THE RENAL CLEARANCE OF PENICILLINS F, G, K, AND X IN RABBITS AND MAN[1]

By HARRY EAGLE and ELLIOT NEWMAN
with the technical assistance of ARLYNE D. MUSSELMAN, MARGOT ROBINSON, and MARION BIRMINGHAM

(*From the Laboratory of Experimental Therapeutics of the U. S. Public Health Service and The Johns Hopkins School of Hygiene, and the Department of Medicine of the Johns Hopkins Medical School, Baltimore 5, Maryland*)

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The factor which most seriously limits the therapeutic efficacy of penicillin is its rapid urinary excretion. Thus, the renal clearance of commercial penicillin in man has been found (1, 24) to vary between 755 and 1,120 ml. per minute, approximating the total renal plasma flow; and when crystalline penicillin G or X is injected intramuscularly in aqueous solution at average therapeutic dosage (0.6 mgm. per kgm.), approximately 60 per cent is excreted in the urine in the first hour (2 to 4). Largely because of that rapid excretion, the blood level of *e.g.* penicillin G falls off, after its intramuscular injection in aqueous solution, at an average rate of 70 to 80 per cent each succeeding hour, or 2 to 3 per cent each minute (4, 19). It is apparent that even a minor decrease in the rate of renal excretion would be reflected in significantly prolonged blood levels and a correspondingly enhanced therapeutic efficacy.

There is considerable evidence that penicillin is secreted by the renal tubules, and by the same secretory mechanism as diodrast and p-aminohippuric acid. Thus, the excretion of penicillin is said to be depressed by the simultaneous administration of either of these 2 compounds in amounts sufficient to saturate the common tubular mechanism (5 to 10). Restriction of the water or salt intake (11) and the administration of benzoic acid or pitressin (12) are also reported to curtail the excretion of penicillin and to prolong the blood penicillin curve correspondingly.

Since the 4 penicillin species known to be produced by penicillium (F, G, K, and X) vary markedly in their pharmacological behavior and bactericidal activity (2 to 4, 13, 14), it was of interest to determine the renal clearance of each, over a widely varying range of plasma concentration, and with varying rates of urine flow. As is shown in the following, in both rabbits and man penicillins F, G, and X were found to have a renal clearance corresponding to the total renal plasma flow. The ratio of the glomerular filtration rate, simultaneously determined with inulin or thiosulfate, to the renal clearance of penicillin did not vary significantly over a wide range of plasma concentrations and was independent of the rate of urine flow. In rabbits, the tubular secretory mechanism was found to have been saturated by serum concentrations on the order of 100 to 1,000 micrograms per ml.

The apparently anomalous renal clearance of penicillin K is discussed later in the text.

At least in the case of penicillins F, G, and X the nature of the side chain which differentiates the several species of penicillin, and which significantly modifies their bactericidal activity, thus has no demonstrable effect on their renal clearance. Further modification in that prosthetic group may nevertheless be a promising approach to the development of penicillins with low renal clearances and correspondingly enhanced therapeutic activity.

EXPERIMENTAL METHODS

Penicillins: The purified penicillins used in these studies were generously provided by the following pharmaceutical firms:

G—Squibb (Lot CRA-214-20)
F—Upjohn (Lot 175-EANW-6)
K—Abbott (Lot RP 309 P2)
Pfizer (Lot 5/2/46)
X—Lederle (Lot CA-3242-IC)

Penicillin assay: The blood and urine concentrations were determined by a modified Rantz-Kirby (1) serial dilution technic (cf. [4, 13]), using the inhibition of hemolysis by streptococci (C-203 strain of Streptococcus pyogenes) as the endpoint. The use of 5 tubes for each

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2-fold difference in concentration (*i.e.*, 0.8, 0.72, 0.6, 0.48, 0.4, etc. ml. of the unknown specimen in a total volume of 0.8 ml.) permitted a reasonably accurate and reproducible assay.

The technic was further modified in that the assays were removed from the incubator after 6 to 9 hours, by which time hemolysis had begun, and were then allowed to remain at room temperature overnight before reading. With this technic, contaminated urine specimens could usually be assayed without preliminary filtration, since the heavy streptococcus inoculum initiated hemolysis at 37° C. before it had been overgrown by the contaminant, and bacterial growth in the following 10 to 15 hours at room temperature was usually too slow to obscure the results.

Calculation of results: The average serum concentration over the time period represented by the successive urine samples was obtained in the usual manner by graphic interpolation (log of serum level plotted against time).

Calibration of glomerular filtration and renal plasma flow: In some of the experiments, the rate of glomerular filtration was simultaneously determined by the administration of inulin or sodium thiosulfate, given either as a single injection, or as a constant infusion following a priming dose. In some of the subjects, the renal plasma flow was determined with para-aminohippuric acid several days before or after the administration of penicillin. The methods used for the determination of inulin and para-aminohippuric acid were those suggested by Goldring and Chasis (16). Thiosulfate was determined by the method of Newman (17).

EXPERIMENTAL

Group I. Human subjects continuously infused with penicilllin F, G, K, or X

The results in 6 experiments are given in detail in Table I and are graphically summarized in Figures 1 to 3.

In subject G. J., the renal clearance of penicillin G averaged 525 ml. per minute. This is to be compared with a calculated renal plasma flow of 717 ml. per minute and an observed clearance for para-aminohippuric acid of 619 ml. The parallelism between the renal clearance of penicillin G and the glomerular filtration rate simultaneously determined with inulin (*cf.* last 2 columns of Table I and Figure 1), and the constancy of their ratio (0.19 to 0.24, averaging 0.23) are particularly to be noted.

The renal clearance of penicillin G in this subject was independent of the blood level and the rate of urine flow, within the experimental range. Periods in which the blood levels averaged 2.4 and 0.25 micrograms per ml. gave clearances of 498 and 416 ml. per minute, respectively; and periods in which the urine flow was 12.5 and 2.1 ml. per minute gave penicillin clearances of 588 and 416 ml. per minute, respectively.

When the same subject was infused with penicillin X (bottom of Table I), the renal clearance averaged 652 ml. per minute, in satisfactory agreement with both the calculated renal plasma flow (717) and the observed clearance of para-aminohippuric acid (619), and 4.6 times the calculated glomerular filtration rate of 135 ml. per minute. The renal clearance was again largely independent of the absolute serum concentration and rate of urine flow. With a 10-fold difference in serum concentration (3.6 and 0.37 microgram per ml.), the renal clearance varied from 456 to 699 ml. per minute; and in periods in which the urine flow averaged 10.3 and 4 ml. per minute, the renal clearances averaged 787 and 722 ml., respectively.

Subject E. W. is of particular interest (Figure 1 and the second section of Table I). This subject was a woman with long-standing hypertension, in whom the urea clearance was 58 per cent of normal, and the phenolsulfaphthalein excretion was 60 per cent in 2 hours. Corresponding to the obvious impairment of renal function, the renal clearance of penicillin G averaged 242 instead of the calculated value of 617, or 40 per cent of normal. Significant also is the fact that as her blood pressure fell from 218/112 to 158/114 during the first 80 minutes of the experiment, the inulin clearance increased from 52 to 97, and the penicillin clearance from 158 to 308, indicative of an increased flow of blood to the kidney. Meanwhile, the ratio of glomerular filtration to total renal clearance remained essentially constant at the abnormally high level of 0.31. As in patient G. J., the rate of urine flow had no significant effect on renal clearance, which varied only from 276 to 230 ml. per minute as the urine flow increased from 2.0 to 7.4 ml. per minute in 5 successive experimental periods.

Penicillin F gave results essentially the same as penicillins G and X. The renal clearances averaged 550 and 900 ml. per minute in 2 patients in whom the calculated renal plasma flow was 750 ml. per minute. The clearance was again independent of the absolute blood level and of the rate of urine flow over the entire experimental range (*cf.* Figure 3 and Table I).

In patient M. B., injected with penicillin F, midway through the experiment the blood flow to the kidney apparently decreased sharply for a period of approximately 40 minutes. This was manifested by a simultaneous and parallel decrease in the renal clearance of *both* penicillin

TABLE I

The renal clearance of penicillins F, G, K and X in man

Experiments with continuous intravenous infusion at a falling rate. Most of the patients received a priming dose of 2.5 mgm. per kgm. and the rate of infusion was slowly reduced from an initial level of 1 mgm. per kgm. per min. to 0.16 mgm. per kgm. per min. over a period of 2 to 3 hours. In all but 2 patients, the urine specimens were collected by catheterization.

Penicillin species	Subject	Urine collection		Urine penicillin	Average serum penicillin	Renal clearance of penicillin	Glomerular filtration rate, experimentally detd. with inulin or thiosulfate	Ratio of glomerular filtration to penicillin clearance
		Time period	Urine flow					
		minutes	*ml. per min.*	*µg. per min.*	*µg. per ml.*	*ml. per min.*	*ml. per min.*	
F**	H. G.	30–50	9.6	550	0.77	714		0.20
	Wt. = 75 kgm.	50–74	10.2	221	0.53	417	142	0.34
	Ht. = 70 in.	74–97	6.1	222	0.41	541	(calcd. from	0.26
	Surface area =	97–114	9.7	156	0.29	540	surface area)	0.26
	1.89 sq. m.	114–130	11.5	111	0.26	426		0.33
		130–142	15.7	165	0.25	660		0.22
					Experimental averages	550		0.26
					Calculated from surface area	750	142	
	M. B.	19–38	0.8	540	0.6	900	121	0.14
		38–56	1.4	300	0.32	937	186	0.20
	Wt. = 75.5 kgm.	56–79	6.7	227	0.21	1080	216	0.20
	Ht. = 68 in.	79–98	4.4	55	0.15	365	116	0.32
	Surface area =	98–118	0.9	32	0.11	291	100	0.34
	1.89 sq. m.	118–137	2.9	55	0.074	737	137	0.18
		137–157	7.5	44	0.052	850		
					Experimental averages	900*	165*	0.18
					Calculated from surface area	750	142	
G	G. J.	24–44	7.9	1195	2.4	498	104	0.21
		44–63	9.1	790	1.4	564	123	0.22
		63–84	12.5	646	1.1	588	131	0.22
	Wt. = 65 kgm.	84–104	8.5	437	0.82	533	118	0.22
	Ht. = 69½ in.	104–125	3.4	381	0.56	670	130	0.19
	Surface area =	125–144	4.6	274	0.48	571	134	0.24
	1.78 sq. m.	144–163	2.3	181	0.41	441		
		163–183	2.4	146	0.335	436		
		183–203	2.1	104	0.25	416		
					Experimental averages	525	123	0.23
					Calculated from surface area	717	135	0.19
					PAHA clearance	619		
	E. W.	34–55†	3.2	1438	9.1	158	52	0.33
		55–74	2.0	1516	5.5	276	76	0.27
	Wt. = 78 kgm.	74–95‡	3.4	1200	3.9	308	97	0.31
	Ht. = 63 in.	95–114	4.9	787	2.9	271		
	Surface area =	114–134	6.7	556	2.25	247		
	1.8 sq. m.	134–155	7.4	387	1.68	230		
		155–174	5.2	281	1.2	234		
		174–194	3.0	198	0.93	213		
	Urea clearance = 50 per cent of normal				Experimental averages	242	75	0.31
	Phenolsulfonphthalein = 60 per cent in 2 hrs.				Calculated from surface area	617	128	0.20

TABLE I—*Continued*

Penicillin species	Subject	Urine collection: Time period	Urine collection: Urine flow	Urine penicillin	Average serum penicillin	Renal clearance of penicillin	Glomerular filtration rate, experimentally detd. with inulin or thiosulfate	Ratio of glomerular filtration to penicillin clearance
		minutes	*ml. per min.*	*µg. per min.*	*µg. per ml.*	*ml. per min.*	*ml. per min.*	
K	E. P. Wt. = 94 kgm. Ht. = 70 in. Surface area = 2.11 sq. m.	35–53	9.5	983	2.6	378	160 (calcd. from surface area)	0.60
		53–70	2.7	433	2.1	206		
		70–96	1.4	176	1.6	110		
		96–112	6.0	418	1.1	380		
		112–140	4.4	309	0.89	348		
		140–161	2.3	152	0.63	241		
		161–180	0.8	64	0.41	151		
		180–200	1.1	63	0.27	233		
		200–219	?	45	0.11	406		
					Experimental averages	272		0.60
					Calculated from surface area	850	160	
	W. J. Wt. = 57 kgm. Ht. = 66 in. Surface area = 1.62 sq. m.	25–67	2.4	481	2.55	189	74	0.39
		67–86	2.3	483	2.0	241	71	0.29
		86–108	5.7	510	1.65	309	112	0.36
		108–129	5.0	414	1.22	340	115	0.34
		129–153	4.0	326	0.90	362	111	0.31
		153–178	4.4	179	0.69	260	108	0.41
		178–197	7.8	172	0.56	307	143	0.47
		197–224	4.6	116	0.41	283	108	0.38
		224–243	2.6	37	0.29	128	68	0.53
					Experimental averages	269	101	0.39
					Calculated from surface area	665	125	0.20
X	G. J. Wt. = 65 kgm. Ht. = 69½ in. Surface area = 1.78 sq. m.	24–41	9.8	1641	3.6	456	135 (calcd. from surface area)	0.19
		41–61	4.0	1444	2.0	722		
		61–82	5.0	1070	1.6	670		
		82–101	10.3	1062	1.35	787		
		101–117	8.5 } 6.7	1045 } 602	1.15 } 0.96	900 } 627		
		117–140	4.8 }	307 }	0.84 }	365 }		
		140–162	4.3 } 4.7	208 } 298	0.55 } 0.51	380 } 584		
		162–179	5.4 }	415 }	0.47 }	883 }		
		179–201	5.6	258	0.37	699		
					Experimental averages	652		0.22
					Calculated from surface area	717	135	0.20
					PAHA clearance (detd.)	619		

* Two periods of obviously decreased renal plasma flow were not included in calculating averages.

** Because of the small amounts of penicillin F available, the dosage in these 2 patients was approximately half that used in the experiments with G, K, and X

† Blood pressure 218/112.

‡ Blood pressure 158/114.

and thiosulfate and a significant increase in the ratio of glomerular filtration to total renal clearance. All 3 values returned to normal levels in the last 2 experimental time periods.

Contrasting with the values obtained for the clearance of penicillin G and X, the renal clearance of penicillin K in 2 normal subjects averaged 272

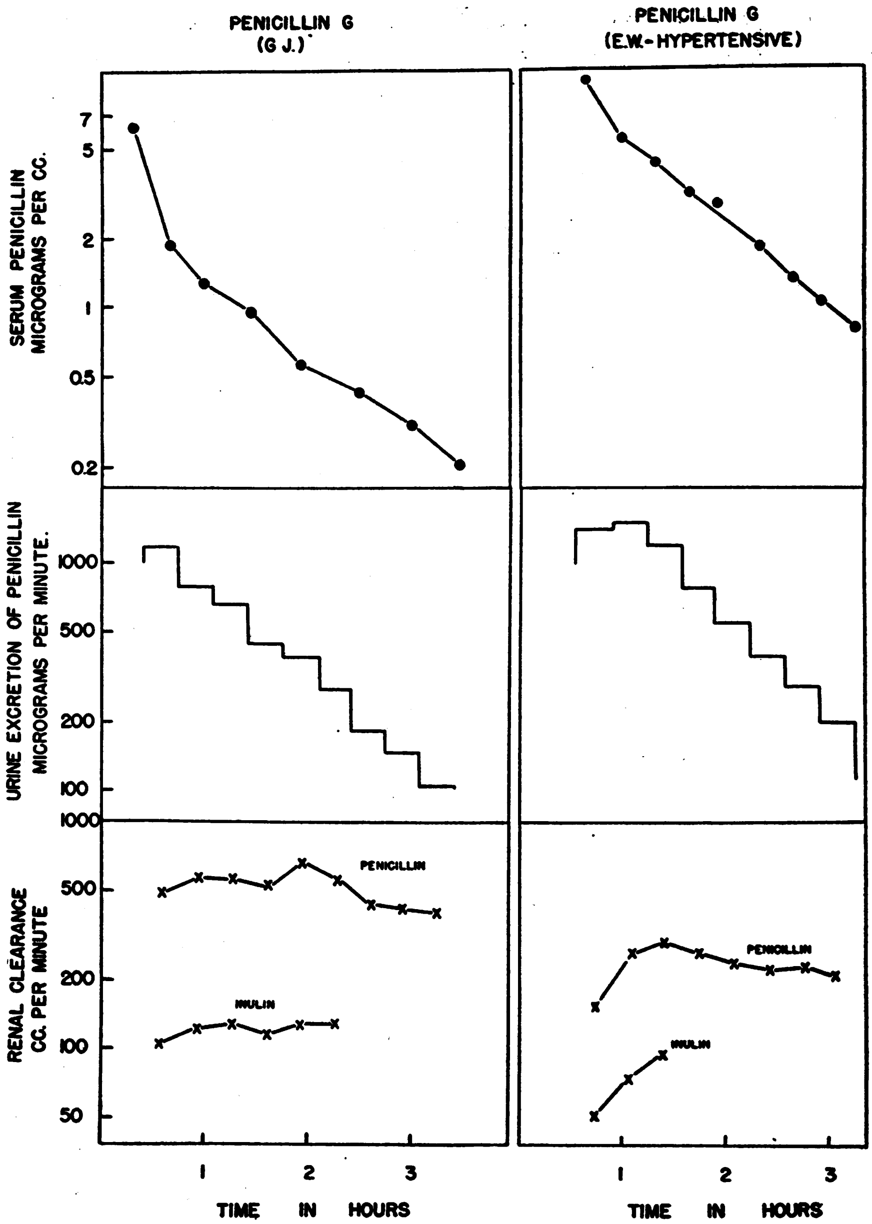

FIG. 1. THE BLOOD LEVEL, URINE EXCRETION AND RENAL CLEARANCE OF PENICILLIN G IN SUBJECTS G. J. AND E. W.

Continuous intravenous infusion at a falling rate (After data of Table I).

and 269 ml. per minute. Within each experiment, however, the results in individual time periods varied widely, the renal clearances varying from 110 to 406 in one subject, and from 128 to 362 in the other. These variations had no demonstrable relationship to either the blood level or rate of urine flow. In these 2 subjects, the calculated renal plasma flow was 850 and 665 ml. per minute, 3 and 2.5 times greater than the clearance of penicillin K. The low values for the renal clearance of penicillin K, which were confirmed in the larger group of patients discussed in the following section, are significant in relation to the low urine recovery of that penicillin species as compared with that of penicillins F, G, or X (*cf.* page 914).

Group II. The renal clearance of penicillins G, K and X in human subjects receiving a single intravenous or intramuscular injection of an aqueous solution

The determination of the renal clearance of penicillin in subjects receiving a single injection of the aqueous solution was far less accurate than the continuous infusion technic used in the experiments of the previous section. The rapidly falling blood level made the "average" value over a given time period of dubious quantitative significance, while a relatively small amount of residual urine in patients who voided voluntarily, or incomplete bladder washing in patients who were catheterized, introduced a large error in the following sample. Despite these limitations, it is clear from the data of Table II that the renal clearance of penicillins G and X generally approximated the total renal

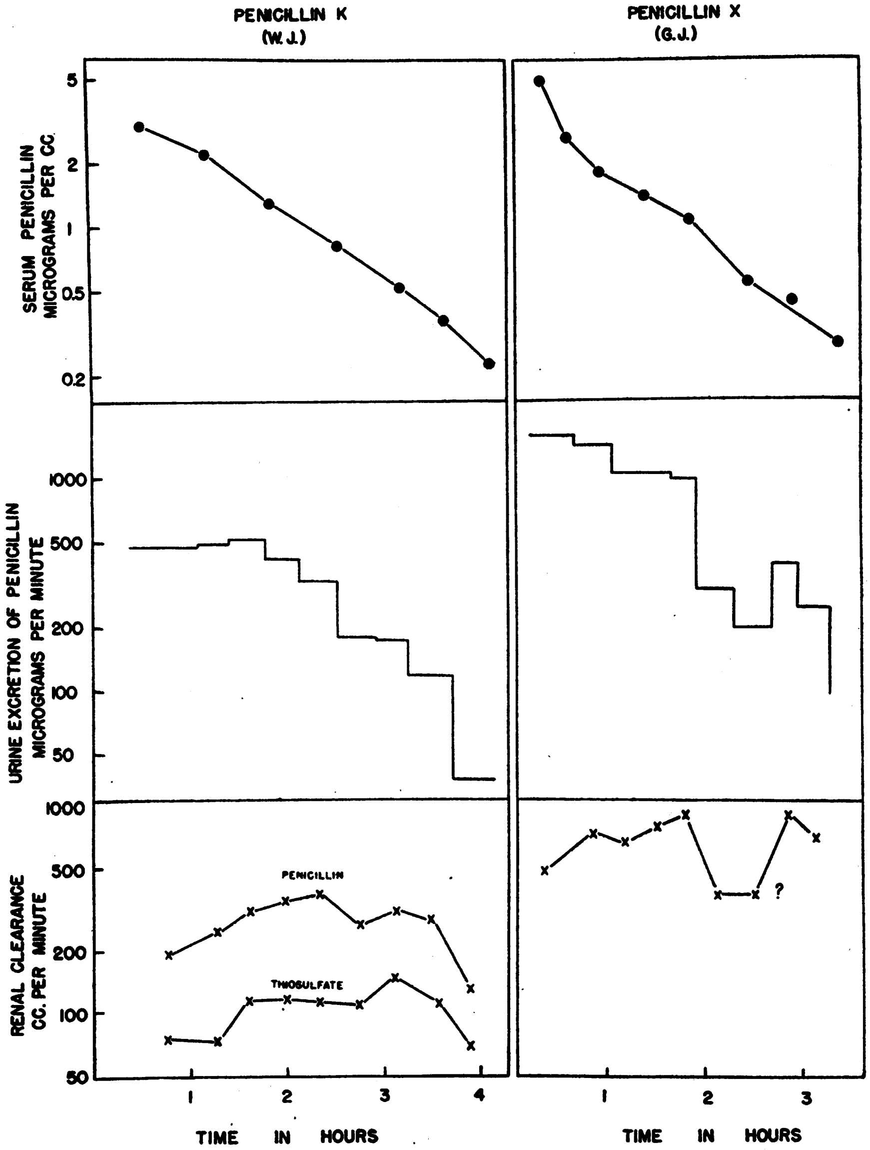

Fig. 2. The Blood Level, Urine Excretion and Renal Clearance of Penicillins K and X in Subjects W. J. and G. J.

Continuous intravenous infusion at a falling rate (After data of Table I).

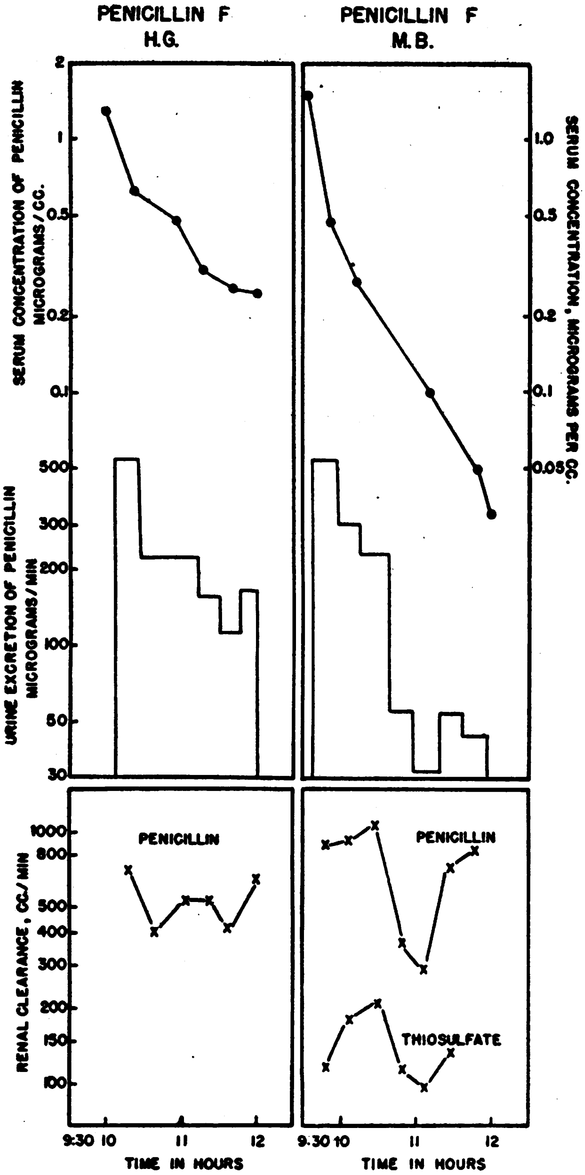

FIG. 3. THE BLOOD LEVEL, URINE EXCRETION AND RENAL CLEARANCE OF PENICILLIN F IN SUBJECTS H. G. AND M. B.

Continuous intravenous infusion at a falling rate (After data of Table I).

plasma flow and averaged 4 to 6 times the glomerular filtration rate.

Patient W. B., an apparent exception, was a hypertensive with a blood pressure of 210/135. The penicillin clearance of G in this patient was considerably less than the calculated normal renal blood flow, and the results in successive time periods were highly variable. However, the ratio of the glomerular filtration rate, experimentally determined with inulin, to the total renal clearance of penicillin was fairly constant, averaging 0.23. The low average clearance in this patient is probably attributable to renal damage associated with long-standing hypertension, and the variability in successive periods can probably be related to the patient's apprehensiveness and incomplete voiding.

Penicillin K again gave results differing from those obtained with penicillins G and X. In the 5 patients studied, the observed renal clearance of K averaged 0.3, 0.2, 0.9, 0.5 and 0.25 of the calculated renal plasma flow. It is particularly to be noted that of these 5 patients, one (D.), when tested with G, gave a normal clearance of 850 ml. per minute, 4 times the value obtained with K; and a second patient (J. W.), who gave an average clearance of 165 ml. per minute with penicillin K, gave clearances of 600 and 1010 ml. per minute when tested with X.

Group III. The renal clearance of penicillin G in in man after its injection as a suspension in peanut oil and beeswax

In 2 patients, the renal clearance of penicillin G was determined after its injection as a finely divided suspension of the potassium salt in peanut oil and 4.8 per cent beeswax (Romansky formula [15]). The prolonged and slowly falling blood levels obtained with this preparation proved admirably suited to the study of renal clearances. In 2 such experiments, summarized in Table III, the average renal clearances were 687 and 471 ml. per minute, to be compared with the calculated renal plasma flows of 796 and 632. These clearances were 4.2 and 3.3 times the glomerular filtration rate as determined with sodium thiosulfate.

Group IV. The renal clearance of penicillin in rabbits

The results obtained in rabbits injected intramuscularly with the crystalline penicillins are summarized in Table IV. The renal clearance of penicillins F, G, and X, studied in a total of 17 rabbits which received 0.35 to 60 mgm. per kgm., varied from 18 to 100. In 4 rabbits receiving penicillin F, the renal clearance averaged 32 ml. per minute (15 to 46 ml. per minute), in 8 rabbits receiving penicillin G at dosages of 0.6 to 60 mgm. per kgm. the average clearance was 59 ml. per minute (17 to 111 ml. per minute), and in 5 rabbits receiving penicillin X the average clearance was 36 ml. per minute (23 to 54 ml. per minute). These results are to be compared with a reported (18) renal plasma flow in rabbits of 1.5 to 4.8 ml. per minute per gram kidney, or a range of 24 to 77 ml. per minute in rabbits with a total kidney weight of 16 grams.

One can only speculate as to the degree to which the technical manipulations of repeated catheterization and cardiac punctures affected the blood flow to the kidney, and contributed to the discrepant results sometimes obtained in successive time periods in the same animal. In most of the experiments the renal clearance of penicillin probably approximated the renal plasma flow; while the significantly lower values sometimes obtained may reflect a decreased blood flow to the kidney under the conditions of the experiment.

Five rabbits were injected with penicillin K at 0.6 mgm. per kgm. However, the speed with which the blood levels fell and the short periods of

TABLE II

The renal clearance of penicillins G, K and X in man

Single intramuscular or intravenous injection. All urine specimens collected by spontaneous voiding, and not by catheterization.

Penicillin species	Subject	Time period	Urine flow	Urine penicillin	Average serum penicillin	Renal clearance of penicillin: Experimental (Aver.)	Renal clearance of penicillin: Calculated from surface area	Rate of glomerular filtration: Experimentally detd. with inulin	Rate of glomerular filtration: Calculated from surface area	Ratio of glomerular filtration to penicillin clearance
		hours	*ml. per min.*	*µg. per min.*	*µg. per ml.*					
G	W. B. (hypertension) Wt. = 73 kgm. Ht. = 67¾ in. Surface area = 1.85 sq. m.	¼–½	7.1	704	1.45	486		95		0.19
		½–1	9.3	234	0.76	308 (335)	745	84	127	0.27
		1–2	6.2	67	0.31	216		49		0.23
	D. Wt. = 79 kgm. Ht. = 75 in. Surface area = 2.06 sq. m.	0–1½		441	0.52	850	822		150	0.18
K	W. B. Wt. = 73 kgm. Ht. = 67¾ in. Surface area = 1.85 sq. m.	¼–½	7.1	408	2.60±	157		98		0.62
		½–1	9.3	204	1.10	185 (225)	745	92	127	0.41
		1–2	6.2	89.6	0.27	332		90		0.27
	D. Wt. = 79 kgm. Ht. = 75 in. Surface area = 2.06 sq. m.	0–1		90	0.48	188	822		150	0.80
	H. Wt. = 57.3 kgm. Ht. = 70½ in. Surface area =	¼–½	5.9	188	0.30	627	685	124	129	0.20
	L. B. Wt. = 61½ kgm. Ht. = 66½ in. Surface area = 1.69 sq. m.	0–½		150	0.40	375	675		127	0.34
	J. W. Wt. = 60.5 kgm. Ht. = 67 in. Surface area = 1.68 sq. m.	0–½		116	0.84	138				
		½–1		69	0.46	150 (165)	670		126	0.76
		1–2		18.6	0.09	207				

TABLE II—*Continued*

Penicillin species	Subject	Time period	Urine flow	Urine penicillin	Average serum penicillin	Renal clearance of penicillin		Rate of glomerular filtration		Ratio of glomerular filtration to penicillin clearance
						Experimental (Aver.)	Calculated from surface area	Experimentally detd. with inulin	Calculated from surface area	
		hours	*ml. per min.*	*μg. per min.*	*μg. per ml.*					
X	T. Wt. = 58 kgm. Ht. = 66¾ in. Surface area = 1.66 sq. m.	¼–½	18.8	579	0.37	1560		140		0.21
		½–1	8.5	147	0.22	668 (920)	?	144	126	0.27
		1–2	2.3	40	0.075	533				
	J. W. Wt. = 60.5 kgm. Ht. = 67 in. Surface area = 1.68 sq. m.	0–1		241	0.40	600 (800)	670		126	0.21
		1–2		202	0.20	1010				0.13
	R. W. Wt. = 53 kgm. Ht. = 64 in. Surface area = 1.55 sq. m.	½–1	2.6	76.5	0.135	567	625		117	0.21
		1–2	6.5	27.9	0.054	517 (540)				0.23
	G. Wt. = 75 kgm. Ht. = 68 in. Surface area = 1.86 sq. m.	¼–½	15.9	635	0.45	1410 ?		154		0.11 ?
		½–1	7.8	169	0.20	845 (865)	750	154	141	0.18
		1–2	4.1	287	0.084	342		69		0.20
	B. H. Wt. = 51 kgm. Ht. = 64 in. Surface area = 1.52 sq. m.	1–2	0.9	188	0.41	460				0.25
		2–3	2.7	72	0.14	534 (450)	453		115	0.22
		3–4	1.0	19	0.05	366				0.31
	S. Wt. = 67 kgm. Ht. = 69¼ in. Surface area = 1.82 sq. m.	0–1		410	0.60	700±	763		137	0.20
		1–2		157	0.19	826 (760)				0.17

time for which penicillin remained at measurable levels precluded a precise measurement of the average blood level during the period of urine collection, and the figures in Table V with respect to the renal clearance of penicillin K are of dubious significance.

In an attempt to saturate the tubular secretory mechanism, rabbits were injected intravenously with 6, 60 and 600 mgm. per kgm. of penicillin G, and blood and urine specimens were obtained for assay in the usual manner. As is shown in Table IV, after injection at 6 or 60 mgm. per kgm. the renal clearance of penicillin remained at a high level which did not vary significantly over the entire range of plasma concentration studied, and approximated the total renal plasma flow. Saturation of the tubular excretory mechanism was, however, achieved by a single intravenous injection of penicillin G at 600 mgm. per kgm., which corresponds to 60 million units in the average human adult. As is shown in Table V, in 2 rabbits so injected, with initial blood levels 5 to 7 minutes after the injection , of 2,667 and 3,200 micrograms per ml., the renal clearance of penicillin in the first hour after the injection was abnormally low (9.0, decreasing to 3 ml., in rabbit 5791, and 7 ml. per minute in rabbit 5939). These values are of the same order of magnitude as the normal rate of glomerular filtration reported by Walker and his associates (18). The renal clearance remained at this low level until the plasma concentration had fallen in 1 instance to approximately 1,500, and in the other to approximately 1,000 μg. Thereafter, the renal clearance rose, in 1 instance sharply,

TABLE III

The renal clearance of penicillin G in man after the intramuscular injection of a suspension in peanut oil and beeswax

300,000 units per ml. equals 180 mgm. per ml.

Patient	Penicillin dosage	Urine collection: Time periods	Urine collection: Urine flow	Urine penicillin	Average penicillin blood level	Renal clearance of penicillin	Glomerular filtration rate*	Ratio of glomerular filtration to total renal clearance
		minutes	*ml. per min.*	*µg. per min.*		*ml. per min.*		
A. K.		35–56	1.0	213	0.36	592	133	0.23
Ht. = 71¾ in.	1 ml. = 2.3 mgm.	56–77	2.1	309	0.40	772	184	0.24
Wt. = 79 kgm.	per kgm.	77–104	2.5	245	0.42	583	187	0.32
Surface area =		104–166	1.6	476	0.60	793		
2.0 sq. m.		166–185	1.5	1010	0.92	1097		
		185–391	0.7	311?	1.10	283		
						Experimental average *687*	*168*	*0.24*
						Calcd. from surface area *796*	*150*	
S. C.		37–56	1.6	361	0.65	555	150	0.27
Ht. = 65½ in.	0.9 ml. = 3.1 mgm.	56–78	1.4	364	0.76	479	112	0.24
Wt. = 52 kgm.	per kgm.	78–96	2.1	507	0.90	563	145	0.26
Surface area =		96–118	2.6	383	1.00	383	111	0.29
1.57 sq. m.		118–145	2.8	383	1.00	383	99	0.26
		145–240	1.2	508	1.10	462		
						Experimental average *471*	*123*	*0.25*
						Calcd. from surface area *632*	*118*	

* Experimentally determined with sodium thiosulfate.

and in 1 progressively, to reach peak values of 18 to 28 and 23 to 57 ml. per minute. As is shown in Figure 4, the rate at which penicillin G disappeared from the blood of these 2 rabbits paralleled its renal clearance. During the phase of tubular saturation, the blood level fell slowly; but as the renal clearance increased toward normal levels there was a parallel accelerating drop in the serum concentration, particularly evident in rabbit 5791.

In the latter rabbit the glomerular filtration rate and renal plasma had been determined experimentally with sodium thiosulfate and para-aminohippuric acid, 2 days before the injection of the penicillin. The observed glomerular filtration rates of 6.0 and 6.4 ml. per minute agree with the renal clearance of penicillin during the period of tubular saturation (3 to 9 ml.); while the para-aminohippuric acid clearances of 17.5 and 18.0 ml. per minute are in reasonably good agreement with the penicillin clearances of 18 to 28 ml. per minute, obtained when the plasma levels had fallen below the level of tubular saturation.

The results in a number of rabbits' experiments in which the animals received varying amounts of commercial sodium penicillin (of unknown composition with respect to penicillins F, G, K, and X), given as a single injection, are summarized in Table V. In 7 rabbits injected at dosages of 4,000, 8,000, or 150,000 units per kgm., the average renal clearances were 53, 57, 40, 28, 42, 24, and 43 ml. per minute. In these experiments the blood level varied from a peak of 45 µg. per ml. to a low of 0.044 µg.

In rabbit 5660, injected with commercial penicillin at 1,200,000 units per kgm., the renal clearance was abnormally low, with observed values of 10, 13, 5.7, and 4.9 ml. per minute in successive time periods. As had previously been found with penicillin G, the tubular secretory mechanism had been saturated by the high blood levels, which in this animal ranged from 580 to 800 µg. per ml.

DISCUSSION

1. The data here presented indicate that in both rabbits and man, penicillins F, G, and X are secreted into the urine by the kidney at a rate which corresponds essentially to their total removal from the blood reaching that organ. The normal renal clearance of penicillin so closely approximates the renal plasma flow as determined experimentally with para-aminohippuric acid that it may be used as a test of kidney function. Indeed, penicillin has

TABLE IV

The renal clearance of penicillins F, G, K and X in rabbits

Single intramuscular injection

Penicillin species	Rabbit no.	Weight	Penicillin dosage	Time of urine collection	Urine penicillin	Average serum penicillin	Renal clearance of penicillin
			mgm. per kgm.	*hours*	*µg. per ml.*	*µg. per ml.*	*ml. per min.*
F	5244	2.25	0.35	0–1	7.7	0.25	31
	5245	2.5	0.6	0–1 1–2	14.3 2.5	0.42 0.063	34 } (37) 40 }
	5296	2.22	0.6	0–1 1–2	8.6 0.86	0.4 0.1	22 8.6
	5446	3.14	0.6	½–1	6.9	0.15	46
G	5318	2.72	0.6	0–1	30	0.27	111
	5428	2.73	0.6	½–1 1–2	10.5 2.83	0.38 0.14	28 } (24) 20 }
	5445	3.08	0.6	½–1 1–2 2–3	10 5.75 3.8	0.18 0.11 0.07	55 } 52 } (54) 54 }
	5467	2.8	0.6	½–1 1–2	12.3 3	0.2 0.038	62 } (70) 79 }
	5159	2.37	1.5	1–2	23	0.42	55
	5187	2.24	1.5	1–2	14.7	0.85	17
	5843	2.74	6	1/12–¼ ¼–½ ½–1 1–2	1,170 384 90.5 21.6	11 3.1 1.3 0.25	106 } 124 } (96) 69 } 86 }
	5823	2.48	60	0–1 1–2 2–4 4–6	1,813 249 66.7 7.5	20 6.3 2.65 0.35	91 } 39 } (44) 25 } 21 }
	5791*	2.44	600	7 min.–¼ ¼–½ ½–1 1–2 2–4 4–6 6–8 8–10 10–12 12–13½	20,800 13,050 4,630 5,000 2,338 452 58 40.8 27.8 21.3	2,300 1,800 1,560 1,500 130 5.2 2.6 1.8 1.0 0.92	9.0 7.3 3.0 3.3 18 90 22 22 28 23
	5939†	2.82	600	0–36 min. 36–66 min. 66–106 min. 106–136 min. 136–166 min. 166–199 min. 199–232 min. 232–262 min.	16,667 7,310 8,890 2,600 1,891 931 415 320	2,400 1,050 350 110 40 16.3 10 6.7	6.9 7.0 23 24 47 57 42 48

TABLE IV—*Continued*

Penicillin species	Rabbit no.	Weight	Penicillin dosage	Time of urine collection	Urine penicillin	Average serum penicillin	Renal clearance of penicillin
			mgm. per kgm.	*hours*	*μg. per ml.*	*μg. per ml.*	*ml. per min.*
K	5186	2.73	0.6	0–1	8.15	0.3±	27
K	5210	2.23	0.6	0–1	12.3	0.12±	100
K	5242	3.16	0.6	0–1	10.1	0.35?	29
K	5319	3.09	0.6	0–1	8.8	0.17±	52
K	5447	2.93	0.6	0–½	9.0	0.22±	41
X	5252	2.35	0.6	1–2	2.9	0.115	25
X	5258	2.11	0.6	1–2	3.6	0.09	40
X	5327	2.85	0.6	1–2	5.7	0.16	36
X	5449	3.03	0.6	½–1	18.3	0.265	69 } (54)
				1–2	5.6	0.11	51
				2–3	1.66	0.04	42
X	5465	2.8	0.6	½–1	2.7(?)*	0.165	17(?) } (23)
				1–2	2.7	0.095	28
				2–3	1.75	0.07	25

* Injected intravenously instead of intramuscularly.
† Average value questionable because of rapidly changing blood level in this period.

certain unique points of superiority over diodrast, para-aminohippuric acid, or any other substance currently used for that purpose. The plasma concentrations of the latter compounds cannot exceed a level of 3 to 5 mgm. per cent, as higher concentrations may so overload the tubular mechanism responsible for their secretion that complete extraction does not take place. On the other hand, plasma concentrations much lower than 1 mgm. per cent do not permit accurate determinations by the usual laboratory methods. In consequence, the useful range of plasma concentration varies only 5-fold. With penicillin, however, because the biological method used for assay is sensitive to as little as 1 part in 80,000,000 (0.00125 mgm. per cent), and because complete renal clearance is observed up to a minimum level of 1 mgm. per cent in man (10 μg. per ml.), and in rabbits of at least 4 mgm. per cent, there is as least a 1,000-fold range of plasma concentration within which the renal clearance of penicillin can be used as a measure of renal function in man.

2. The low renal clearance of penicillin K in man, approximately ½ to ⅕ that of penicillins F, G, or X, would at first sight imply that penicillin K is excreted more slowly than the other species. This should be reflected in a more sustained blood level. Instead, previous work in this and other laboratories (2 to 4) has shown that penicillin K disappears from the blood more rapidly than do the other penicillins. Moreover, the total urinary excretion in man has been shown to average only 30 per cent of the amount injected, as compared with recoveries for G and X of 80 to 100 per cent. The contradictions involved in a low renal clearance, a rapidly falling blood level, and a low urinary recovery may be more apparent than real. The low urinary recovery of penicillin K, and its rapid disappearance from the blood are probably referable to the fact that it is bound and inactivated by both the plasma (14, 20) and tissues (21, 22, 23) to a greater extent than is e.g. penicillin G. That combination with plasma protein may be not only quantitatively more complete, but also less freely reversible, and thus prevent the complete removal of penicillin K from the blood by the renal secretory mechanism.

3. The fact that penicillins F, G, and X have a renal clearance approximating the total plasma flow through the kidney is reflected in the rapidly falling blood levels observed after their intravenous or intramuscular injection in aqueous solution.

Attempts to modify the rate of excretion by reducing the rate of urine flow, as by restricting salt and water intake, or by administering pitressin, are physiologically unsound. As is true of other substances with maximal tubular secretion, the renal clearance of penicillin has been shown to be unaffected even by wide variations in the rate of urine flow. Such measures could modify the rate of secretion only by affecting the blood flow to the kidney.

A second suggested method of delaying the excretion of penicillin is to block its excretion by the administration of other substances excreted by the same tubular mechanism. Diodrast, para-aminohippuric acid and benzoic acid (5 to 10, 12) have all been reported as effective in this respect. The difficulty lies in the fact that these blocking substances are as rapidly excreted as the penicillin itself. To maintain an effective concentration of such blocking agents may prove no less laborious, and with some of these agents, no less costly, than to repeat the injections of penicillin or to increase the dosage.

The most effective method yet suggested of prolonging the time for which penicillins F, G, and X remain in the blood at effective concentrations is to delay its absorption from an intramuscular depot. This has been accomplished by injecting the drug as a suspension in peanut oil and beeswax (15). The absorption then proceeds at a slower rate than the excretion, and the time for which the penicillin remains in the blood in demonstrable and effectively bactericidal concentrations is significantly prolonged.

4. It is clear from the data here reported that the therapeutic efficacy of penicillin would be greatly enhanced were it possible by appropriate chemical modification to decrease its renal clearance. An antibiotic with the same bactericidal activity as

TABLE V

The renal clearance of penicillin in rabbits

Single intramuscular injection of commercial sodium salt

Rabbit no.	Weight	Penicillin dosage	Time of urine collection	Urine penicillin	Average serum penicillin	Renal clearance of penicillin
	kgm.	*units per kgm.*	*hours*	*units per min.*	*units per ml.*	*ml. per min.*
3851	2.5	4,000	1–2 2–3	8.55 2.3	0.16 0.044	53 52 }53
3925	2.8	4,000	1–2 2–3	12.4 4.5	0.28 0.065	44 69 }57
4100	2.64	8,000	1–2 2–3	38.1 6.9	1.05 0.16	36 43 }40
4157	2.62	8,000	1–2 2–3 3–4	20.5 6.7 0.78	1.0 0.18 0.03	21 37 }28 26
4132	2.43	8,000	1–2	41.5	1.0	42
4158	2.32	8,000	1–2	7.1	0.3	24
5961	3.7	150,000	¼–½ ½–1 1–2 2–3 3–4	1,408 2,432 1,360 737 596	43 45 34 19 13	33 54 40 }43 39 46
5660	2.7	1,200,000	¼–½ ½–1 1–2 2–3	5,713 9,856 4,576 3,422	580 770 800 700	10 13 5.7 }8.4 4.9

TABLE VI

The renal clearance of penicillins F, G, K, and X in man and in rabbits

Summary of all experiments

Penicillin species	Renal clearance, ml. per minute: Man: Observed clearances: Continuous infusion	Man: Observed clearances: Single injection, aqueous	Man: Observed clearances: Single injection, POB	Man: Mean of all expts.	Rabbit: Observed clearances	Rabbit: Mean
F	550 900			725	31, 37, 15, 46	32
G	525	335 850	687 409	560	111, 24, 54, 70, 55, 18, 96, 44, 24, 65	56
K	272 269	225 188 627 375 165		300		
X	652	920 800 542 865 450 763		710	26, 40, 36, 54, 23	36
Commercial penicillin					53, 57, 40, 28, 42, 24, 43	41

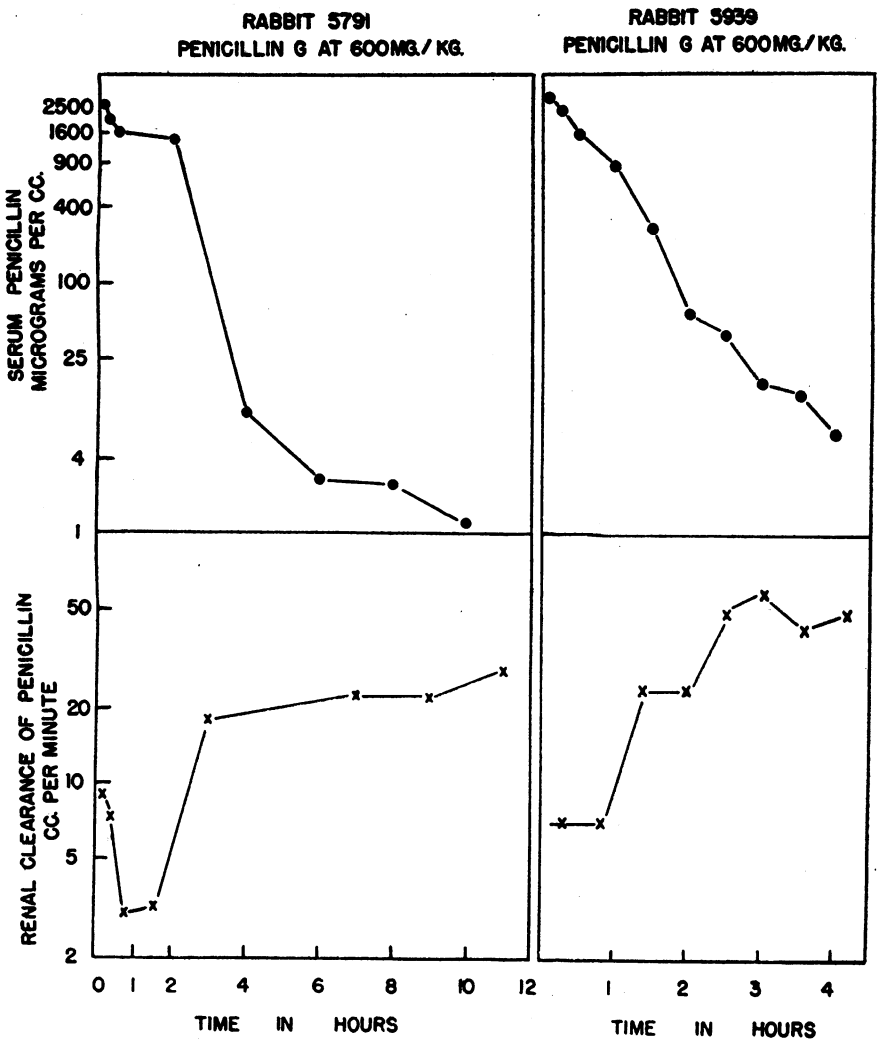

FIG. 4. THE SATURATION OF THE RENAL SECRETORY MECHANISM FOR PENICILLIN G BY A SINGLE MASSIVE INTRAVENOUS DOSE OF 600 MGM. PER KGM.

penicillin *in vitro,* but with a renal clearance in man of *e.g.,* 150 instead of 600 ml. per minute, might well be many times more active, since both the serum concentration of penicillin and the time for which an effective level was maintained would thereby be increased. The present experiments with F, G, and X indicate that the groupings present in these 3 species have no demonstrable effect on the rate of tubular secretion; and the apparently lower renal clearance of K is more than counteracted by some of its other pharmacological properties. It is nevertheless possible that derivatives of penicillin produced either by direct chemical modification or by the addition of appropriate precursors to the culture medium may have a significantly lower renal clearance than the 4 natural penicillins here studied, and a correspondingly enhanced therapeutic activity.

SUMMARY

1. The renal clearance of penicillins F, G, and X in man was found to approximate the total renal plasma flow and was approximately 4 to 5 times greater than the renal clearance of inulin or sodium thiosulfate. The penicillin clearance was independent of the absolute blood level over the entire

range 0.05 to 10 μg. per ml. and was similarly independent of the rate of urine flow.

2. The possibility is suggested that penicillin can be used in lieu of para-aminohippuric acid or diodrast as a test of renal plasma flow and renal function.

3. The renal clearance of penicillin K in man varied from 1/4 to 1/2 that of F, G, or X. Possible explanations for this anomalous result are discussed in the text.

4. The tubular excretory mechanism was completely saturated in 2 rabbits receiving 600 mgm. per kgm. of penicillin G. In these the initial blood levels were 2,667 and 3,200 μg.; and the initial renal clearances of 3 and 7 ml. per minute corresponded to the glomerular filtration rate. As the serum concentration fell to less than the saturation level for the tubular mechanism, the renal clearances rose to normal levels of 18 to 28 and 23 to 57 ml. per minute.

5. Although no differences were found between the renal clearance of penicillins F, G, or X, the possibility is suggested that penicillin derivatives may be produced with significantly lower clearances than those of the natural penicillins so far identified, and with correspondingly enhanced therapeutic activity *in vivo*.

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