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Research Article



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RENAL FUNCTION IN PATIENTS WITH GOUT¹

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There are several theories of the pathogenesis of urate² accumulation in patients with gout. A disturbance of elimination of this substance by the kidneys is probably the most popular. This has been challenged, however, in a previous communication from this laboratory (1), since it appears to be inconsistent with certain experimental data. Whether or not this theory is valid, it deserves serious consideration because urates as naturally occurring end-products of purine metabolism are disposed of by the body largely by excretion through the kidneys. If one pursues the hypothesis to a logical conclusion, any defect of elimination might be inherited or it might be an acquired phenomenon following damage to the functioning units of the kidneys.

The accepted theory (2, 3) of renal physiology in man assumes that urates are present in glomerular urine as are other ultrafiltrable substances and reabsorbed in part by the cells lining the tubules. If the kidneys were primarily at fault in the gouty diathesis, accumulation of urate might be attributed either to (a) a reduction of the number of functioning glomeruli or (b) an increased reabsorption by the tubules. Both of these phenomena are partially susceptible of quantitative analysis now that improved methods for the study of kidney function are available.

A presentation and discussion of kidney function data, as determined by five experimental procedures, are contained in this communication. These include tests for the excretion of substances normally present in the body such as urea, creatinine, urate, sodium and chloride and for the excretion of foreign substances introduced parenterally such as phenolsulphonphthalein, neo-iopax and inulin. Studies were made of normal persons and of patients suffering from diseases other than gout, as well as of patients with classical gout. The action of drugs used therapeutically in the treatment of acute and chronic gouty arthritis was investigated.

SUBJECTS

Thirty-one persons acted as experimental subjects. Twenty-two were afflicted with gout; six were patients with diseases other than gout; three were normal persons. The patients with gout were selected without regard to extent of disease or duration of symptoms. It was necessary only that the criteria for the diagnosis of gout were satisfied (1, 4, 5) and that the patients consented to hospital admission for study. All except K. He. were males. Their ages varied from 28 to 81 years. Each patient had had two or more attacks of acute arthritis, and on two or more occasions the concentration of fasting serum urate had been greater than 6.0 mgm. per 100 cc. Osseous or cartilagenous tophi were suspected from the roentgenogram in thirteen. Subcutaneous tophi were present in seventeen. All the patients seen during an acute attack of arthritis had responded to full doses of colchicine. Renal stones, composed largely of urates, had been passed by seven. A summary of the clinical data for each patient with gout is given in Table I. Several of the patients have been described in previous communications (1, 6, 7). Identical initials refer to the same patient. Four men and four women, none of whom showed impairment of kidney function, acted as controls. Their ages varied from 20 to 54 years. A normal inulin clearance (greater than 95 cc. per minute) and a concentration of fasting serum urate less than 6.0 mgm. per 100 cc. were observed in each control subject. One woman with advanced Bright's disease and malignant hypertension completed the group of controls.

METHODS

All of the data were collected while the subjects were in the metabolism ward of the Massachusetts General Hospital. The patients with gout were allowed, during the period of observation, a low-purine diet containing about 70 grams of protein, 90 grams of fat and 300 grams of carbohydrate. The control subjects consumed the usual hospital diet which was moderately low in purine. The five methods of studying renal function were: (a) determination of nonprotein nitrogen of the

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² The term urate is preferable to uric acid in a consideration of acid-base equilibrium of biological media just as chloride is preferable to hydrochloric acid and phosphate is preferable to phosphoric acid.

TABLE I

Summary of clinical observations on twenty-two patients with gout

Patient	Dura- tion of symp- toms	Severity of disease	Serum urate	Subcu- taneous tophi	Os- seous tophi by x-ray	Renal urate stones
	years		mgm. per 100 cc.			
E.Dw.	3	Minimal	10.0			
S.Co.	3	Minimal	11.9			+
F.To.	1	Minimal	9.8			•
H.Wa.	30	Extensive	6.4	+	+	
L.Mu.	6	Moderate	9.3	+	·	
J.Ce.	3	Minimal	8.9			
P.Le.	5	Minimal	7.8	+		+
M.Co.	19	Minimal	9.2	+		
I.Co.	5	Moderate	11.5	+		+
W.G.B.	27	Extensive	8.3	+	+	+
W.Da.	44	Extensive	11.7	+	+	
P.Fa.	12	Moderate	8.7	+	+	+
L.Si.	12	Minimal	8.2	+		
J.Go.	6	Minimal	7.9			
F.Na.	10	Extensive	14.0	+	+	+
J.Sm.	21	Extensive	9.7	+	+	
J.Co.	41	Moderate	10.4	+	+	
A.Cas.	26	Extensive	11.3	+	+	
A.Ca.	38	Extensive	8.9	+	+	
C.Cr.	12	Moderate	10.4	+	+	
A.De.	9	Extensive	9.2	+	+	+
K.He.	35	Extensive	9.2	+	+	

serum, (b) testing ability to concentrate solids, (c) measuring excretion of phenolsulphonphthalein dye, (d) pyelography after intravenous injection of neo-iopax, and (e) estimation of rate of clearance of inulin, creatinine, urate, sodium and chloride.

Prior to July 1, 1938, urine concentration tests were done by a slight modification of the overnight method described by Fishberg (8). We have arbitrarily set 1.022 as the lower limit of normal. After this time, except for I. Co., S. Co., and J. Sm., the "37-hour test" (9) was used. Correction of specific gravity for albumin was made. Under these conditions normally functioning kidneys are able to concentrate to a specific gravity greater than 1.028. Fractional phenolsulphonphthalein tests were done according to the method described by Chapman and Halsted (10). Intravenous pyelography followed the standard technique.

Clearance tests for inulin, creatinine and urate, and in some patients sodium and chloride, were performed simultaneously. The procedure outlined by Shannon and Smith (11) was followed. Inulin was chosen because its excretion is believed to be an accurate measure of glomerular filtration (3). Creatinine data are included although evidence suggests that this substance is excreted by tubules as well as in the glomerular filtrate. The clearance tests are reported as cc. of *plasma* cleared per minute and are corrected to a standard body surface area of 1.73 square meters. The clearance data represent an average of at least 3 periods. In some patients as many as 9 periods were studied. Good agreement between the successive periods was obtained. The tests were begun while the subjects were in a basal state. No food, fluid or activity was allowed from 7:00 o'clock in the evening before the test until 7:00 o'clock in the morning on the day of the test. During the hour following 7:00 a.m., 2,000 cc. of tap water were ingested.

Inulin (Pfanstiehl and Company) was prepared as a 10 per cent solution by heating in 0.9 per cent sodium chloride in water. Immediately before use it was passed through a Seitz filter (12). Prior to July 1, 1938, 50 grams of inulin were injected intravenously 15 minutes before the collection of urine and blood specimens was started. After that date 16 grams were given 15 minutes before the first collection period and an additional 7 to 9 grams were given by a slow infusion throughout the collection periods. Before June 1, 1938, 10 grams of creatinine were given orally 90 minutes before collection of specimens was begun; after that date 3 grams were given intravenously just prior to the inulin. A few "reactions" occurred. Headache and chills were encountered most frequently. No untoward symptoms persisted longer than 24 hours. It was concluded that no serious hazards accompany this method of parenteral administration of creatinine and inulin.

All urine specimens were collected by a urethral catheter. We have relied on the conclusion of Hayman and associates (13) that bladder washings do not increase significantly the recovery of urine if the technique of catheterization is faulty. The urine collection periods were timed by a stopwatch. They were usually 10 minutes in length. In some of the first tests they varied from 10 to 20 minutes. Three or more consecutive collection periods were made in one morning. A blood sample was taken at the half way mark in each period.

Blood samples for determination of electrolytes were collected under oil. The tubes were centrifuged immediately. The urine samples were diluted to proper volume within 30 minutes after collection. Inulin was estimated from an iron filtrate of plasma (14) by the difference in the concentration of reducing substances before and after acid-hydrolysis (15). Creatinine was determined according to the method described by Folin and Wu (16); urate according to the method described by Benedict and Behre (17); sodium according to the method described by Butler and Tuthill (18). Serum chloride was determined according to the method described by Keys (19) and urine chloride according to the method described by Harvey (20).

EXPERIMENTAL RESULTS

Inulin and creatinine clearance and routine clinical tests

The patients with gout (Table II) were divided into 3 groups according to their ability to clear plasma of inulin: Group I, normal kidney function with inulin clearances of 95 cc. or more per minute; Group II, moderate disturbance of kidney

526

Intravenous pyelography, interpretation				Normal Normal Normal, mall kidneys Normal Normal left pelvis indistinct Normal		Calices indistinct Calices indistinct Branal right kidnory, stornes in calices, bilaterally Incomplete filling of calices Palves not well outlined Palves not well outlined Normal Slow exerction of dye Incomplete filling of calices		Left kidney not visualized Kidneys small, excretion slow, dilatation and	nuunaug rugar ya kaya Blight accretion of dye in 2 hours by left kidney Bmall kidneys, dye accreted alowly
Serum non- protein	nitrogen	mgm. per 100 cc.		8888 88 888		33888988888888888888888888888888888888		49 80	4 5
Maximum specific gravity	of urine			1.026 1.022 1.022 1.015 1.015 1.015 1.020 1.020 1.022		1.016 1.016 1.018 1.018 1.018 1.009 1.009 1.018 1.018		1.012 1.008	1.013
Excretion of phenol- sulphon- phthalein	during first 15 minutes	per cent	ARANCE TESTS	588188888888 58818888888888888888888888		288 288 288 288 288 288 288 288 288 288		юФ	10 4
(1 - Urate clearance)×100		per cent	INULIN AND CREATININE CLEV	91.9 91.9 90.7 91.9 91.9 91.9 92.0 92.0 92.0	TON OF RIDNEY FUNCTION	88.8 96.2 913.8 913.8 913.8 91.8 91.8 91.8 91.8	TION OF KIDNET FUNCTION	73.0 81.8	62.8 64.2
(Urate clearance)×100		•	AL KIDNET FUNCTION BY	4.7 8.1 8.1 8.1 8.1 8.1 8.1 8.1 8.1 8.1 8.1	UP II. MODERATE REDUCI	11.2 4.8 8.7 8.7 5.4 5.4 8.2 8.2 8.2 8.2 8.2	ROUP III. SEVERE REDUC	27.0 18.2	87.2 35.8
red per eof 3 ds	Urate		I. NORM	6.6 8.6 8.6 8.6 8.6 8.6 8.6 8.6 8.6 8.6	GRO	8888 868 753,00 751,60 751,60 751,60 751,60 751,60 751,60 751,60 751,60 751,60 751,60 751,60 751,60 751,60 751,60 751,60 751,60 752,700,700,700,700,700,700,700,700,700,70	Ū	8.4 5.3	9.3 4.3
plasma clea te. Averag more perio	Creatinine		GROUP	122 122 122 122 122 122 122 122 122 122		88888888888888888888888888888888888888		46	38
Ce. of minutor	Inulin	<i>.</i>	1	88880000000000000000000000000000000000		22 6 6 8 8 2 7 3 3 7 8 8 8 9 7 3 3 7 9 8 8 9 7 3 3 7 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9		81 29	128
Average urine flow during	clearance testa	cc. per minute		22. 24. 2. 2. 2. 2. 2. 2. 2. 2. 2. 2. 2. 2. 2.		8.5 8.5 9.6 1.7 9.6 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0		6.6 5.4	6.6
Blood	, [mm. Hg		148,96 144,96 180,90 180,98 110,70 120,80 142,80 134,76		150/68 150/80 150/88 150/88 150/88 158/90 158/90 158/90 158/90 180/106 184/82		138/78 164/114	170/70 174/100
A Go				82 82 83 83 83 83 83 84 83 83 83 83 83 83 84 83 83 83 83 83 83 83 84 83 83 83 83 83 83 83 84 84 84 84 84 84 84 84 84 84 84 84 84 84 8		67 81 82 82 82 82 82 82 82 82 82 82 82 82 82		38 72 38 42	388 388 49 49
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Date of te				April April Novembr Decembe May May May May Decembe		March May June June June Nureh June Novemb		March May	No vemb October
Patient				A C C C C C C C C C C C C C C C C C C C		A.C.B. J.C.C. J.C.C. J.C.C. J.C.C. A.C.B.		A.C. C.C.	A.De. K.He.

Renal function observations on patients with gout TABLE II

 ullet The blood pressure is believed to be normal although the original observations are lost.

RENAL FUNCTION IN GOUT

527

function with inulin clearances between 55 and 75 cc. per minute; and Group III, severe disturbance of renal function with inulin clearances below 45 cc. per minute. In most tests a ratio of approximately 1:1.3 was observed between inulin and creatinine clearances.

There were nine patients in Group I. Their ages varied from 28 to 59 years. All except H. Wa. had a systolic blood pressure below 150 and a diastolic pressure below 100 mm. Hg. The blood pressure of H. Wa. was 160/90. Four patients only, E. Dw., S. Co., M. Co., and I. Co., were able to excrete a urine with a specific gravity of 1.022 or greater in the overnight test. F. To. was unable to reach the minimum normal level of 1.029 in the "37-hour test." All except L. Mu. excreted more than 25 per cent phenolsulphonphthalein dye within 15 minutes after injection. The serum nonprotein nitrogen was less than 35 mgm. per 100 cc. in all patients. Intravenous pyelography was performed in all except E. Dw. The excretion of neo-iopax was prompt in each instance. Patient H. Wa. showed kidney shadows which were believed to be smaller than normal. According to his history he probably had had a mild attack of Bright's disease (? acute glomerular nephritis) as a young man. P. Le. had had a urate stone removed from the left kidney pelvis one month before admission to the metabolism ward. The finding of an indistinct pelvis on the left has been attributed to trauma at operation and subsequent diminution in capacity. Thus, while all patients in this group showed normal kidney function by the inulin and creatinine clearance tests, only four showed normal function by all of the tests. Inability to concentrate urine maximally appears to be the first indication of renal impairment in patients with gout.

There were nine patients in Group II. Their ages varied from 31 to 81 years. Five patients, W. G. B., P. Fa., L. Si., F. Na., and J. Sm., had a normal blood pressure. Two of the remaining four, J. Go., and A. Cas., with slight and moderate elevation of systolic pressure, respectively, had had attacks of hypertensive encephalopathy and elevation of systolic blood pressure over 200 mm. Hg. All patients showed an inability to concentrate urine maximally. The specific gravities ranged from 1.018 to 1.009. Only three patients, P. Fa., J. Go., and F. Na., were able to excrete more than 25 per cent phenolsulphonphthalein in 15 minutes. The concentration of nonprotein nitrogen in the serum was within normal limits in all. Neo-iopax was injected intravenously in each patient except W. G. B. Only two pyelograms, those of F. Na. and J. Sm. were interpreted as normal. P. Fa. showed prompt excretion of dye but the right kidney was small and shadows suggestive of stones were visible bilaterally in the calices. W. Du., L. Si., and A. Cas. exhibited indistinct or incomplete filling of the calices, and J. Go. indistinct kidney pelves. J. Co. showed a slight delay in the excretion of the dye.

There were four patients in Group III. Profound impairment of renal function was present in all. The ages varied from 42 to 72 years. Three of the four showed an elevation of systolic or diastolic blood pressure. The specific gravities in the concentration tests varied between 1.013 and 1.008. The excretion of phenolsulphonphthalein dye in 15 minutes was 6 per cent or less. The concentration of serum nonprotein nitrogen varied between 45 and 70 mgm. per 100 Following the injection of neo-iopax in A. cc. Ca. the left kidney was not visualized; the right kidney excreted the dye promptly. C. Cr. had small kidneys bilaterally; on the right there was dilatation and blunting of the kidney pelvis. The pyelogram of A. De., taken after right-sided nephrectomy, showed a small amount of dye excreted by the left kidney at the end of 2 hours. K. He. had small kidneys with slow excretion of dye. All of the patients had an albuminuria which varied from one plus to three plus.

Clearance studies on the controls are given in Table III. Eight exhibited normal renal function; *i.e.*, the clearance of inulin was greater than 95 cc. per minute. H. Mc., suffering from advanced Bright's disease, had an inulin clearance of 8.5 cc. per minute.

Urate clearance

If urates are filtered completely by the glomerulus (3, 21, 22) and reabsorbed partially by the tubules (23), then the percentage of filtered urate appearing in bladder urine is measured by the ratio $\left(\frac{\text{urate clearance}}{\text{inulin clearance}}\right) \times 100$. Likewise,

RENAL FUNCTION IN GOUT

TABLE III

Clearance studies on patients without gout

Patient	Sex	Age	Cc. of plasma cleared per minute. Average of 3 periods					$\left(\frac{\text{Urate clearance}}{\text{Urate clearance}}\right) \times 100$	$\left(1 - \frac{\text{Urate clearance}}{1 - \frac{1}{2}}\right) \times 100$	Diagnosis	
			Inulin	Creatinine	Urate	Sodium	Chloride	\ Inum clearance /	(Inuin clearance /		
									per cent		
	NORMAL KIDNEY FUNCTION										
L.B. B.D. V.M. G.E. R.J. G.A. F.B. L.G.	F F M M M F	22 29 54 23 39 24 20 25	148 127 118 114 105 98 97 96	190 144 162 161 149 123 125 155	10.6 15.9 11.8 12.4 12.4 8.6 7.8 8.9	3.75 2.09 1.57 1.80 1.88 0.65	5.12 2.60 2.11 3.01 2.83 1.00	7.2 12.5 10.0 10.9 11.8 8.8 8.1 9.3	92.8 87.5 90.0 89.1 88.2 91.2 91.9 90.7	Hyperparathyroidism, renal stones Normal Hyperparathyroidism Epidermolysis bullosa Normal Ecsema Normal Latent syphilis	
SEVERE IMPAIRMENT OF KIDNEY FUNCTION											
H.Mc.	F	42	8.5	12.8	7.5			88.3	11.7	Malignant hypertension, Bright's disease	

 $\left(1 - \frac{\text{urate clearance}}{\text{inulin clearance}}\right) \times 100$ expresses the per-

centage of filtered urate reabsorbed by the tubules. Such observations on the nine gouty subjects in Group I, Table II, and on the eight control subjects in Table III with normal kidney function are similar. In both groups, approximately 10 per cent of the urate which crossed the glomerular membrane appeared in the bladder urine; 90 per cent was reabsorbed. It is concluded, therefore, that a normal urate clearance is approximately 10 cc. per minute.

The gouty patients in Group II showed a moderate reduction in urate as well as in inulin clearance. The averages were 6.5 cc. and 68 cc. per minute, respectively. The reduction in urate clearance appeared to be related to reduction in inulin clearance as the ratio $\left(\frac{\text{urate clearance}}{\text{inulin clearance}}\right) \times 100$ was only slightly greater than that in Group I. It is possible that W. Da. and J. Sm. did not have a diuresis sufficient to produce a maximum excretion of a threshold substance such as urate. The urate clearances in these two patients, therefore, were probably lower than might be produced under better experimental conditions.

The four patients with severe impairment of renal function (Group III) showed an average urate and inulin clearance of 6.8 and 24 cc., respectively. The average value for the ratio $\left(\frac{\text{urate clearance}}{\text{inulin clearance}}\right) \times 100$ increased to 28 and,

hence, tubular reabsorption decreased to 72 per cent. H. Mc. (Table III) was the only control studied who had terminal Bright's disease. The urate clearance on this patient was 7.5 cc. per minute. More than 88 per cent of the filtered urate was excreted in the urine and less than 12 per cent was reabsorbed.

The relationship between inulin clearance and percentage tubular reabsorption of urate is shown in Figure 1. It is apparent that progressive renal damage in gouty as well as in non-gouty patients is associated with an increase in urate excretion relative to glomerular filtration. The percentage reabsorption of urates by the tubules is not depressed, however, until the inulin clearance is decreased below 50 cc. per minute or approximately one-half of the normal rate. Only when glomerular filtration is reduced to a negligible amount does retention of urate from failure of renal excretion assume pathological significance.

Action of drugs

The effects of cinchophen in therapeutic amounts on the clearance of inulin, urate, sodium and chloride are given in Table IV. Two grams of cinchophen were given orally in divided doses on the day before the clearance tests were done and an additional dose of 0.5 gram each was given at 6:00 and 7:00 on the morning of the test. The clearances of inulin, sodium, and chloride were un-



changed following the ingestion of this quantity of cinchophen. Urate clearances, however, were increased significantly. Four patients with moderate reduction of renal function, F. Na., J. Go., L. Si., and A. Cas., showed urate clearances which were two- or threefold greater than during the control period. R. J., one of the non-gouty patients who was given cinchophen, showed a similar increase. The percentage of urate reabsorbed from the glomerular filtrate decreased from 90 per cent without cinchophen to between 62 and 75 per cent with cinchophen. The patients with severe renal damage, A. De. and C. Cr., showed slight increases in urate clearance after ingestion of cinchophen, although the per cent reabsorbed by the tubules was similar to that of the other patients. The serum urate concentration during

each cinchophen experiment was decreased from the value observed during the control experiment.

Salyrgan was given intravenously on two occasions to F. Na. and on one occasion to J. Sm. (Table V). Neither patient suffered from acute gout following the administration. An increase in urate clearance was observed in all experiments. The urate reabsorption decreased from approximately 90 per cent to between 30 and 50 per cent. Salyrgan was given to J. Sm. 3 hours before the clearance tests were started. A satisfactory urine flow was obtained although the diminution in inulin clearance was appreciable. The clearances of urate, sodium, and chloride were increased several fold. In the first experiment on F. Na. the clearance data were collected 10 hours after the administration of the drug. A diuresis of 2 liters

TABLE IV

Action of cinchophen

Patient	Date	Serum	Cc. of	plasma cle Average o	eared per r f 3 periods	ninute.	$\left(1 - \frac{\text{Urate clearance}}{\text{Invite clearance}}\right) \times 100$	Medicine given
		urate	Inulin	Urate	Sodium	Chloride	(Inum clearance /	
		mgm. per 100 cc.					per ceni	
F.Na. F.Na.	January 16, 1939 January 30, 1939	14.0 8.8	68 65	7.0 15.7	1.23 0.61	1.90 1.10	90.0 75.8	3 grams cinchophen
J.Go. J.Go.	June 21, 1938 June 24, 1938	7.9 6.0	69 74	8.2 18.0			88.0 75.5	3 grams cinchophen
L.Si. L.Si.	December 9, 1938 December 15, 1938	8.2 5.0	71 74	6.2 16.6	0.91 1.69	1.60 2.50	91.3 77.8	3 grams cinchophen
A.Cas. A.Cas.	November 11, 1938 October 27, 1938	11.3 6.3	56 53	7.5 20.1			86.6 62.2	3 grams cinchophen
A.De. A.De.	November 22, 1938 December 2, 1938	9.2 7.4	25 28	9.3 13.4	2.23 3.39	3.18 4.90	63.0 54.0	3 grams cinchophen
C.Cr. C.Cr.	May 12, 1938 June 4, 1938	10.4 7.5	29 23	5.3 6.4			82.0 71.7	3 grams cinchophen
R.J. R.J.	January 4, 1939 January 12, 1939	4.6 2.4	105 102	12.4 29.5	1.88 1.43	2.83 2.58	89.0 71.0	3 grams cinchophen

in excess of the usual output was noted. The urine flow was reduced at the time of clearance studies although the customary amount of water was ingested. The small urine flow and decrease in clearances of inulin, urea, sodium and chloride suggest that certain aspects of the diuresis had passed before the test was started. The second experiment on F. Na. was considered the best one to illustrate the relevant tubular effects. Salyrgan was given 3 hours before the tests. Clearances of inulin and urea were similar to the control experiment. Urine flow and clearance of urate, sodium and chloride were increased many fold. These data are difficult to interpret. Salyrgan may precipitate an attack of acute gout (4, 24) and no therapeutic claims have been made for it in this malady. Inspection shows, however, that its effect on urate clearance is similar to that of cinchophen.

Five patients were given 5 mgm. each of crystalline colchicine (Table VI) in divided doses during a 24-hour period prior to the test. This is an

TA	BL	Æ	v	

Detion t	Data	Diumaia	s Serum urate	Cc. of plasma cleared per minute. Average of 3 periods				ute.	(1 Urate clearance) v 100	Medicine given
rauent	Date	Diffests		Inulin	Urea	Urate	Sodium	Chlo- ride	(I Inulin clearance) A 100	intelletine given
		cc. per minule	mgm. per 100 cc.						per cent	
F.Na. F.Na.	January 16, 1939 February 13, 1939	9.6 5.6	14.0 11.7	68 67	43	7.0 7.1	1.23 1.58	1.90 2.46	90.0 89.4	
F.Na. F.Na.	February 15, 1939 February 21, 1939	3.5 16.3	8.8 11.0*	55 69	23 46	32.9	0.33	18.00	52.3	2 cc. salyrgan, 10 p.m. February 14, 1939 2 cc. salyrgan, 7:45 a.m.
J.Sm. J.Sm.	March 24, 1939 April 3, 1939	1.7 12.6	9.7 7.0	67 37		3.5 25.6	9.05	11.60	90.0 30.7	2 cc. salyrgan, 7:45 a.m. April 3, 1939

Action of salyrgan

* Serum urate was 14 mgm. per 100 cc. on the previous day.

Patient	Date	Cc. of plas per minute of 3 p	sma cleared e. Average periods	$\left(1 - \frac{\text{Urate clearance}}{\text{Inulin clearance}}\right) \times 100$	Medicine given	
		Inulin	Urate			
A.Cas	November 11, 1938	56	7.5	per cent 86.6		
A.Cas	November 12, 1938	56	8.1	85.6	5 mgm. colchicine	
J.Co J.Co	June 28, 1938 June 30, 1938	62 64	5.1 6.0	91.8 90.6	5 mgm. colchicine	
P.Fa P.Fa	June 17, 1938 June 19, 1938	72 80	9.5 11.1	86.9 86.1	5 mgm. colchicine	
L.Si	December 9, 1938 December 13, 1938	71 68	6.2 6.3	91.3 90.6	5 mgm. colchicine	
A.De A.De	November 22, 1938 November 28, 1938	25 26	9.3 9.0	63.0 66.0	5 mgm. colchicine	

TABLE VI

Action of colchicine

average therapeutic amount used by us in the treatment of an acute attack of gouty arthritis and is effective in most patients. No significant change in inulin or urate clearances was observed. It is apparent that the beneficial effect of colchicine is not accompanied by any demonstrable change in urate clearance.

DISCUSSION

This study of *renal function* on patients with gout confirms many clinical observations (25, 26, 27). The constancy of the results by the 5 methods employed is satisfactory. Eighteen of the twenty-two patients in Table II show some limitation of renal function. The inability to concentrate solids maximally (28) appears to be the first evidence of failure. In Group I, five patients with normal inulin and creatinine clearance rates were unable to concentrate maximally. In Group II, each patient had a lowered specific gravity. All of the patients in Group III showed renal deterioration by each of the tests. As an approximation, it may be stated that neither duration of symptoms of gouty arthritis nor degree of elevation of serum urate are the sole determining factors in producing renal dysfunction. It is noteworthy that the age of the patient appears to be of secondary importance and longevity may not be impaired.

Hypertension and arteriosclerosis have been associated with a reduction in kidney function (29)

in various maladies. It is pertinent, therefore, to consider their incidence in patients with gout. In our series only eight had hypertension; in each of these it corresponded to the benign rather than the malignant type (30). K. He. developed hypertension under observation but not until 3 years after laboratory tests was there severe impairment of renal function. She had recurring cystitis and mild pyelonephritis, factors which probably contributed to the hypertension. A. Ca., on the other hand, also had had cystitis but at no examination was hypertension noted. A. De. had bilateral renal stones and a systolic blood pressure of 170 mm. Hg. The other patients with hypertension gave no history of urinary tract infection nor did they have any signs or symptoms suggesting it. The development of arteriosclerosis in patients with gout occurs probably earlier than hypertension. All of the patients in Group II, which includes F. Na., a man of 31, had sclerosis of the peripheral arteries. Two of the four in Group III, A. Ca. and A. De., showed similar changes. Each of the three who were studied at necropsy, J. Sm., A. Cas. and A. Ca., had renal arteriosclerosis. The narrowing of the lumina of the vessels in each patient was believed to have been sufficient to have reduced the blood flow through the kidneys. Evidence of interference with the blood supply to the tubules through the afferent glomerular vessels was seen in the microscopic sections from A. Ca. In J. Sm. and A. Cas. the

large renal vessels showed similar changes. It seems reasonable, therefore, to attribute a portion of the reduction in kidney function in these patients to reduced blood flow (31, 32). In sixteen out of eighteen patients who died with gout, Brogsitter (27) observed a systolic blood pressure greater than 170 and a diastolic greater than 104. Since his observations were collected late in the course of the disease, we conclude that, if hypertension occurs in gout, it is a late manifestation secondary to prolonged renal damage and diminished renal flow.

The deposition of urates in the kidney parenchyma may be significant in the production of renal deterioration. In each of the kidneys which was studied at necropsy urates were visible grossly and microscopically. The medullary portions showed the most extensive deposits. In J. Sm. and A. Ca. the collecting tubules showed many small urate calculi. Most of these would be passed without producing symptoms of urinary tract obstruction; it might be the fate of others to develop into larger urate calculi. Obstruction and infection are possible sequellae.

The term nephritis has been avoided purposely in this discussion. The pathological diagnosis in the three patients studied at necropsy was chronic vascular nephritis. One should not quarrel about an anatomical diagnosis. The use of the term gouty nephritis in describing renal insufficiency in patients with gout is more hazardous. Many retain the term for late manifestations. Our data show that most patients with gout have some impairment of renal function. It is likely that the impairment is irreparable, although the progression appears to be very slow. A better term than gouty nephritis would be "renal impairment of gout" which carries with it no special etiologic implications.

The term *urate clearance* has been employed rather freely in this discussion. It implies and embodies a process similar to the clearance of other substances which are excreted by the kidneys. Inherent aspects of urate clearance include appearance of urates in glomerular filtrate in approximately the same concentration as they exist in plasma, and absorption in part by contiguous cells as the glomerular filtrate passes through the tubular lumina. This theory assumes that excretion of urates by the tubules does not occur. The elimination of urates by the kidney is of more than academic interest and once correctly defined possesses considerable etiologic significance. Future thinking and investigation concerning the etiology of gout will not be definitive until it is settled as to whether or not the kidneys are responsible for the accumulation of urates in patients with this malady. It was hoped that this study would help in the solution of the problem. That it has done but it has not clinched the argument. It is believed that our data show no differential inability of the kidneys to clear urate in gouty patients. This conclusion, however, is based upon certain assumptions, the proof for which is not yet available.

The urate clearance data of Berglund and Frisk (33) and Brøchner-Mortensen (34) were reported relative to creatinine clearance and not relative to inulin. If inulin is used as the standard, a normal urate clearance is approximately 10 per cent of glomerular filtration. In gouty patients without impairment of renal function the urate clearance is similar. In gouty patients with a significant diminution in glomerular filtration, as measured by inulin clearance, a quantitative decrease occurs in the reabsorption of urate by the tubules. The amount of urate excreted daily, therefore, shows little or no diminution.

There are at least three interpretations of the pathogenesis of depressed reabsorption. The cells of the tubules may be damaged and their efficiency lowered. An "all or none" law for the functioning of a nephron has not been demonstrated, and it is likely that activity of a glomerulus and its tubule may be impaired without being completely destroyed. If the pathological processes causing kidney changes were to progress, reabsorption in individual nephrons would approach zero. Patient H. Mc. (Table III), with advanced Bright's disease, illustrates this. The inulin clearance was reduced to 8.5 cc. per minute while the urate was 7.5 cc. per minute. Reabsorption of urate from the glomerular filtrate was about 10 per cent instead of the normal of 90 per cent.

The second interpretation utilizes the hypothesis advanced by Hayman *et al* (13). They have suggested that the failure of reabsorption of urea in dogs with damaged kidneys may be attributed to increased urine flow through the tubules. It is possible that retarded reabsorption of urate in patients with impaired kidneys may be explained similarly. The abnormal data may represent the average of the combined filtration and reabsorption of normal and partially damaged nephrons.

In discussing this subject with Dr. S. J. Thannhauser, he has called our attention to yet a third interpretation. If urates were excreted in part by the tubules, similar data might be obtained. This assumption is plausible if the premise were correct, *i.e.* urates are excreted by the tubules. We believe that direct evidence in mammals and indirect evidence in man does not support this premise and that the explanation, therefore, must be held in abeyance for the present.

The action of drugs on renal function concludes the discussion. Cinchophen and salyrgan depress tubular reabsorption of urate, with subsequent increase in urate clearance. These changes may be demonstrated in patients with and without gout. They occur without significant change in inulin excretion. Patients with advanced renal insufficiency, however, do not show decreased urate reabsorption after cinchophen ingestion, as do those patients with little or no damage. It is believed that cinchophen damages normally functioning cells of the tubules and prevents reabsorption of urate just as salyrgan damages tubular cells and prevents reabsorption of urate as well as of sodium and chloride. Colchicine appears to have no effect on the renal excretion of urate. The pharmacological action of this drug in the treatment of acute or chronic gout is unknown.

SUMMARY

Kidney function has been investigated in twentytwo patients with gout. The function tests included accepted clinical procedures as well as clearance of inulin, creatinine, urate, sodium and chloride. Eight subjects with normal kidneys and one subject with terminal Bright's disease were used as controls. Most of the gouty patients showed some evidence of renal damage. The earliest change was inability to concentrate solids. In the absence of severe renal impairment, all except 10 per cent of the urates which were filtered through the glomeruli were reabsorbed by the tubules. With severe renal impairment, reabsorption of urates by the tubules was depressed and clearance tended to be maintained. No constitutional inferiority of the kidneys to excrete urate was demonstrated. Cinchophen and salyrgan caused a diminution in tubular reabsorption of urate and an increase in urate clearance. Colchicine did not appear to influence the renal elimination of urates. Kidney changes in patients with gout are believed to be the result and not the cause of the metabolic dyscrasia.

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