OBSERVATIONS ON RENAL FUNCTION IN UNILATERAL DISORDERS OF THE KIDNEY.*

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IT is unlikely that chemical analysis of the urine can be of much use in the differential diagnosis of unilateral kidney disorders, because various pathological conditions may produce similar effects on renal function; but analysis of the urine will seldom fail to distinguish the affected from the normal kidney. The urine from the affected kidney is nearly always less concentrated, as Fullerton's[1] specific gravity test usually shows; and chemical methods are more sensitive than the specific gravity test in detecting this change. In considering the results of analysis it must be remembered that urines collected separately from the two kidneys are not always identical in volume or in composition, even when both kidneys are normal.[2] The differences then, however, seem to be comparatively small, and may be due, for the most part, to irritation produced by the ureteral catheters.

The chief value of chemical analysis lies not in diagnosing the presence of calculus or tubercle, but in the possibility of estimating the degree of injury to the kidney cells.

There is no doubt that a unilateral diuresis of reflex origin can be produced without injury to the kidney. This diuresis is an effect of irritation on the nervous control of the blood supply, and is probably the first result of ureteric calculus and of the toxins of tubercle. The most important problem, from a biochemical aspect, is to distinguish this reflex diuresis from loss of concentrating power due to inefficiency of the kidney epithelium. The volumes of the urines from the two kidneys cannot as a rule be determined with accuracy, since the amount of leakage past the catheters cannot be ascertained. The recognized characteristics of diuresis must be compared with those of renal failure and the results applied to the study of unilateral kidney disorders.

Diuresis.

1. In diuresis the urine becomes more like the plasma, perhaps because the kidneys have less time to produce alterations. This generally means that all the constituents of the urine become more dilute. But if the concentration of chloride in the urine before diuresis was lower than that in the plasma, this approach to the plasma involves an *increase* in the concentration of chloride while the concentrations of other substances are reduced.

In the usual forms of diuresis a rise in chloride concentration can rarely be observed, since the plasma dilution which causes the diuresis also lowers the plasma chloride, and hence tends to lower the chloride of the urine. In unilateral reflex diuresis plasma dilution does not occur, and in any case a comparison is made between urines excreted simultaneously by two kidneys supplied with the same blood, and not between urines excreted in two different periods during which the composition of the plasma has altered. Therefore, in suitable conditions, a rise in the concentration of chloride may be expected. To say that during diuresis the urine approaches the plasma in composition is probably less correct than to say that it approaches the glomerular fluid. And if, as is generally supposed, this fluid is a protein-free filtrate from the plasma, we cannot escape the conclusion that a Donnan[3] equilibrium exists at the filtering membrane, and that the concentration of chloride in the filtrate is higher than in the plasma (cf. cerebro-spinal fluid). Wearn and Richards's[4] analyses of glomerular filtrate furnish direct evidence that it is higher. This point is mentioned in the interests of accuracy, but has not been considered in examining the results. It may render interpretation difficult when the concentration of chloride in the urine happens to be near the plasma concentration, since it may determine the borderline between rise and fall in the urine chloride as an effect of diuresis.

2. In diuresis the various constituents of the urine do not all suffer an equal lowering of concentration. Chloride is less affected than other substances, and urea is probably somewhat less affected than phosphate and creatinine. The following explanation is given by Cushny.[5]

The urine is concentrated by absorption of water from the glomerular filtrate and not by secretion into it of dissolved substances. Chloride is readily absorbed with the water, and although in diuresis the escape of fluid may result in a lower concentration of chloride in the urine, this effect is partly counterbalanced by the fact that less of the chloride itself is absorbed. Urea is normally absorbed to some extent, but much less easily than chloride, while it is doubtful whether creatinine is absorbed at all. Urea thus shares a little of the advantage gained by chloride in diuresis, but always shows a net loss of concentration; and since creatinine, unabsorbed in any case, has nothing to gain by rapid passage through the kidney, its loss of concentration is more extreme. The rejection of this theory will not, of course, affect the validity of the observations.

Renal Failure.

In this, as in diuresis, there is a fall in the concentration of the urine, but careful study reveals certain distinguishing features.

1. There is evidence of failure in chloride excretion, and in the later stages the concentration of chloride in the urine remains below that in the plasma even when salt is given to the patient.[6 7 8]

2. There may be defective excretion of urea. This is not easily recognized, except by concentration tests or by examination of the blood; and both of these methods would probably fail in the present investigation. But urea excretion suffers before that of creatinine,[9] and if the concentrations of these substances can be compared in corresponding samples of normal and abnormal urine any existing defect should become apparent.

The best examples of renal failure are witnessed in chronic interstitial nephritis and in arterio-sclerosis of the kidney. The order in which this failure involves the various constituents of the urine seems related to the degree of resistance which the normal tubule epithelium offers to their passage back from the glomerular filtrate to the blood while absorption of water is proceeding. Thus, chloride passes back most readily, next urea, next phosphate, and creatinine with the greatest difficulty. And in nephritis chloride excretion appears to suffer first, then that of urea, phosphate, and creatinine, in this order. To avoid misunderstanding it should be mentioned that nephrosis or pure hydraemic nephritis is not a good example of renal failure. Function tests give no evidence of failure, and the low water and chloride output in this disease can be attributed for the most part to other causes.[8] In dealing with unilateral kidney disorders blood urea estimation is usually of little value, because one healthy kidney is sufficient to keep the blood urea normal. Concentration tests may have a limited field, but require less direct interpretation than in nephritis; for reflex diuresis, even without renal failure, would probably prevent good concentration of urea.

There remains the application of the above criteria to unilateral disorders, as a method of distinguishing reflex diuresis from renal failure. The urines from the normal and the affected kidney must be compared. The following statements are deduced from the considerations already discussed.

(*a*) In reflex diuresis the ratio of the chloride concentration in the urine from the affected kidney to the chloride concentration in the urine from the normal kidney should be greater than the corresponding ratios for urea, phosphate, and creatinine. (See Table I.)

TABLE I.

Urine in Reflex Diuresis (Movable Kidney).

	Chloride (NaCl).	Urea.	Phosphate (P_2O_5).
	Per cent.	Per cent.	Per cent.
(*a*) Normal kidney ...	1.72	1.74	0.094
(*b*) Affected kidney ...	1.53	1.39	0.069
Proportion of (*b*) to (*a*)	89	80	73

Note that the concentration of chloride is *less* reduced than those of urea and phosphate.

* A paper read in the Section of Surgery at the Annual Meeting of the British Medical Association, Cardiff, 1928.

Urine from Damaged Kidney (Pyonephrosis).

	Chloride (NaCl).	Urea.	Phosphate (P_2O_5).
	Per cent.	Per cent.	Per cent.
(*a*) Normal kidney ...	1.45	1.02	0.062
(*b*) Affected kidney ...	0.63	0.59	0.039
Proportion of (*b*) to (*a*)	43	58	63

Note that the concentration of chloride is *more* reduced than those of urea and phosphate.

(*b*) In reflex diuresis the chloride concentration in the urine from the affected kidney should probably not fall below that in the plasma (about 0.6 per cent. sodium chloride), so long as the chloride in the normal urine remains above this level. (See Table II.)

TABLE II.

Urine in Diuresis (Denervated Kidney).*

	Chloride (NaCl).	Urea.
	Per cent.	Per cent.
(*a*) Normal kidney	0.77	0.81
(*b*) Affected kidney	0.60	0.51
Proportion of (*b*) to (*a*)...	78	63

* Not reflex, since nerve connexions have been destroyed; but circulatory in origin, and thus of similar type.

Note that although the concentration falls in diuresis, it does not fall below that of the plasma (about 0.6 per cent. NaCl).

Urine from Damaged Kidney (Pyonephrosis).

	Chloride (NaCl).	Urea.
	Per cent.	Per cent.
(*a*) Normal kidney	0.87	1.69
(*b*) Affected kidney	0.41	0.64
Proportion of (*b*) to (*a*)...	47	38

Note that while the concentration of chloride from the normal kidney is higher than that of the plasma, the concentration of chloride from the affected kidney is lower than that of the plasma.

(*c*) If the chloride concentration in the urine from the normal kidney is below that of the plasma, reflex diuresis should cause a higher chloride concentration in the urine from the affected kidney than exists in the normal urine. (See Table III.)

TABLE III.

Urine in Diuresis (Denervated Kidney).

	Chloride (NaCl).	Urea.
	Per cent.	Per cent.
(*a*) Normal kidney	0.30	0.75
(*b*) Affected kidney	0.60	0.21
Proportion of (*b*) to (*a*)...	200	28

Note increase in concentration of chloride caused by diuresis when the "normal" concentration is lower than that of the plasma (about 0.6 per cent. NaCl). Diuresis renders the urine more like the plasma.

Urine from Damaged Kidney (Hydronephrosis).

	Chloride (NaCl).	Urea.
	Per cent.	Per cent.
(*a*) Normal kidney	0.32	1.00
(*b*) Affected kidney	0.14	0.28
Proportion of (*b*) to (*a*)...	44	28

Note that even when the concentration of chloride from the normal kidney is below that of the plasma, the concentration of chloride from the affected kidney may be still lower.

This statement and the previous one may require slight modification if there is a Donnan[3] equilibrium at the glomerular membrane. None of the results yet obtained are of assistance in deciding whether any modification should be made.

(*d*) In reflex diuresis the ratio of the urea concentration in the urine from the affected kidney to the urea concentration in the urine from the normal kidney should probably be somewhat greater than the corresponding ratio for creatinine. (See Table IV.)

TABLE IV.

Urine from Slightly Damaged Kidney (Calculus in Pelvis; Moderate Dilatation).

	Chloride (NaCl).	Urea.	Phosphate (P_2O_5).	Creatinine.
	Per cent.	Per cent.	Per cent.	Per cent.
(*a*) Normal kidney ...	1.36	1.32	0.142	0.112
(*b*) Affected kidney ...	0.63	0.75	0.050	0.053
Proportion of (*b*) to (*a*)	46	57	35	47

Note injury shown by greater reduction in chloride than in urea. But urea is less reduced than either phosphate or creatinine.

Urine from Severely Damaged Kidney (Pyonephrosis).

	Chloride (NaCl).	Urea.	Phosphate (P_2O_5).	Creatinine.
	Per cent.	Per cent.	Per cent.	Per cent.
(*a*) Normal kidney ...	1.45	1.02	0.052	0.066
(*b*) Affected kidney ...	0.63	0.59	0.039	0.047
Proportion of (*b*) to (*a*)	43	58	63	71

Note that urea is reduced more than either phosphate or creatinine, indicating some failure in urea excretion. Phosphate is sometimes also much reduced in comparison with creatinine.

In spite of numerous estimations the position occupied by phosphate has not been ascertained. The excretion of phosphate often bears a close resemblance to that of creatinine, but is apparently much more sensitive to changes in the kidney.

The disturbance of one or more of these relations is regarded as indicating some degree of renal failure. The extent of the disturbance is of assistance in estimating the damage to the kidney.

Finally, it should be stated that only about fifty cases have as yet been examined. All were patients of Professor Fullerton, who performed the ureteral catheterizations and obtained the specimens of urine. Most of the results are in harmony with the observations made by the surgeon, but a few apparent exceptions have still to be explained. Some possible sources of doubt may be mentioned. Clinical confirmation can only be considered satisfactory when the surgeon has had an opportunity of seeing the kidney; but in some cases an operation is not thought advisable or is refused by the patient, and in the remainder a complete examination can only be made when the kidney is sufficiently diseased to justify nephrectomy. Again, it must be borne in mind that the kidney which is taken as a normal control may not in reality be normal, although the blood urea is probably a safe guide in most cases. A less obvious error may be the cause of other misleading results. It is possible for fluid introduced into the bladder to travel up the ureter and dilute the urine which is passing down the catheter, particularly when the ureteral orifice has lost its valve-like character. Professor Fullerton has been careful to avoid this accident. Further, the urine from a very bad kidney can probably contain enough serum or pus to increase materially its low concentration of chloride; and perhaps enough to reduce the concentration of phosphate and other substances.

It is fair to point out, in conclusion, that the examples given in this paper are chosen for the purpose of illustration. A general survey of the results justifies the application of principles discussed, but at the same time emphasizes the need for further investigation, directed especially towards reflex diuresis in the healthy kidney.

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