COMPARATIVE STUDIES ON ENDOGENOUS CREATININE AND UREA CLEARANCES IN PARAPLEGICS AND TETRAPLEGICS

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THE most serious consequence of injuries to the spinal cord is progressive deterioration of renal function as a result of the ascending infection of the paralysed bladder. Although the advances made in the management of paraplegics since World War II have eliminated the early high mortality from renal infection experienced in World War I, there is still a high morbidity and mortality in the late stages from renal failure.

The most recent statistical review on patients suffering from spinal cord lesions has been published by Guttmann (1964). There were 1963 traumatic paraplegics and tetraplegics among 3000 patients treated between 1944 and 1963 at the National Spinal Injuries Centre. The mortality among the 1963 traumatic cases was 331 (16·9 per cent.), the corrected figure, *i.e.* excluding those who died from causes unrelated to the spinal cord injury, being 11·5 per cent. Renal failure was still the main cause of death; this confirmed his earlier findings (Guttmann, 1953). In an analysis of 91 autopsies from this series, Tribe (1963) found that 53 of the deaths could be attributed to chronic pyelonephritis, amyloidosis and hypertension. Similar observations have been made in recent years by other workers in this field (Reingold, 1953; Damanski & Gibbon, 1956; Dietrick & Russi, 1958; Nyquist, 1960; Breithaupt, Jousse & Wynn-Jones, 1961; Comarr, Kawaichi & Bors, 1961).

Since the prognosis of paraplegic patients is largely determined by the functional integrity of their kidneys, it is desirable to have reliable tests of renal function which can be conveniently performed at regular intervals. Rogers and Bors (1950), Comarr (1954), Morales, Sullivan and Hotchkiss (1956) and Magee (1957, 1958) have studied the renal function of paraplegics using various tests of glomerular and tubular function, including the Inulin and P.A.H. clearances. However, Inulin and P.A.H. clearances require infusions and frequent blood samples. Moreover, these investigations were carried out almost exclusively on patients suffering from chronic infection of the urinary tract in later stages following spinal cord injuries. On the other hand, although the blood urea and the urea clearance tests are more convenient to perform, their validity as tests of renal function has been criticised (De Wardener, 1961; Wrong, 1962; Berlyne *et al.*, 1964).

In the present paper an account is given of a comparative study on the endogenous creatinine and urea clearances as well as serum creatinine and blood-urea as tests of renal function in paraplegic and tetraplegic patients. The patients were studied at various stages following spinal cord injuries. Special attention was paid to the study of patients in the immediate and very early stages after spinal cord transection.

Clinical Material. Twenty-eight patients were examined: 26 resulted from trauma of the spine. One patient had a haemangioma and another had multiple sclerosis. They were all men aged between 15 and 59. With the exception of three,

all had complete lesions at various levels ranging from C5 to S2. They can be conveniently divided into two groups. The first group, called 'acute' cases, consists of 10 subjects who were first examined within three days of sustaining a complete lesion of the spinal cord between the fifth cervical and the third lumbar segments. They were studied on at least four successive days and six were followed up from 13 to 32 days after injury.

The second group, called 'chronic' cases, consists of 18 subjects with renal impairment. Three of these had developed their renal impairment within 14 months of injury. The remaining 15 subjects were studied $5\frac{1}{2}$ to 20 years after they had developed their cord lesion. All patients in this group were suffering from chronic pyelonephritis with recurrent pyrexial attacks, persistent positive urine cultures and proteinuria. Some had calculosis, hypertension, vesico-ureteric reflux, or hydro- or pyonephrosis as shown by pyelography or at operation. In 11 of these subjects a diagnosis of amyloidosis was established either by rectal biopsy or post-mortem. In one of these (T. H.), a man aged 41 with a T12 lesion, amyloidosis was diagnosed by rectal biopsy as early as 19 months after injury.

Analytical Methods. A total of 121 creatinine clearance tests and 99 urea clearance tests have been performed. Creatinine clearances were carried out over 24-hour periods in all cases. Urea clearances in the chronic cases and in four of the acute cases were carried out over two one-hour periods; in the remainder of the acute cases 24-hour collections were used. In all cases except C. L., who passed urine by expression of the bladder, urine was obtained by catheter.

Urine creatinine was determined by the method of Bonsnes and Taussky (1945), which is based on the Jaffe reaction. Immediate analysis of the urine was not crucial as it was found that after standing for four days at room temperature, the changes in creatinine concentration of 10 random specimens ranged from -2 to $+4$ mg./100 ml., with an average of $+0{\cdot}8$ ml./100 ml. Urine urea was determined on the autoanalyser by a diacetyl method in the majority of cases; in a limited number of the acute cases it was measured by the hypobromite method. It is recognised that the latter method does not give as accurate results as the diacetyl method. A much more serious source of error in determining the urinary urea arises from the presence of urea-splitting organisms (*e.g.* Proteus), in the bladder, leading to breakdown of urea before and after voiding, with the result that it is impossible to be certain that an accurate estimate of the urea output is being obtained.

One sample of blood was taken during the period of urine collection and analysed for creatinine by the method of King and Wooton (1956), in which the effect of interfering chromogens is minimised by adsorption on Lloyd's reagent prior to the carrying out of the Jaffe reaction. The drawback of this method, in the non-specificity of the colour reaction, is recognised, but it is the best available for routine use. Blood urea was determined on the autoanalyser by the diacetyl method.

In four of the chronic patients with amyloidosis the ability to concentrate urine was investigated by depriving them of food and drink from 7 p.m. the previous evening until 10 a.m. on the day of investigation. Separate hourly specimens of urine were taken from 7 a.m. until 10 a.m. The osmolality of the urine was determined on an advanced osmometer.

The results have not been corrected for surface area; this is never measured directly but is derived from a formula incorporating the height and weight of the patient. The clinical state of the acute cases and the presence of traction apparatus in tetraplegic patients precluded their being weighed. Moreover, the retention of fluid in the early stage, in particular following spinal cord injuries at higher level, could have led to considerable fluctuations in weight. In the chronic cases the pathological changes in the kidneys were generally of such a degree that such correction seemed superfluous.

RESULTS

(a) *Acute Cases.* Five of the ten acute cases were examined as soon as within 24 hours of injury, three within 48 hours of injury, and two within 72 hours of injury. Follow-up studies were carried out for a minimum of four days. The results of the parallel clearance studies on these 10 acute cases are shown in Table I. They are arranged in order according to the level of the cord injury.

Figures are given for the serum creatinine level in mg./100 ml., the creatinine clearance in ml./min. (performed on 24-hour specimens of urine), the blood urea concentration in mg./100 ml. and the urea clearance as percentage of average normal.

In six patients (T. J., G. McH., L. S., N. L., D. A. and W. G.) together with the final clearance on D. W. the urea clearance tests were performed over 24 hours. In the remaining four patients (S. I., D. K., D. W. and R. T.) the urea clearance tests were performed over two consecutive one-hour periods; the results for these periods are presented in brackets preceded by the average values. In most clearances the urine flow was less than 2 ml./min. and every subject had at least one clearance study when the urine flow was less than 1 ml./min. The Van Slyke formula was used to correct for this.

On three occasions (S. I. third day, D. K. fourth day and D. W. third day) it was impossible to collect two one-hour specimens of urine, because the catheters were blocked; accordingly, no figures are given for those days. On five other occasions (S. I. fourth day, D. K. first day, D. W. second day and R. T. fourth and sixth days) there was such a divergence between the urea clearance values obtained during the two separate one-hour periods that the tests were regarded as technically unsatisfactory and no average figure for urea clearance has been given; the reasons for these discrepancies were gross differences in the volumes and urea concentrations in the two specimens. Taking the lower limit of normal for urea clearance as 70 per cent. average normal, there were seven low-urea clearance values, but there were 12 other instances in which no value has been recorded for various reasons. Bearing in mind the fact that the Van Slyke correction formula had to be used, the poor correlation of the one-hour tests and the inherent error of a 24-hour urea clearance test, it was not thought profitable to pay too much attention to the urea clearance.

In only two cases (T. J. and D. K.) was a serum creatinine level found above the normal maximum (1.2 mg./100 ml.). In each case this was on the first day after injury. Taking the lower limit of normal for creatinine clearance in men as 78 ml./min. (Tobias, McLaughlin & Hopper, 1962), seven of the creatinine clearance figures in Table I were below normal. It may be noted that the abnormally low creatinine clearance figures coincided only in two cases (T. J. and D. K.) with increased serum creatinine levels, while in the other cases (G. McH., L. S. and D. A.) the serum creatinine was within normal limits.

Only two patients (R. T. and D. A.) did not show on at least one occasion a blood urea level above a widely accepted normal limit of 40 mg./100 ml. (Varley, 1954). One patient (D. K.), who had a fractured pelvis and large haematomata in the groins, showed a figure of 83 mg./100 ml. on the first day after injury. The final column gives some clinical details, from which it can be seen that the two patients had normal blood urea concentrations throughout, had minor abrasions only in addition to their cord injury, whereas four of the remaining patients with raised blood

TABLE I

Acute Complete Lesions

Name	Age	Lesion	Days after Injury	Creatinine		Urea		Additional Injuries
				Serum (mg./100 ml.)	Clearance (ml./min.)	Blood (mg./100 ml.)	Clearance (% average normal)	
T. J.	24	C5	1	2·0	57	54	69	No other injuries. Previously fit.
			2	1·1	151	37	140	
			3	1·1	148	33	120	
			4	1·1	143	49	69	
G. McH.	31	C5	3	0·8	215	41	126	Cerebral concussion. Minor abrasions only.
			4	1·0	76	41	66	
			5	0·9	176	—	—	
			6	1·0	56	41	48	
S. I.	42	C7	1	1·0	148	54	76 (66; 91)	Previously fit. Minor abrasions only.
			2	1·0	140	54	61 (80; 43)	
			4	1·0	247	49	* (12; 105)	
			5	1·0	154	—	—	
			6	0·9	175	59	119 (120; 118)	
			9	0·8	188	62	96 (88; 105)	
			15	0·8	101	49	—	
L. S.	44	C8	2	1·0	66	48	96	Previously fit. Cerebral concussion.
			3	0·7	100	50	92	
			4	0·8	99	42	95	
			5	1·0	88	41	120	
			6	0·8	57	35	76	
			17	0·7	94	34	—	
			19	0·9	127	38	90	
			21	0·7	151	39	97	
			24	0·6	99	27	61	
			28	0·9	109	26	90	
M. L.	15	T6	3	0·9	149	—	—	Head Injury, concussion, fractured skull and pneumothorax.
			4	0·9	141	54	112	
			5	0·8	118	51	101	
			6	0·8	139	55	117	
D. K.	19	T10	1	2·7	73	83	* (12; 62)	Severe fracture and disruption of pelvis with injury to urethra; bilateral haematomata in groins.
			2	0·9	190	47	120 (102; 138)	
			3	0·8	120	34	136 (143; 129)	
			5	0·7	156	39	129 (118; 140)	

			6	1·1	102	40	93 (108; 79)	
			9	0·7	162	45	122 (133; 111)	
			11	0·7	160	32	146 (139; 154)	
			13	0·7	152	37	143 (147; 139)	
			16	0·7	140	40	101 (96; 107)	
			23	0·9	99	33	175 (154; 197)	
			31	0·7	122	50	68 (48; 89)	
D. W.	24	L2	1	0·9	125	38	140 (117; 164)	Fractured femur.
			2	0·7	147	45	— (15; 209)	
			4	0·7	231	40	121 (152; 91)	
			5	0·7	174	48	249 (255; 243)	
			6	0·6	176	40	235 (205; 266)	
			13	0·6	148	28	142	
R. T.	49	L3	1	0·8	160	39	81 (111; 51)	Abrasions only.
			2	0·6	149	37	223 (246; 200)	
			3	0·6	147	38	220 (157; 284)	
			4	0·6	105	39	* (515; 147)	
			5	0·6	149	39	132 (144; 121)	
			6	0·5	167	37	* (795; 221)	
			8	0·6	136	30	202 (180; 224)	
			14	0·6	129	27	139 (141; 137)	
D. A.	31	L3	2	0·7	66	25	148	Abrasions only.
			3	0·8	132	23	161	
			4	0·7	166	26	186	
			5	0·7	111	28	153	
			6	0·5	181	33	166	
			7	0·5	166	32	160	
			8	0·5	163	36	148	
			9	0·6	167	—	—	
			13	0·6	149	28	140	
			17	0·6	209	24	166	
			20	0·7	137	22	149	
			24	0·6	115	26	118	
			32	0·6	108	24	84	
W. G.	26	L3	2	0·8	191	42	127	Potts fracture with massive haematoma.
			3	0·8	224	38	150	
			4	0·7	243	—	—	
			5	0·6	199	39	169	

Urea clearance figures for T. J., G. McH., L. S., M. L., D. A., W. G. and the last test on D. W. are based on 24-hour urine collections only. In the remaining patients, S. I., D. K., D. W. and R. T. the average figures are based on two one-hour collections of urine (values given in brackets). In the five instances marked with an asterisk, the discrepancy between the two one-hour urea clearances was so great that the figures were regarded as technically unreliable; therefore, no average figure has been given.

urea levels had obvious major injuries from which the absorption of haematoma could be expected to cause a pre-renal azotaemia.

(b) *Chronic Cases*. Eighteen patients were suffering from chronic pyelonephritis. There were two groups: the first group concerned five patients who were injured at least 10 years previously and 10 patients who were diagnosed either by rectal biopsy or post-mortem as suffering from amyloidosis. The results obtained are shown in Table II.

Four of the five patients without signs of amyloidosis (C. H., G. B., C. L. and B. J.) had raised serum creatinine values and creatinine clearances below the normal range. There was a poor correlation between the blood urea levels and the urea clearance figures. In these cases and in the cases L. H. and C. L. the blood urea was found to be normal although the urea clearance was pathologically low. It is of interest that G. T. L., who had been injuried for 20 years, had normal blood and clearance values of both creatinine and urea in spite of long-standing infection leading to renal calculosis, hydronephrosis and bilateral reflux.

The ten cases suffering from amyloidosis can be divided into: (*a*) those in terminal renal faulure (H. M., M. F., P. R., W. C. and G. A.) in whom, as one would expect the blood values are greatly raised and the clearance figures extremely low, and (*b*) the remaining five (G. W., K. W., G. M., P. O'D. and W. B.), all but one (P. O'D.) of whom had normal blood values and only slightly or moderately impaired clearance figures. Case P. O'D. appeared to be more severely affected, with raised blood values and very low clearance figures. Additional studies of tubular function were carried out on the four less severely affected cases (G. W., K. W., G. M. and W. B.) where in all cases an impaired concentrating ability was found as none could raise the osmolality of the urine above 577 mOsm./kg. (normal, 750 mOsm./kg., De Wardener, 1956).

The second group of chronic cases consists of three patients who showed signs of renal impairment within 14 months of injury. Table III gives the details and is arranged in a similar manner to Table I. The reasons why these patients developed such early renal impairment are of the greatest interest and importance.

D. B. had in addition to his spinal cord injury at T5, a large haemothorax; two days after injury his serum creatinine and blood urea were raised and creatinine clearance was below normal. The serum creatinine and blood urea had fallen by the 11th day, but the creatinine clearance had not altered. He developed a persistent urinary infection after two months and a cystogram at six months showed reflux on the right. At that time his serum creatinine (1·1 mg./100 ml.) was in the upper range of normal, his creatinine clearance (86 ml./min.) was low normal, the blood urea (32 mg./100 ml.) was normal, and the urea clearance (48 per cent. av. normal) was low. The infection proved resistant to all forms of treatment and he now uses an indwelling catheter. By seven and a half months the serum creatinine was normal but the clearance had fallen to its lowest value (40 ml./min.) and although the blood urea was normal, the urea clearance was also low (57 per cent. av. normal). It would appear that the persistent infection is not limited to the lower urinary tract but has affected the functional integrity of the kidney.

T. H. is in contrast with the previous case in that, following his cord lesion at T12, his bladder was well rehabilitated and he was discharged from hospital eight months after injury with a blood urea of 41 mg./100 ml. and with sterile urine, wearing a condom urinal. He was readmitted after a further five months with a residual urine of 20 oz. and little secretion on the I.V.P. His urine was infected and there was proteinuria. Since that time there has been a persistent impairment of renal function as shown by the raised

TABLE II

Long-standing Chronic Cases

Patient	Age	Lesion	Time after Injury	Relevant History	Creatinine		Urea	
					Serum (mg./100 ml.)	Clearance (ml./min.)	Blood (mg./100 ml.)	Clearance (% average normal)
C. H.	36	T3 compl.	19 years	Injured at 17. Immediate suprapubic cystotomy. Closed after 2 years. Automatic micturition established. Persistent infection and hydronephrosis. Hypertensive since 27, B.P. 200/140. Nephrectomy at 35; at present working on clock repairs.	1·2	64	26	65
G. T. L.	39	T6 compl.	20 years	Injured at 19. Immediate suprapubic cystotomy. Closed after 5 years. Passing automatically. Persistent infection. Sheltered work at home. Normotensive.	0·8	123	20	100
G. E.	59	T9 compl.	10 years	Injured at 49. At 56, micturition by straining. Bilateral calculi and hydronephrosis; stone removed from left kidney. At 57 bilateral reflux; indwelling catheter. At 59 stone removed from right kidney. Not working.	2·7 2·2 2·2 1·8 2·0 1·8	23 27 22 29 26 27	88 74 59 46 44 39	19 23 25 30 20 29
C. L.	40	L3 compl.	18 years	Injured at 22. Immediate suprapubic cystotomy. At 24, calculi removed from right kidney. At 27 suprapubic discontinued. Micturition by expression. Persistent infection. Sheltered work (carpentry).	2·5	27	26	42
B. J.	41	S2 compl.	19 years	Injured at 22. Immediate suprapubic cystotomy, subsequently discontinued. Expressed urine. Remained sterile until 32, since then persistent infection and hypertension. B.P. 150/100. At 38, hydronephrosis. Civil servant at the Ministry of Health.	1·5	69	41	74

TABLE II (*continued*)

Patient	Age	Lesion	Time after Injury	Relevant History	Creatinine		Urea	
					Serum (mg./100 ml.)	Clearance (ml./min.)	Blood (mg./100 ml.)	Clearance (% average normal)
H. M.	48	C6 compl.	13 years	Injured at 35. Severe pressure sores with osteomyelitis. Automatic micturition for next 12 years with normal I.V.P. but persistent infection. Epileptic fits at 47. Admitted at 48 with blood urea of 54 mg./100 ml., rising to 175 mg./100 ml. Amyloidosis diagnosed by rectal biopsy. Normotensive. Died at home.	3·6 2·9	6 7	144 103	8 12
G. W.	59	T2 compl.	6 years	Injured at 53. Persistent urinary infection but normal I.V.P. Pressure sores with osteomyelitis. Oedematous: Serum albumin 1·9 g./100 ml., serum globulin 3·65 g./100 ml. Proteinuria 4·9 g./24 hrs. Amyloidosis (rectal biopsy). Normotensive. Maximum urine concentration 552 mOsm./kg.	0·8 0·7	69 79	31 —	44 —
K. W.	32	T6 compl.	12 years	Injured at 20. Immediate suprapubic cystotomy. Vesical stones. Pressure sores with osteomyelitis. Serum albumin 3·2 g./100 ml.; serum globulin 4·1 g./100 ml. Proteinuria 7·5 g./24 hrs. Amyloidosis (rectal biopsy). Maximum urine concentration 459 mOsm./kg.	0·8 0·7	34 65	30 29	33 26
M. F.	32	T7 compl.	6 years	Injured at 26. Pressure sores with osteomyelitis. Automatic micturition. At 31, oedematous; serum albumin 0·9 g./100 ml.; serum globulin 200 g./100 ml. Proteinuria 12·8 g./24 hr. Positive Congo Red test; positive rectal biopsy. Died after subarachnoid haemorrhage. Amyloidosis confirmed.	3·8	19	99	—
P. R.	31	T7 compl.	10 years	Injured at 21. Automatic micturition. At 26, hydronephrosis left, no secretion on right; bilateral reflux; diverticula of bladder. At 31, hypertensive retinopathy. Post-mortem diagnosis of renal amyloidosis.	5·2 4·9 9·3 10·1	10 8 2 2	67 70 109 156	11 12 8 4

G. M.	27	T10 compl.	8½ years	Injured at 19. Pressure sores with osteomyelitis and a periurethral abscess. Suprapubic cystotomy performed. Hydronephrosis, hydroureter and diverticula. Oedematous; serum albumin 0·4 g./100 ml. serum globulin 2·4 g./100 ml. Serum cholesterol 450 mg./100 ml. Proteinuria, 13·6 g./24 hr. Amyloidosis (rectal biopsy). Maximum urine concentration 528 mOsm./kg.	0·7 0·8 0·7	86 65 73	30 29 38	— — 34
P. O'D.	48	T11 compl.	6 years	Haemangioma of cord at 42. Pressure sores with osteomyelitis. Discharged at 45 with automatic bladder, sterile urine and bilateral hydronephrosis. At 48, B.P. 150/100. Proteinuria 2g./24 hr. Amyloidosis (rectal biopsy).	2·8 2·9	15 23	99 66	11 20
W. C.	56	T12 compl.	19 years	Injured at 37. Immediate suprapubic cystotomy. Infected urine. At 46, B.P. 175/110. At 52, nephrectomy for renal calculus; at 53, pressure sores; serum albumin 3·6 g./100 ml. serum globulin 3·7 g./100 ml. At 54, proteinuria 2·8 g./24 hr. Admitted terminally, confused and obliguric. Post-mortem amyloidosis.	6·8	3	100	—
G. A.	55	L3 incompl.	15 years	Injured at 40. Pressure sores. Dribbling incontinence of urine. At 43, hydronephrosis. B.P. 220/150; at 45 indwelling catheter. Amyloidosis (rectal biopsy). Died at 55, chronic pyelonephritis and renal amyloidosis.	5·1	11	90	10
W. B.	43	Multiple Sclerosis	20 years	Diagnosed as multiple sclerosis at 23. Unable to walk by 38. At 39, sores causing osteomyelitis I.V.P. showed vesical calculus; serum albumin 2·1 g./100 ml. serum globulin 3·35 g./100 ml. Amyloidosis (rectal biopsy). Maximum urine concentration 577 mOsm./kg.	0·5 0·4	81 72	24 18	77 —

serum creatinine and blood urea and the reduced creatinine clearance. A diagnosis of amyloidosis was made by rectal biopsy 19 months after injury.

I. M. showed a response similar to other cases in the first days after injury (cf. Table I); he had a normal serum creatinine level, all three creatinine clearances were normal, two blood urea levels were above normal and the urea clearance was normal. He developed a severe urinary infection at eight weeks; subsequently a dilated right ureter was found. At 19 weeks he had a severe exacerbation of his urinary infection, his blood urea rising to 204 mg./100 ml. The severe impairment of renal function is shown by the serum creatinine of 2·0 mg./100 ml., with a clearance of 41 ml./min. His subsequent improvement under intensive therapy can be seen in the falling serum creatinine and blood urea levels and the rising creatinine clearance.

DISCUSSION

From all the data given in this paper it would appear that in the acute cases urea clearance is not a suitable test of renal function, as the rate of urine secretion is generally much less than 2 ml./min. owing to fluid retention, especially in high lesions, and cannot be increased by increasing the water intake. When urine is secreted at these low rates the proportion of urine reabsorbed in the tubules is increased. Various formulae have been devised to allow for this, but they do not express the true clearance. In our cases when the urine flow was less than 2 ml./min. we used the formula of Van Slyke $\frac{U}{B}\sqrt{V}$. As can be seen from Table I when two one-hour collections were used there was generally a definite discrepancy between the clearances for the two consecutive hours. We had to use 24-hour collections in some urea clearance tests, as some of the patients were on intermittent catheterisation and were secreting low volumes of urine.

The endogenous creatinine clearance does not suffer from these disadvantages since the clearance does not vary with the urine flow. As the serum of creatinine remains stable for long periods (Tobias *et al.*, 1962) 24-hour level collections can be used minimising the inaccuracy of the clearance test arising from the technique of urine collections and from careless timing. The greater stability of creatinine in urine as compared with that of urea is an additional advantage.

Miller and Winkler (1938) introduced endogenous creatinine clearance tests and this has been widely used as a measure of glomerular filtration rate. While in healthy individuals the clearance gives values essentially the same as those determined by inulin clearance, it is controversial whether this is the case in disease. Tjan *et al.* (1963) used creatinine clearance tests to study the question of acute and chronic renal disease in non-paraplegic patients. Graber and Sevitt (1959) used the creatinine clearance as a measure of glomerular filtration rate in oliguric patients following severe burns and presented evidence to show that the ratio $\frac{\text{creatinine clearance}}{\text{inulin clearance}}$ is the same in a wide variety of conditions including surgical shock following trauma.

On the other hand Berlyne *et al.* (1964) found in five out of six cases with mild impairment of renal function (five nephrotic and one with hypertension) gross discrepancies between glomerular filtration rate measured by inulin clearance and that measured by creatinine clearance and came to the conclusion that endogeneous creatinine clearance was not a reliable measure of glomerular filtration rate in their cases.

TABLE III

Patients with Early Renal Impairment

Name	Age	Lesion	Days after Injury	Creatinine		Urea		Clinical Details of Progress
				Serum (mg./100 ml.)	Clearance (ml./min.)	Blood (mg./100 ml.)	Clearance (% average normal)	
D. B.	33	T5 compl.	2	3·6	61	173	—	Previously fit, fractured ribs and haemothorax in addition to spinal cord injury. After 60 days developed persistent urinary infection with reflux on the right and delayed secretion on the left. Uses indwelling catheter.
			11	1·6	60	69	—	
			185	1·1	86	32	48	
			233	0·9	40	28	57	
T. H.	41	T12 compl.	405	1·7	44	81	24	Admitted within 10 days of injury, urine rendered sterile; discharged with blood urea 41 mg./100 ml. 252 days after injury. Re-admitted 150 days later with residual of 20 oz., little secretion on I.V.P. Infected urine, proteinuria; treated by tidal drainage. Amyloidosis (rectal biopsy).
			472	1·3	67	36	44	
			580	2·0	50	46	—	
			682	1·7	56	62	29	
I. M.	33	T12 incompl.	2	0·9	125	32	93	Previously fit, sustained penetrating wound of his spinal cord, no other injuries; urine remained sterile for 56 days with a normal cystogram; it then became infected and at 108 days his bladder was contracted with diverticula; right ureter dilated. On the 133rd day a severe urinary infection with residual urine 20 oz. with a blood urea of 204 mg./100 ml. Was given indwelling catheter which he has used subsequently. Discharged home 162 days after injury.
			4	0·9	85	43	92	
			5	0·9	115	54	104	
			137	2·0	41	84	—	
			139	1·5	50	54	35	
			140	1·5	50	45	34	
			141	1·4	56	38	44	
			142	1·3	51	37	35	
			144	1·2	60	23	40	
			145	1·3	51	24	34	
			147	1·2	55	19	39	
			160	0·9	78	24	52	

The major disadvantage of creatinine clearance tests lies in the difficulty of deciding what is actually measured in the serum. The use of Lloyd's reagent with a filtrate produced from a mixture of serum and protein precipitants in the recommended proportion 'provides at present the most satisfactory method in the determination of creatinine' in serum (Owen, *et al.*, 1954). Bearing this in mind we found that the creatinine clearance test gave reproducible results.

In the group of acute cases we studied the effect of the level of the spinal cord transection on the renal function. In particular, we were interested whether or not the sudden interruption of the sympathetic control in complete lesions above T5 and in cervical lesions had any influence on renal function. No other work on this problem seems to have been published so far. Our findings clearly indicate that the level of the cord injury does not influence the creatinine clearance. The creatinine clearance as a reflection of glomerular filtration rate was found to be remarkably normal in the early stages following cord transection, thus indicating that the continuity of the spinal cord with the brain stem and the segmental innervation of the kidneys is not essential for the maintenance of a normal glomerular filtration rate. It is possible that the abnormal creatinine values on the first day after injury in T3 and D. K. (Table I) are due to severe traumatic shock. In contrast, the blood urea level was profoundly raised in the early days following spinal injury as a reflection of tissue breakdown resulting from more or less large haematomata and other associated injuries of the spinal cord lesion.

In the chronic cases we were studying the effects of chronic urinary infection on renal function. Our findings of low creatinine clearance in these cases confirm the results of other workers in this field, suggesting as the main cause of damage chronic pyelonephritis (Rogers & Bors, 1950; Morales *et al.*, 1956; Magee, 1957, 1958). Morales *et al.* and Magee in serial studies using the inulin clearances test as a measure of glomerular filtration rate found a progressive decrease in the clearance. Our findings in the chronic cases are in accordance with this work. The terminal cases of chronic renal infection all showed a low glomerular filtration rate, and there was a good agreement between creatinine clearance and urea clearance tests. In the other chronic cases including those in whom a diagnosis of amyloidosis was made by rectal biopsy, the various figures were not generally severely reduced, but the presence of tubular damage in four instances could be deduced from the marked impairment of concentrating ability. That renal damage may occur within as short a time as 14 months is well brought out by the three cases reported above (Table III).

Finally, attention is drawn to a major error which, in any clearance study in paraplegic and tetraplegic patients may be caused by the technique of urine collection. When urine secretion over a given period of time is not completely recovered from the bladder large errors may be introduced into the calculation. It is well known that in paraplegic patients who are not catheterised the residual urine may be as high as 300 ml. Even when a catheter is inserted it may be difficult to empty the bladder completely, in particular in flaccid lesions. Smith (1951) suggested washing out the bladder with saline and subsequent expulsion of this by air in order to achieve complete emptying. It was found in this and other spinal centres for some time that in the recumbent paraplegic patient the lowest point of the bladder is not necessarily drained by the catheter and that further urine may be obtained by abdominal expression of the bladder or at sitting or standing such a patient up. Rosenheim (1963) has emphasised that when reflux is present further urine may be

obtained after the act of micturition has been completed. Guttmann (1963) has pointed out that in paraplegics and tetraplegics in whom bladder infection can be avoided and the urine remains sterile, the incidence of reflux is either non-existent or very rare, but there is no doubt that the incidence of reflux amongst paraplegics with infected urinary tract is appreciable and can be a further source of error.

We have examined the problem of residual urine in 20 patients. In 10 the bladders were drained and expressed when the patients were in the recumbent position, and as their clinical condition precluded their standing the head of the bed was elevated two feet and the procedure repeated. The greatest quantity of urine thus obtained was 16 ml. In 10 chronic patients with indwelling Foley catheters, who were already able to stand in parallel bars or on crutches, the bladders were first drained while they were recumbent on a couch, and then aspirated by syringe. Finally the patients stood between parallel bars and the procedure was repeated. The volume of urine obtained varied from 0 ml. to 14 ml. Therefore, while in patients who are catheterised the error in urine collection may be smaller, in the chronic patients who are expressing their bladder or passing automatically the presence of considerable residual urine would suggest that clearance studies in paraplegics may be useless unless a catheter is used.

Summary

Comparative studies on the endogenous creatinine and urea clearances were undertaken in 28 paraplegic and tetraplegic patients. The patients were studied at various stages following spinal cord injury. Special attention was paid to the renal function in the immediate and very early stages after spinal cord transection.

The creatinine clearance test was found superior to the urea clearance test as a measure of glomerular filtration rate.

No significant influence of the level of the spinal cord transection on renal function was observed.

In the acute stages glomerular filtration rate as indicated by the creatinine clearances test was found remarkably normal. In contrast the blood urea level was profoundly raised as a reflection of the tissue breakdown.

Our findings of low creatinine clearance in the chronic cases were in accordance with the results of other workers in this field, indicating that the main cause of renal damage is chronic pyelonephritis.

Résumé

Les études comparatives des clearances endogènes de la créatinine et de l'urée ont été entreprises chez 28 paraplégiques et tétraplégiques.

Ces malades ont été étudiés à différents moments après l'atteinte médullaire.

L'étude de la fonction rénale a été spécialement étudiée, immédiatement après et dans la phase aiguë, suivant l'atteinte médullaire.

Le test de clearance à la créatinine a été trouvé comme plus indicatif que celui de l'urée comme mesure du taux de filtration glomérulaire.

Aucune influence significative du niveau de l'atteinte médullaire par rapport à la fonction rénale n'a été observée. Au stade aigü, le taux de filtration glomérulaire indiqué par la clearance à la créatinine était remarquablement normal. Par contre, le taux d'urée sanquine était considérablement élevé, ceci réfléchissant les perturbations cataboliques tissulaires.

Nos résultats sur l'abaissement de la clearance à la créatinine, dans les cas chroniques, en comparaison avec les résultats des autres chercheurs dans ce domaine, indiquent que la pyélonéphrite est la principale cause de l'atteinte rénale.

ZUSAMMENFASSUNG

Vergleichende endogene Kreatinin und Urea Ausscheidungsstudien wurden an 28 Paraplegikern und Tetraplegikern ausgeführt. Die Patienten wurden in verschiedenen Stadien nach der Rückenmarksverletzung untersucht. Besondere Aufmerksamkeit wurde der Nierenfunktion in den Frühstadien der Querschnittslähmung gewidmet.

Die Kreatinin-Ausscheidungsmethode war der Urea-Ausscheidungsmethode überlegen.

Ein Einfluss der Höhe der spinalen Läsion auf die Nierenfunktion wurde nicht gefunden.

In den acuten Stadien war die glomuläre Filtrationsrate im allgemeinen normal. Dagegen waren Ureawerte im Blut erheblich erhöht als Ausdruck von Gewebszerstörungen.

Unsere Befunde einer erniedrigten Kreatinin-ausscheidung in den chronischen Fällen stimmen mit denen anderer Autoren überein und bestätigen als Hauptursache der Nierenschädigung die chronische Pyelonephritis.

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