and chondroitin sulfate in a small series of rats and rabbits. They used purified hyaluronate prepared from human umbilical cord but did not give any analysis for the degree of purity. They administered only single doses which were much smaller than the large doses which we used. Their findings were essentially the same as ours with the exception that there may have been an antigenic response in their animals. In our study there were no signs of antigenic response in the tissues nor could we detect antibodies to hyaluronate in the blood of our animals.

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Creatinine Excretion in Renal Failure.* (20912)

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Early studies on the metabolism of creatinine revealed that the daily urinary excretion was remarkably constant for a given individual(1). It was hoped that if this were the case at varying levels of function, establishment of this constant value for urinary creatinine would allow for its subsequent replacement by k in the conventional clearance equation, $C = UV/P$.† Rewriting the equation $C = k\ P$ would then permit an approximate estimation of C, adequate for clinical purposes, by the single determination of P. The studies to be reported revealed that UV decreased gradually as P increased in renal failure, and therefore UV could not be replaced by a constant. Attempts to determine the mechanism of this decrease are described.

Methods and materials. The Brod and Sirota(2) modification of the Bonsnes and Taussky(3) method was used for the determination of serum and urine creatinine. A modification of this method was used to determine the urine creatine. Fecal creatinine was determined by the method of Williams and Dick(4). All patients were males. Twenty-four hour urine collections were made on patients with chronic renal disease and on normal controls. Patients with acute renal disease may have rapidly changing serum and urine creatinine values, and were excluded. It was believed that the creatinine recovered from these patients would be affected by rapid changes in renal function, and would not always represent the actual 24-hour excretory requirement.

Observations. Table I summarizes the relationship of the serum creatinine values to the amount of creatinine excreted into the urine. Calculation of the relationship of the individual urine creatinine values (y) to the related serum creatinine values (x) by the method of least squares revealed a regression with the equation $y = 1.35 - 0.042x$. Application of Student's distribution(5) indicated that the p value for zero slope was less than 0.01. It therefore is apparent that there is a significant decrease in urinary creatinine as the serum creatinine increases. To our knowledge the only previous reference to this observation was made by Steinitz and Türkand(6), who reported that the product of

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† Where C is clearance in ml/unit time, U is urinary concentration of creatinine in mg/ml, V is urine volume/unit time, and P is plasma concentration of creatinine in mg/ml.

TABLE I. Relationship of Serum to Urine Creatinine.

Range of serum creatinine, mg/100 ml	Avg serum creatinine, mg/100 ml (P)	Avg urine creatinine, g/day (UV)	Stand. dev.	Avg clearance, ml/min. (C)	No. of cases
0-2	1.16	1.32	.42	85.1	85
2-4	2.95	1.20	.43	29.9	29
4-6	4.84	1.11	.47	16.5	17
6 up	10.37	.88	.38	6.4	22

the creatinine clearance value times the serum creatinine value is constant (implying constant excretion) until the value of 6 mg % creatinine is reached. A group of 9 patients with higher serum creatinine values were found to have a much smaller product. Lippman(7) also has made this observation and therefore uses the creatinine clearance rather than the serum creatinine alone as a measure of renal function and a guide to prognosis. The data of Table II demonstrate that in the individual patient the urinary creatinine excretion decreases as renal failure progresses and that the trend shown in Table I is not due to a peculiar selection of patients.

There is no evidence that the retention of the excess creatinine within the body is sufficient to account for the difference observed. A decrease in excretion of 400 mg per day at a serum creatinine level of 10 mg % should cause a daily rise of 0.8 mg % if the creatinine is equally dispersed through an average of 50 liters of body water. This does not occur except in extreme anuria or oliguria. Therefore, the explanation must lie either in a decreased rate of creatinine production or in an alternative route of excretion.

TABLE II. Decrease in Urine Creatinine Excretion as Renal Failure Progresses in Individual Patients.

Patient	Serum creatinine, mg/100 ml (P)	Urine creatinine, g/day (UV)	Clearance, ml/min. (C)
E	4.39	1.86	29.4
	19.0	.52	1.91
T	4.7	1.31	19.5
	6.9	1.16	11.8
Ed	2.8	1.68	42.0
	10.8	1.13	7.3
M	7.3	1.68	18.9
	11.5	.99	6.0
O	4.52	.93	14.7
	10.2	.55	3.4

Earlier investigators have claimed a direct relationship between creatinine production and total muscle mass. However, most of the patients studied had lost little weight until just before death, and the decrease in muscle mass did not appear proportionate to the decreased creatinine production. The high level of creatinine may inhibit release of creatine from the muscle or its further conversion to creatinine. The elevation of the serum creatine level in renal failure which was demonstrated by Behre and Benedict(8) could account for only a small fraction of the missing creatinine by the same calculations that showed the elevation in serum creatinine was inadequate. The data of Table III indicate that creatine excretion is not significantly increased in uremia. Glycocyamine, a precursor of creatine, gives a color reaction in the same procedure, and may contribute to the reported creatine.

TABLE III. Creatine Excretion in Advanced Renal Failure.

Patient	Serum creatinine, mg/100 ml	Urine creatinine, g/24 hr	Urine creatine, g/24 hr
P	14.0	.63	.017
P	14.8	.54	.026
K	16.4	.54	.017
B	4.0	.63	.014
W	10.2	.70	.023
D	6.4	.74	.023
S	12.0	.42	.013

Alternative routes of creatinine excretion include the stool, skin and lungs. Uremia does not appear to increase fecal creatinine excretion (Table IV). The recoveries which were obtained were within the same range as those of Williams and Dick(4) and were rather insignificant in absolute amount. Ex-

TABLE IV. Daily Fecal Creatinine Excretion.

Patient	Diagnosis	Creatinine excretion, mg/day	Serum creatinine, mg/100 ml
K	Hypogonadism	3.88 2.41 5.05	.84
D	Hodgkin's disease	6.16 3.57 5.06	.82
M	Hemochromatosis	5.68 11.24	1.2
V	Nephrosis	21.7 22.9	1.3
P	Pyelonephritis	10.72 7.15	11.8
G	Chronic glomerulonephritis	10.41 5.32	27.8
B	"	11.11	4.8

cretion of creatinine through the skin and lungs by insensible fluid loss probably can be discounted. Bass and Dobalian(9) have demonstrated a fairly large amount of creatinine and non-creatinine chromogen in the normal sweat, which may be significant in uremia, should actual sweating be sufficient in volume. Several of these possibilities merit further study.

Summary and conclusions. 1. The urinary excretion of creatinine decreases as the filtration rate falls and the serum creatinine rises in chronic renal failure. This is especially apparent when the serum creatinine exceeds 6 mg/100 ml. 2. This decrease is due to either a reduced rate of creatinine production or an alternate excretory pathway. The muscle mass is not significantly decreased, and therefore should not account entirely for decreased production. Alternative excretion in the urine as creatine, or in the feces as creatinine is excluded by the data presented. Other possible mechanisms are suggested, but have not been studied.

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Joint Disease in Mice "Thyroidectomized" with Radio-iodine I^{131}.* (20913)

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In the course of investigations on the skeletal effects of thyroid deficiency in various strains of mice, an unusual joint disease not seen in untreated animals(1) was observed in DBA mice made "athyroid" by administration of I^{131}.

Material and methods. One hundred and thirty-four mice (66 males and 68 females) of the closely inbred strain DBA raised in our laboratory and kept on a stock diet of Purina Laboratory Chow and water *ad libitum* were used. At the age of one month, the animals received a single dose of 200 μc of I^{131} corresponding to about 20 μc/g body weight. Most animals were sacrificed at the ages of 6, 8, or 12 months (age Group I), and of 15 and 18 months (age Group II); some died prematurely or were killed because of symptoms caused by hypophyseal tumors induced by the isotope(2). At necropsy, the

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