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ENDOGENOUS CREATININE CLEARANCE*

A Valuable Clinical Test of Glomerular Filtration and a Prognostic Guide in Chronic Renal Disease

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FOR many years creatinine clearance has been used as an estimate of glomerular filtration rate. In 1926 Rehberg[1] first suggested that exogenous creatinine clearance could be used for this purpose. Shannon,[2] however, in 1935, demonstrated exogenous creatinine clearance at high plasma levels of creatinine to be greater than inulin, because of tubular excretion of some creatinine at these high levels. Two years later Popper and Mandel[3] first suggested the use of endogenous creatinine clearance (C_{cr}) as a measure of glomerular filtration rate. In 1938 Miller and Winkler[4] were able to measure accurately the normal low serum levels of endogenous creatinine. They established that C_{cr} in normal subjects was usually equal to inulin clearance. Nevertheless, C_{cr} was not widely accepted as a clinical measure of glomerular filtration rate until 1940, when Steinitz and Türkand,[5] followed in 1948 by Brod and Sirota,[6] showed that excretion of endogenous creatinine was largely dependent on glomerular filtration and closely approximated the glomerular filtration rate as measured by inulin in both normal subjects and those with impaired renal function.

Inulin clearances are generally accepted as the most accurate method for the estimation of glomerular filtration rate.[7] Unfortunately, the technics required are complicated to perform and generally useful only as a research tool. The C_{cr}, on the other hand, does not possess these practical limitations and, because of reasonably close correlation with inulin, is well suited for general clinical use. De Wardener[8] has lucidly described the simplicity, the pitfalls and the advantages of using C_{cr} as compared with inulin and urea clearances.

The present study was undertaken to evaluate the clinical significance of endogenous creatinine clearance in chronic renal disease. Serum creatinine and C_{cr} were measured in healthy subjects and patients with various forms of chronic renal disease. Comparisons have been made between these and other commonly employed tests of renal function. The C_{cr} has been found to provide a good index of glomerular filtration and, when used serially in patients with chronic renal insufficiency, a valuable guide to prognosis.

Methods and Selection of Healthy Subjects and Patients

Timed urine collections for the determination of creatinine were usually made overnight from about 7 p.m. to 7 a.m. We have successfully used both longer and shorter periods, from twenty minutes to twenty-four hours, as others have.[9-12] Although the duration of collection is not critical precise timing to the closest minute is essential. With periods as short as an hour, to avoid the need of catheterizing the urinary bladder it is important to have a good diuresis induced by water[9]; also, in our experience C_{cr} tends to be impaired at low urine flows. If a low urine volume is obtained during the timed period, assuming normal urine volume to be approximately 1500 ml. per twenty-four hours, incomplete collection or insufficient urine flow (as a result of suboptimal hydration) should be suspected. The determination of clearance should then be repeated after the patient has been reinstructed. To ensure good emptying of the bladder and accurate collections, subjects were requested to void when the bladder was full enough to produce a natural urge, both in the evening to start (this specimen was discarded) and in the morning to end the collection period. In the morning the

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urine specimen was submitted to the laboratory, together with measurements of the subject's height and weight, so that the clearance value could be corrected to a constant body-surface area of 1.73 square meters. A fasting blood sample was then drawn. Serum and urinary creatinine were determined according to Peters's modification of the method of Folin and Wu.[13] Inulin clearances were measured by standard technics.[7] Inulin was determined by the method of Roe, Epstein and Goldstein.[14]

TABLE 1. *Serum Creatinine Concentration and Endogenous Creatinine Clearance in 78 Normal Men and 24 Normal Women.**

	MEN		WOMEN	
	SERUM CREATININE *mg./100 ml.*	CREATININE CLEARANCE† *ml./min.*	SERUM CREATININE *mg./100 ml.*	CREATININE CLEARANCE† *ml./min.*
Range	1.0-1.6	72.0-141.0	0.8-1.4	74.0-130.0
Mean	1.274	105.4	1.09	95.4
Standard error	0.014	1.57	0.03	3.67
Standard deviation	0.122	13.9	0.145	18.0

*Taken from Hopper,[15] by permission of Lange Medical Publications; subjects included medical students, technicians & physicians, 19-52 yr. of age.

†Corrected to surface area of 1.73 square meters.

TABLE 2. *Range of Serum Creatinine Concentration, Urinary Creatinine Excretion and Creatinine Clearance in a Healthy Male (J.H.).*

DATE	SERUM CREATININE		URINARY CREATININE*		CREATININE CLEARANCE	
	DAY	NIGHT†	DAY	NIGHT	DAY	NIGHT
	mg./100 ml.	*mg./100 ml.*	*gm./24 hr.*	*gm./24 hr.*	*ml./min.*	*ml./min.*
12/8/48	1.5		2.40		105	
12/15/48	1.5		2.15		88	
12/22/48	1.4		2.25		112	
12/28/48	1.5		3.16		129	
1/4/49	1.5		2.12		88	
1/12/49	1.2		2.45		126	
1/19/49	1.4		3.03		134	
1/26/49	1.5		2.44		99	
2/2/49	1.4		2.38		106	
2/9/49	1.4		2.15		110	
2/17/49	1.4	1.4	2.37	2.34	104	103
2/24/49	1.4	1.4	2.40	2.40	105	104
3/2/49	1.4	1.4	2.45	2.24	108	100
3/9/49	1.5	1.5	2.31	2.23	94	93
3/16/49	1.4	1.4	2.23	2.58	98	114
6/15/49	1.3		2.45		116	
8/1/49	1.6		2.93		113	
9/14/49	1.5		2.29		94	
12/28/49	1.35‡	1.3	3.01	2.60		
11/6/51	0.9	0.9	1.94	1.91	148	147
7/16/52	1.1		2.14		115	
7/18/60	1.3		2.21		105	

*Urine collections for approximately 12 hr.; 24-hr. excretions extrapolated from a single 12-hr. sample.

†Values for serum creatinine from blood samples drawn at night before evening meal.

‡Serum creatinine levels in 5 specimens drawn before & after lunch & dinner between 1.3 and 1.35 mg./100 ml.

Normal Subjects

To establish normal values, endogenous creatinine clearances were determined in 102 healthy adults (78 men and 24 women), varying in age from nineteen to fifty-two years (Table 1).[15] In 3 healthy subjects a series of determinations were performed over an extended period. Data from 1 subject are presented in Table 2. Similar results were obtained from the other 2.

Chronic Renal Disease

By the same technics serial measurements of endogenous creatinine clearance have been used to follow patients with renal disease since 1948. Several thousand determinations of serum creatinine and creatinine clearance have been done. The 500 reference points used in plotting serum creatinine against C_{cr} (Fig. 1) were obtained from over 300 patients. We selected them by proceeding alphabetically through the Renal Service file until 500 such determinations had been plotted. Urinary output was checked in all cases, and, if it was suspiciously low for the twelve-hour period (suggesting incomplete collection), the figures were not used and the next subject was selected. Further selection was made to the extent that if the clearance was below the limits of normal that we have established with a serum creatinine that fell within normal range (Table 1) the figures were not used unless there had been a repetition of the entire test (on serum and urine at a time closely approximating the study in question), thereby corroborating it. Often, as many as three separate clearance studies had been done in rapid succession in patients who had low clearances but had serum creatinine concentrations within the range that we have established for normal.

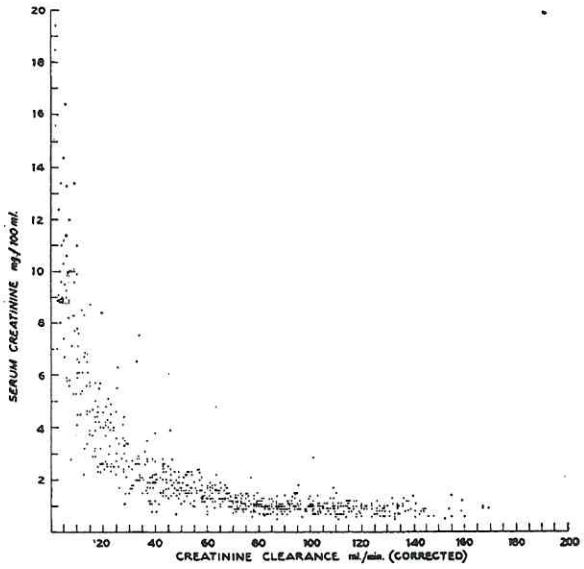

FIGURE 1. *Range of 500 Serum Creatinine Levels and Creatinine Clearance Rates in More than 300 Renal Patients.*

Cases 1 through 5 (Table 3) were selected because they had normal or near normal serum creatinines but diminished clearances. C_{cr}'s were used to

corroborate the C_{cr}'s. Cases 6 through 15 (Table 4) were used to compare C_{cr} and C_{in} over a wide range of glomerular function.

To study the value of endogenous creatinine clearance in following patients with chronic renal insufficiency, 21 patients (Cases 16 through 36 in Table 5) in whom death was directly attributable to renal failure were chosen. These patients were selected because they had been particularly well followed, from both a clinical and a laboratory point of view, for prolonged periods. When C_{cr}'s dropped to 30 ml. per minute, the determinations were repeated at least every three months, and more frequently as further deterioration occurred.

TABLE 3. *Data in 5 Cases Demonstrating the Superiority of Creatinine Clearance to Serum Creatinine as an Index of Glomerular Filtration Rate (as Established by Inulin Clearance).*

Case No.	Sex	Age	Diagnosis	Serum Creatinine	Clearance		C_{CR}/C_{IN}
					creatinine	inulin	
		yr.		*mg./100 ml.*	*ml./min.*	*ml./min.*	
1	M	19	Nephrotic state	1.3*	63.8	56.3	1.13
2	F	15	Chronic glomerulonephritis	1.1	52.0	52.0	1.0
3	M	37	Acute glomerulonephritis	1.2	58.0	62.5	0.93
4	M	70	Absent right kidney; diabetes mellitus.	1.7	31.9	34.8	0.92
5	M	16	Congenital heart disease	0.9	57.5	62.5	0.92

*8 yr. later serum creatinine again 1.3 mg./100 ml., but creatinine clearance 96 ml./min.

Results and Discussion

Normal Values

Data obtained from 102 healthy adults appear in Table 1. The values for serum creatinine are higher and C_{cr} rates lower than some appearing in the literature recently summarized by Doolan, Alpen and Theil.[10] This is because the chemical technic used in the present study for the determination of creatinine measures creatininelike chromogens as well as true creatinine. For clinical purposes the refinement of removing noncreatinine chromogen appears unnecessary.[9,16] The normal values for C_{cr} listed in Table 1 are nearly identical with those reported by Blegen, Haugen and Aas,[17] who used a technic that includes noncreatinine chromogen. Sirota, Baldwin and Villarreal[18] using a method believed to exclude some noncreatinine chromogen, obtained similar clearance values.

Repeat Determinations in the Same Healthy Person

In Table 2, data for serum and urinary creatinine and C_{cr} from 1 subject studied repeatedly over an extended period are given. It may be seen that both urine and serum creatinine and C_{cr} varied considerably in spite of constant diet and fluid intake.

Although this subject's serum creatinine level fluctuated considerably over an extended period, it should be noted that over brief periods, the level was very stable (Table 2). Similar findings have been observed by Addis[11] and others[10,16,19] during brief periods. It is particularly noteworthy that, within the range of normal, high creatinine concentrations did not necessarily correspond to low clearances.

TABLE 4. *Inulin and Creatinine Clearance during One Twenty-four-Hour Period in 10 Patients with Widely Varying Glomerular Function.*

Case No.	Sex	Age	Diagnosis	Serum Creatinine	Clearance		C_{CR}/C_{IN}
					creatinine	inulin	
		yr.		*mg./100 ml.*	*ml./min.*	*ml./min.*	
6	F	11	Nephrotic state	0.6	63.0	69.0	0.91
7	F	11	Nephrotic state	0.4	129.0	133.0	0.97
8	M	24	Nephrotic state	2.1	44.5	31.2	1.42
9	M	18	Nephrotic state	1.0	94.0	73.0	1.29
10	F	11	Nephrotic state	0.7	86.0	81.0	1.06
11	F	36	Chronic glomerulonephritis	12.4	4.6	4.2	1.11
12	F	29	Chronic glomerulonephritis	2.9	27.5	22.0	1.25
13	F	39	Unilateral hydronephrotic kidney	4.1	11.0	13.0	0.85
14	M	16	Congenital heart disease	0.9	62.0	68.0	0.91
15	M	16	Aortic coarctation	1.1	95.5	86.0	1.11

To a large extent, the presently noted long-term variations of C_{cr} in the same subjects probably represent biologic variation. The possibility that variation in C_{cr} is caused by change in serum noncreatinine chromogen is contradicted by our observation that not only serum creatinine but also the urinary excretion of creatinine (known not to contain appreciable chromogen) fluctuates. It has commonly been held that creatinine excretion is very constant[20]; however, other recent observations[21] indicate that significant fluctuations occur in both health and chronic renal insufficiency. The maximum error in chemical determination of creatinine by the technic that we have used is 4 per cent.[18] This amount is insufficient to account for the variations seen, even

if the errors in urine and serum were in opposite directions, causing a maximum error in the clearance.

That variations of clearance in the same subject are mainly biologic gains further support from the fact that clearance rates in successive periods of twelve or twenty-four hours are usually very similar.[10,11,19] Winberg[19] has shown that the error of determining C_{cr} with urines collected in successive twenty-four-hour periods is only 6.7 per cent. This relatively small error, which includes biologic variation as well, demonstrates that the chemical error in the measurement of creatinine is not large and is consistent with the 4 per cent chemical error mentioned above.

It is important to realize that a healthy person's serum and urinary creatinine and C_{cr} will vary throughout the full range of normal during any prolonged period (Tables 1 and 2). Similar observations were made by Van Slyke,[22] using the urea clearance technics, twenty years ago. He also noted that a clearance fixed at the lower limits of normal suggests the presence of renal impairment.

In this regard, comparison of the values presented in Tables 1 and 2 demonstrates that wide fluctuation of the C_{cr} in a given subject is a characteristic of normal renal function. The converse finding of a fixed C_{cr}, even though within lower normal limits, is abnormal and is likely to indicate the presence of renal insufficiency. One of our group (J.H.), in a study as yet unpublished, found marked anatomic damage in percutaneous-renal-biopsy specimens taken from patients with clearances fixed in the lower ranges of normal.

Effect of Age on Clearances

C_{cr}'s can be used both in elderly subjects[23] and in children.[19,24] If assays are used in children, for comparison with adult standards, values must be corrected to equivalent surface area.[7] Davies and Shock[23] observed that glomerular filtration tends to decline with age in healthy males, and provided a formula by which normal values can be predicted for any given age. In children, however, glomerular function does not assume adult characteristics until one to three years after birth.[19]

Effect of Pregnancy on Clearances

It has been demonstrated that C_{cr} closely parallels C_{in} in pregnancy and that they are increased.[25-27]

Endogenous Creatinine Clearance in Disease

Figure 1, which simultaneously relates serum creatinine level to the appropriate creatinine clearance, presents data from 500 clearances determined on over 300 patients. It may be seen that serum creati-

TABLE 5. *Clinical and Laboratory Data in 21 Cases* of Fatal Chronic Renal Disease.*

Case No.	Sex	Age at Death	Diagnosis	Autopsy	End-Stage Renal Function†				Average Blood Pressure for 6 Mo. before Death	Total Survival	
					Lowest specific gravity of urine	Blood non-protein nitrogen	Serum creatinine	C_{CR}		Creatinine of 30 ml./min. or below	Clearance of 10 ml./min. or below
		yr.				*mg./100 ml.*	*mg./100 ml.*	*ml./min.*	*mm. Hg.*	*mo.*	*mo.*
16	F	28	Chronic glomerulonephritis	No‡	1.005	59	5.7	9.6	240/120	26	6
17	M	18	Chronic glomerulonephritis	Yes	1.010	415	27.0	1.0	220/130	—	2
18	F	36	Chronic glomerulonephritis	Yes	1.007	260	8.0	3.0	130/80§	108	36
19	M	53	Chronic glomerulonephritis	Yes	1.005	145	10.0	6.1	210/120	7	3
20	M	52	Chronic glomerulonephritis	Yes	1.006	200	19.2	1.9	150/90§	3	1
21	M	68	Chronic glomerulonephritis	No	1.009	95	17.8	9.0	170/100	—	3
22	M	38	Chronic glomerulonephritis	Yes	1.007	124	10.8	4.1	190/120	9	1
23	F	17	Chronic glomerulonephritis	Yes	1.006	255	10.8	4.4	230/130	—	2
24	M	19	Chronic glomerulonephritis	Yes	1.002	112	9.6	6.4	130/88§	48	6
25	F	18	Chronic glomerulonephritis	Yes	1.007	152	16.4	1.6	210/130	16	7
26	F	18	Chronic glomerulonephritis	Yes	1.010	179	9.4	1.2	170/130	24	20
27	M	47	Chronic glomerulonephritis	Yes	1.006	220	9.2	4.8	220/120	3	1
28	M	38	Chronic glomerulonephritis	No	1.005	134	10.4	7.4	180/100	16	1
29	F	47	Chronic pyelonephritis	No	1.008	71	3.4	13.6	130/70§	48	—
30	M	44	Chronic pyelonephritis	Yes	1.009	141	18.8	3.8	230/150	12	4
31	F	54	Chronic pyelonephritis	Yes	1.007	203	14.0	4.2	210/125	—	6
32	M	48	Malignant hypertension	Yes	1.003	173	8.4	19.4	220/170	2	—
33	M	56	Malignant hypertension	Yes	1.007	97	3.4	11.9	240/140	4	—
34	F	15	Lupus erythematosus	Yes	1.010	288	7.4	13.2	180/120	2	—
35	F	48	Lupus erythematosus	No	1.007	102	3.8	8.3	190/100	3	2
36	F	47	Polycystic renal disease	Yes	1.005	118	6.4	9.4	140/90§	30	9

*Includes all cases in which adequate data available up to & including last 3 mo. of life & in which death clearly attributable to chronic renal failure.

†Last 3 mo. of life.

‡Renal biopsy.

§No specific antihypertensive treatment.

nine concentration can vary markedly for any specific clearance rate. This clearly illustrates that clearance can neither be determined nor estimated from creatinine concentration alone and that similar creatinine concentrations can be associated with vastly different clearances. These findings are in agreement with those shown by De Wardener[8] and by Camara et al.[12]

Recently, serum creatinine has been used to estimate glomerular filtration rate. Edwards and Whyte,[28] for example, reported that the rate can be predicted from the serum creatinine alone. Their predicted filtration rates are reportedly accurate only to within ±27 ml. per minute. Effersøe[29,30] has similarly attempted to predict creatinine clearance. Such predictions are unreliable in advanced renal insufficiency, and apparently do not explain the numerous cases shown in Figure 1, in which serum creatinine concentration fails to provide an accurate index of creatinine clearance. Table 3, showing 5 such cases checked by inulin clearance, serves to emphasize this point. It further demonstrates that C_{cr} may be diminished despite a normal serum creatinine concentration. It is noteworthy that Hamburger and Masson[31] similarly demonstrated that blood urea may lie within normal limits in the presence of diminished mannitol and urea clearances.

Prediction of glomerular filtration rate from serum creatinine alone also fails to take into account that there is no clinically accurate way of estimating urinary creatinine output, which fluctuates for reasons not well understood. Doolan, Alpen and Theil[10] have pointed out that creatinine formation is directly related to the total store of creatinine-creatine phosphate and amounts to 1 to 2 per cent of this store per day. They further stated that cases are encountered clinically in which creatinine formation is depressed independently of total-body creatine-creatinine phosphate. Hoberman, Sims and Peters[32] have shown that endogenous creatine formation can be suppressed by exogenous creatine. Goldman[33] and Goldman and Moss[34] found that creatinine production and excretion is sometimes suppressed in severe renal failure. Clearly, then, a number of factors can influence C_{cr} output. In renal failure suppression of creatinine excretion is probably related to wasting of tissues. It is of interest that the group presented in Figure 1 and Table 3 included a number of patients with considerable weight loss, and especially decreased muscle mass, resulting from such diverse causes as cancer, anorexia nervosa and liver disease, as well as different types of advanced renal disease.

Included in Figure 1 are 3 patients with low serum potassium (below 2.8 milliequiv. per liter) in whom the creatinine clearance was a much better indication of glomerular filtration rate than the serum creatinine alone.

Comparison of Endogenous Creatinine and Inulin Clearances

To demonstrate the reliability and broad range of creatinine clearance methods as an estimate of glomerular filtration rate 10 cases of widely varying glomerular function were studied by both inulin and creatinine clearances measured within the same twenty-four-hour period (Table 4). It can readily be seen that the results are closely comparable from the lowest levels of function to normal. Nevertheless, in the severer grades of renal insufficiency due to chronic renal disease, C_{cr}/C_{in} ratios tend to exceed 1, reflecting an excretion of creatinine into tubular urine.[7]

For practical clinical purposes C_{cr} can be considered equal to C_{in}, even in severe renal failure, for as De Wardener[8] pointed out, at low glomerular filtration rates, although C_{cr} tends to be 10 to 30 per cent higher than C_{in}, the absolute difference in terms of milliliters per minute is small — for example, a C_{cr} of 13 ml. per minute as compared to a C_{in} of 10 ml. per minute.

Creatinine Clearance in Comparison with Other Clinical Tests of Renal Function

C_{cr}, like C_{in}, reflects functional change in the kidneys over a remarkably broad range in contrast to other clinical tests of either tubular or glomerular function. Measurement of phenolsulfonphthalein excretion is less sensitive than C_{cr} as an index of disease, especially in severe renal insufficiency. With creatinine clearances of 20 ml. per minute or below, phenolsulfonphthalein return is often too low to be accurately determined (Table 5). Nonprotein nitrogen components of the blood are affected by a variety of extraneous factors. They may either increase or decrease in relatively advanced stages of renal damage. Even in the absence of renal damage significant elevations may occur, as in association with gastrointestinal hemorrhage. In addition to being responsive to renal function, their concentration is influenced by the rate of fluid intake, output of urine and protein catabolism. Also, nonprotein nitrogen and urea are particularly influenced by dietary protein intake, unlike creatinine concentration, which is virtually unaffected at usual levels of protein consumption.[11] Thus, measurement of these components provides a rather poor index of glomerular filtration.[7,11,20,31] Ability to concentrate the urine is also lost in advanced renal insufficiency. Diluting power is usually not lost until after concentrating power has disappeared. However, its persistence is markedly variable and correlates poorly with the actual degree of functional impairment (Table 5).

Endogenous Creatinine Clearance as a Prognostic Guide

C_{cr} is sensitive over an unusually wide range of renal damage. Determined frequently and at regular

intervals, it is particularly useful as a prognostic guide in following patients with more advanced degrees of renal insufficiency. Even relatively small changes in clearance rates are significant in these subjects. Table 5 summarizes data obtained during the last three months of life from 21 carefully studied patients with chronic renal failure and includes survival times with C_{cr} of below 30 and below 10 ml. per minute. Also recorded are average blood pressures during the last six months of life. Analysis of these data demonstrates the prognostic value of serially performed determinations of C_{cr}'s in chronic renal insufficiency.

Of these 21 patients dying in chronic renal failure 17 had creatinine clearances below 10 ml. per minute, and the values in the remaining 4 were all below 20 ml. per minute when last measured. In contrast, determinations of nonprotein nitrogen taken at the same time as the clearances showed poor correlation with either clearance or clinical condition. Three were between 50 and 100 mg., 10 between 100 and 200 mg., and 7 between 200 and 300 mg., and 1 was 415 mg. per 100 ml. Serum creatinines were also widely scattered. Three were between 3 and 5 mg., 8 between 5 and 10 mg., and 9 between 10 and 20 mg., and 1 was 27.2 mg. per 100 ml. Phenolsulfonphthalein excretion was too low to be measured in all cases except 1, in which a total of 10 per cent excretion of dye was recorded in one hour. Multiple urinalyses showed that the specific gravity in the stages of disease under consideration was 1.010 or less in all. However, diluting power to specific gravities of 1.005 or less persisted until death in 6 cases for periods of six to twenty-four months after the ability to concentrate urine above a specific gravity of 1.010 was lost. When the creatinine clearance remained below 10 ml. per minute, 15 of 17 patients with such clearances died in nine months or less. One (Case 26, Table 5) survived twenty months, and 1 rather unusual patient (Case 18, Table 5) survived for thirty-six months. Only 3 patients with creatinine clearances of 30 ml. per minute or below survived for four years or more. Each had normal blood pressure. With the exception of 2 patients with malignant hypertension, both of whom died less than eight months after the diagnosis was made, there was no correlation between clinical diagnosis and survival time. Prognosis in chronic renal disease frequently appears to depend importantly on the rate of change as well as on the actual rate of glomerular filtration and the presence or absence of hypertension. In the presence of chronic renal insufficiency a rapid decline in C_{cr} is an ominous prognostic sign and, with the addition of hypertension, survival times become even shorter.

Progressive deterioration of the creatinine clearance was noted in all these 21 cases before death. The serum creatinine concentration, however, actually showed improvement during the last six months of life in 7, possibly in part as a result of relative starvation and decreased muscle mass. In addition, the C_{cr} often provided information not apparent from change in serum creatinine alone. For example, 1 patient (Case 33, Table 5) had only a slight increase in serum creatinine (2.7 to 3.4 mg. per 100 ml.) whereas the creatinine clearance dropped sharply from 34 to 11.9 ml. per minute, thus revealing a marked decrease of glomerular filtration rate that was not accurately reflected by the small increase in serum creatinine.

In the patients with creatinine clearances below 30 ml. per minute electrolyte disturbances frequently developed. Patients with higher clearances seldom had significant electrolyte abnormalities, unless they had one of the rare qualitative tubular defects such as renal tubular acidosis, Fanconi syndrome[35] or electrolyte disturbances from nonrenal causes such as vomiting or diarrhea.

Most of these patients were able to remain active and continue their work despite C_{cr}'s below 30 ml. per minute, but in only a few cases with clearance levels below 10 ml. per minute was this possible. There was no close correlation between clinical manifestations, such as dehydration, vomiting and weakness, and the rate of creatinine clearance.

Lastly, with C_{cr} at 30 ml. per minute or below, patients tend to tolerate poorly sympatholytic antihypertensive drugs (such as hexamethonium) and saluretics (such as chlorothiazide and organic mercurials).

Case reports illustrating the usefulness of the C_{cr} in following and treating patients with chronic renal disease will appear elsewhere.

Summary

A technic of measuring creatinine clearance has been employed to study patients with various forms of chronic renal disease. A wide normal range was previously demonstrated in healthy controls. Fixation of clearance rates, even within the lower limits of normal, was noted to suggest abnormal function. As an estimate of all ranges of glomerular filtration rate, this simply performed clearance technic was found to compare favorably in accuracy and reliability with the inulin clearance, a test that is, in contrast, impractical for general clinical use. It was found that the estimate of glomerular filtration rate provided by creatinine clearance was far more accurate than that resulting from measurement of concentration of any of the nonprotein nitrogen components of the blood, including creatinine. Data from 500 creatinine clearances showed that clearance rates can be neither determined nor estimated from creatinine concentration alone and that similar creatinine concentrations can be associated with vastly different clearance rates. The endogenous creatinine

clearance was found to provide more information regarding functional status than any other single clinical test commonly used in the study of renal insufficiency. This test, followed over a long period, proved to be a valuable prognostic guide in the clinical study of 21 patients dying directly as a result of chronic renal failure. In all these patients creatinine clearance rates were below 20 ml. per minute in the last three months of life, whereas the nonprotein nitrogen and serum creatinine levels were widely variable. Fifteen of 17 of these patients died in less than nine months when creatinine clearance remained below 10 ml. per minute. In the presence of chronic renal insufficiency a rapid decline in creatinine clearance was found to be a grave sign. Superimposed hypertension appeared to promote even more rapid deterioration. Patients with normal blood pressures, however, tended to survive longer in spite of persistently impaired creatinine clearance.

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