney function tests with inulin have shown that during diabetic coma and in certain other conditions:

(*a*) The creatinine/inulin clearance ratios may be very much below 1.

(*b*) The urea/inulin clearance ratios may be extremely low and also the urine/plasma urea ratios.

(*c*) Glucose may be almost absent from the urine when the glucose in the plasma is over 550 mg./100 c.c. and when inulin is passing freely into the urine.

(*d*) The percentage of urinary sodium and chloride may be very low in spite of extremely high plasma values.

(*e*) Other functions of the kidney such as the excretion of ammonia may be unimpaired.

2. Two possible explanations of these results have been discussed:

(*a*) That they are due to excessive reabsorption by the tubule cells caused by the loss of some normal restraining influence.

(*b*) That the glucose and chloride results are due to a pronounced fall in the glomerular filtration rate in kidneys with relatively normal tubules.

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