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Acute renal response to large doses of intravenous prednisolone in kidney homograft recipients and in normal subjects

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The immediate renal response to large intravenous doses of prednisolone was studied in 18 kidney homograft recipients and in 6 normal subjects. Clearance rates of inulin (C_{IN}), creatinine (C_{CR}), p-aminohippurate (C_{PAH}), and electrolytes were measured over 3 one-hour periods following intravenous infusion of prednisolone (1 Gm.) and compared with corresponding clearance rates after a placebo infusion. C_{IN}, C_{CR}, and C_{PAH} rates and $\left(\frac{C_{CR}}{C_{IN}}\right)$ ratios exhibited a substantial decrease during all collection periods following the infusion of prednisolone, both in the normal subjects and in the patients. Fractional excretion of potassium $\left(\frac{C_K}{C_{IN}}\right)$ increased in a progressive fashion reaching peak values after 3 hours. Biphasic variations were observed in the fractional excretion of sodium $\left(\frac{C_{NA}}{C_{IN}}\right)$; an increase during the first hour was followed by a decrease during the third hour. The changes in the fractional excretions of ultrafiltrable calcium $\left(\frac{C_{Ca}}{C_{IN}}\right)$, ultrafiltrable magnesium $\left(\frac{C_{Mg}}{C_{IN}}\right)$, and phosphorus $\left(\frac{C_P}{C_{IN}}\right)$ were minimal. Normal subjects exhibited significant decreases in $\frac{C_{Ca}}{C_{IN}}$ and $\frac{C_{Mg}}{C_{IN}}$ following the infusion of prednisolone; there was no significant change in the patients. $\frac{C_P}{C_{IN}}$ increased significantly both in the normal subjects and in the patients. These results indicate that acute suppression of kidney function is a general renal response to large doses of glucocorticoids. The marked decrease in the creatinine clearance ratio $\left(\frac{C_{CR}}{C_{IN}}\right)$ observed after the administration of prednisolone is consistent with a depressed tubular secretion of creatinine and emphasizes the inadequacy of C_{CR} as an indication of glomerular filtration rate (GFR) under conditions in which large doses of glucocorticoids are employed.

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Intermittent large intravenous doses of glucocorticoids have been employed in treatment of homograft recipients as a supplement to the maintenance immunosuppression regimen.[1-3] The benefit accruing from this combined management has not been established fully as yet; however, clinical[2-3] and experimental[4] observations support its possible therapeutic effect.

The response of renal homografts to large doses of glucocorticoids may reflect at least 2 different aspects of hormonal action: (1) immunologic suppression of homograft rejection with a resulting improvement in renal function and (2) direct (nonimmunologic) effect on renal hemodynamics and/or tubular transport.

The present study was undertaken to evaluate the acute renal response to large doses of glucocorticoids in recipients of kidney homografts and in a control group of normal subjects.

Methods

Eighteen patients and 6 normal subjects were investigated. The patients were managed with intermittent intravenous prednisolone, in addition to oral maintenance doses of prednisone and azathioprine (Table I). In most patients, the kidney function, as measured by daily creatinine clearances, was stable within several days preceding the study. All patients and normal individuals were given prednisolone sodium phosphate (1 Gm.) (Hydeltrasol) intravenously in about 50 ml. of normal saline over one hour. Fourteen of 18 patients and all 6 normal individuals also received intravenously normal saline with placebo (50 ml.) which consisted of the liquid vehicle of prednisolone. The experiments with prednisolone and placebo were no more than one week apart.

Clearance studies. The clearance studies were conducted in a fasting state, at the same time of day, both in the prednisolone and in the placebo experiments. An oral water load was given prior to the study (20 ml. of tap water per kilogram of body weight). During the study, urine volumes were replaced with equal amounts of water. In patients whose water intake had been restricted, the water load was reduced accordingly. Priming doses of inulin (IN) and *p*-aminohippurate (PAH) based on body weights were injected intravenously and were followed by sustaining doses. The latter were infused with a Sigmamotor pump delivering 1 ml. of normal saline per minute, with IN and PAH in amounts calculated on the basis of the presumptive glomerular filtration rates (GFR). Forty-five minutes were allowed for equilibration before timed urine collections were started. Each collection period lasted 30 to 60 minutes, and a blood sample was obtained at its midpoint. The patients and the normal individuals remained supine during the whole study with the exception of assuming upright positions for voluntary voiding. Following at least 2 control collections, either prednisolone or placebo infusion was started and urine samples were collected during the following 3 hours. All serum and urine specimens were assayed for IN, creatinine (CR), PAH, sodium (Na), potassium (K), phosphorus (P), calcium (Ca), and magnesium (Mg). IN,[5] CR,[6] and PAH[7] were determined by a Technicon AutoAnalyzer. Na and K were measured with an Instrumentation Laboratory Flame Photometer Model 143. Total and ultrafiltrable Ca and Mg were measured with the Norelco Unicam Atomic Absorption Spectrophotometer. All samples and standards were diluted with lanthanum chloride to prevent phosphate and protein interference. Ultrafiltrates of serum were prepared with the use of colloidian bags.[8] Inorganic P was measured utilizing the methodology developed by the American Monitor Co.[9]

Results

The individual baseline data representing the average values of the control periods of all patients and normal subjects are shown in Table II. Ca and Mg clearances were determined in terms of the ultrafiltrable fractions of these

Table I. Clinical data for all patients and control subjects

Subjects	*Age*	*Sex*	*Body surface (M^2)*	*Diagnosis**	*Days after transplant*	*Donor†*	*Prednisone (mg. per day)*
Patients							
C. B.	38	M	1.85	CGN	60	C	20
S. J.	37	M	1.71	CGN	14	C	120
S. E.	38	M	1.51	CGN	60	R	45
W. D.	34	M	1.75	CGN	14	C	120
M. P.	35	M	1.73	CGN	457	R	25
L. C.	18	F	1.45	CGN	611	R	25
T. W.	38	M	1.72	PN	92	R	20
J. M.	45	M	2.00	CGN	91	C	20
B. J.	35	M	1.91	CGN	61	C	40
G. C.	14	M	1.30	CGN	30	R	60
C. E.	19	M	1.62	CGN	5	R	170
H. R.	40	M	1.93	CGN	213	R	25
L. E.	33	M	1.64	CGN	488	R	35
C. D.	34	M	1.89	PN	42	R	25
K. R.	45	M	1.76	CGN	153	R	90
T. S.	14	F	1.28	CGN	21	C	60
D. J.	23	M	1.79	CGN	2,007	R	40
J. C.	41	M	1.95	PCK	154	C	45
Normal							
C. A.	31	M	2.08				
P. M.	35	M	1.79				
R. J.	29	M	1.90				
A. G.	40	M	1.78				
P. W.	31	M	1.72				
G. S.	30	M	1.73				

*(CGN) Chronic glomerulonephritis; (PCK) polycystic kidneys; (PN) chronic pyelonephritis.
†(C) Cadaver; (R) related.

cations. All clearance values are for a body surface area of 1.73 square meters. The clearance data were divided into 4 consecutive periods: (1) one control clearance which was the average of all preinfusion clearances, (2) 3 postinfusion clearances which were hourly averages of clearances determined from urine collections started after the beginning of the infusion and completed 3 hours later. The mean changes in the clearances of inulin (C_{IN}), creatinine (C_{CR}), and *p*-aminohippurate (C_{PAH}) associated with prednisolone and placebo infusions are presented graphically in Figs. 1, *A* and *B*, 2, *A* and *B*, and 3, *A* and *B*, which illustrate sequential deviations of the postinfusion clearances from the preinfusion clearance rates as the per cents of control: $\frac{\text{postinfusion clearance}}{\text{control clearance}} \times 100$. All results represent mean values and standard deviation for each group. The individual absolute clearance values, C_{IN}, C_{CR}, and C_{PAH}, during the 4 consecutive collection periods with prednisolone infusion are shown on Table III. Renal handling of Na, K, Ca, Mg, and P are expressed in terms of their fractional

Table II. Control clearances (C) in all patients and in normal subjects

Subjects	C_{IN} *(ml./min.)*	C_{CR} *(ml./min.)*	C_{PAH} *(ml./min.)*	S_{Na}* *(mEq./L.)*	C_{Na} *(ml./min.)*	S_K* *(mEq./L.)*	C_K *(ml./min.)*
Patients							
C. B.	89	123	490	127	1.00	3.1	28.5
S. J.	76	78	465	127	1.73	3.3	15.7
S. E.	76	94	365	144	1.40	4.3	25.2
W. D.	59	84	335	133	1.43	4.0	19.0
M. P.	57	76	410	132	2.24	2.5	13.8
L. C.	69	80	650	135	1.01	3.3	11.1
T. W.	54	91	354	143	1.48	3.8	18.8
J. M.	45	64	310	134	1.49	3.6	9.2
B. J.	45	75	255	131	1.15	3.3	28.0
G. C.	66	95	580	132	0.99	4.1	41.0
C. E.	50	66	360	141	0.11	4.3	16.0
H. R.	39	50	145	135	2.59	3.1	40.5
L. E.	41	65	226	141	2.34	3.1	7.5
C. D.	34	94	191	132	1.00	2.8	22.6
K. R.	23	35	165	141	1.49	3.7	17.3
T. S.	27	37	242	142	0.48	3.3	18.5
D. J.	19	36	294	134	0.56	3.1	7.3
J. C.	13	22	88	138	0.76	3.4	11.6
Mean	49.0	70.3	323.6	135.8	1.29	3.4	19.5
± S.D.	21.3	26.2	153.3	5.3	0.6	0.5	10.0
Normal							
Mean	105.2	126.3	543.8	140.9	1.4	3.54	15.76
± S.D.	10.5	8.9	42.3	0.97	0.5	0.23	10.8

*(S_{Na}) Sodium concentration in the serum; (S_K) potassium concentration in the serum; (S_P) calcium concentration in the serum; (S_{Mg}) magnesium concentration in the serum; (DS_{Mg})

excretions: $\frac{C_{Na}}{C_{IN}}, \frac{C_K}{C_{IN}}, \frac{C_{Ca}}{C_{IN}}, \frac{C_{Mg}}{C_{IN}}, \frac{C_P}{C_{IN}}$. The quantitative assessment of the alteration in renal handling of these ions was attained by subtracting the preinfusion fractional excretion from the postinfusion values, with results indicating either increments or decrements in the fractional excretion of a given ion.

The analysis of the variations associated with prednisolone infusion is based on the comparison of the observations during prednisolone infusion with the corresponding observations during placebo infusion. The determination of significant differences between parallel observation periods was made with the use of the Student's t test.

Inulin clearances. C_{IN} rose progressively following placebo infusion both in the patients and in the normal subjects. The C_{IN} rates during the 3 consecutive hourly periods in patients equalled (mean ± S.D.) 106 ± 11, 114 ± 24, and 117 ± 23 per cent, and in the normal subjects, 106 ± 6, 110 ± 9, and 106 ± 9 per cent of the preinfusion control C_{IN}. Following prednisolone infusion, C_{IN} decreased in both groups. The values in the patient were 80 ± 14, 87 ± 19, and 88 ± 18 per cent, and in the normal subjects, 88 ± 2, 92 ± 12, and 93 ± 9 per cent of the preinfusion

S_P* (mg./ 100 ml.)	C_P (ml./min.)	S_{Ca}* (mg./ 100 ml.)	DS_{Ca}* (mg./ 100 ml.)	C_{Ca} (ml./min.)	S_{Mg}* (mg./ 100 ml.)	DS_{Mg}* (mg./ 100 ml.)	C_{Mg} (ml./min.)
2.1	3.6	10.0	4.7	3.40	2.6	1.6	16.2
1.6	0.8	9.6	4.7	1.70	2.2	1.4	9.6
0.4	36.0	8.2	4.2	11.40	2.2	1.6	12.6
1.8	33.5	12.4	5.6	10.00	3.1	2.1	17.4
2.2	12.5	—	—	—	—	—	—
3.7	18.0	10.0	4.6	3.45	1.9	1.3	4.3
1.6	19.4	9.9	4.7	5.31	2.5	1.5	11.1
2.8	13.6	9.2	4.1	0.58	1.9	1.2	8.3
2.3	27.0	11.0	4.3	0.73	2.7	1.4	9.5
3.7	6.3	9.2	3.8	0.75	3.3	1.6	29.9
1.9	41.3	12.4	5.2	5.40	2.3	1.9	18.1
3.5	9.8	9.6	5.0	5.60	2.6	1.7	16.2
2.4	4.6	10.0	4.4	0.94	—	1.8	17.4
2.3	1.7	10.9	3.8	2.16	3.0	1.5	9.6
2.1	6.5	10.2	4.1	1.82	3.4	1.7	11.6
2.0	17.8	9.6	5.0	0.24	2.7	1.7	2.4
4.6	11.9	9.2	5.7	4.85	2.3	1.9	16.4
3.5	9.4	10.4	4.0	1.86	2.6	1.5	10.5
2.4	15.2	10.1	4.6	3.5	2.6	1.6	13.0
1.0	12.1	1.0	0.5	3.2	0.4	0.3	6.3
2.89	17.8	10.12	4.47	4.9	2.0	1.51	8.2
0.89	5.8	0.2	0.21	2.6	0.24	0.08	2.8

phosphorus concentration in the serum; (S_{Ca}) calcium concentration in the serum; (DS_{Ca}) diffusible diffusible magnesium concentration in the serum.

control C_{IN}. The differences between the C_{IN} variations during prednisolone and placebo infusion were significant in all periods in both groups (Fig. 1, *A* and *B*). The average discrepancies between the corresponding variations in C_{IN} during the 3 hours following prednisolone and placebo infusions were 26, 27, and 29 per cent in the patients and 18, 18, and 13 per cent in the normal subjects.

Creatinine clearances. Following placebo infusion, the values of C_{CR} in the patients equalled 104 ± 17, 109 ± 19, and 107 ± 20 per cent, and in the normal individuals, 106 ± 4, 109 ± 6, and 109 ± 7 per cent of preinfusion clearances. The corresponding variations after prednisolone infusion were: in the patients, 73 ± 13, 74 ± 13, and 73 ± 13 per cent, and in the normal individuals, 84 ± 7, 86 ± 4, and 86 ± 5 per cent of the preinfusion C_{CR} (Fig. 2, *A* and *B*). The serum levels of creatinine remained constant throughout the study.

Creatinine: inulin clearance ratios. $\frac{C_{CR}}{C_{IN}}$ varied minimally after placebo infusion, whereas following prednisolone the ratio decreased markedly; in the patients, the decrements in $\frac{C_{CR}}{C_{IN}}$ during the 3 postinfusion periods were –0.16 ±

Table III. Clearance rates of inulin (C_{IN}), creatinine (C_{CR}), and *p*-aminohippurate (C_{PAH}) before and after prednisolone infusion

	C_{IN} (ml./min.)				C_{CR} (ml./min.)				C_{PAH} (ml./min.)			
Subjects	*Control*	*1**	*2*	*3*	*Control*	*1**	*2*	*3*	*Control*	*1**	*2*	*3*
Patients												
C. B.	89	68	83	78	123	82	90	114	490	410	443	355
S. J.	76	53	58	85	78	56	53	51	465	385	405	500
S. E.	76	35	21	51	94	37	36	36	365	188	265	275
W. D.	59	56	53	45	84	69	60	42	335	315	315	267
M. P.	57	39	46	49	76	52	68	64	410	395	315	377
L. C.	69	65	67	72	80	62	67	69	650	582	600	570
T. W.	54	40	54	35	91	62	86	55	354	247	384	246
J. M.	45	40	41	50	64	49	45	57	310	265	266	365
B. J.	45	38	44	44	75	50	52	49	255	230	275	287
G. C.	66	54	46	46	95	68	55	54	580	470	527	400
C. E.	50	43	37	38	66	57	56	61	360	359	460	402
H. R.	39	33	34	22	50	39	40	39	145	127	142	74
L. E.	41	31	37	38	65	59	53	45	226	182	204	204
C. D.	34	27	33	34	94	45	56	47	191	126	197	234
K. R.	23	17	21	22	35	23	28	24	165	110	153	109
T. S.	27	26	21	23	37	32	28	30	242	222	215	205
D. J.	19	18	19	18	36	32	25	25	194	176	165	134
J. C.	13	13	12	10	22	18	18	14	88	77	86	45
Normal												
C. A.	112	96	108	106	130	95	110	110	610	445	495	545
P. M.	120	110	95	109	125	110	103	105	490	480	470	475
R. J.	105	88	79	84	122	112	103	98	553	510	480	465
A. G.	106	95	84	97	118	101	110	116	525	435	475	495
P. W.	98	88	98	97	142	124	115	118	510	505	455	465
G. S.	89	79	93	84	126	99	116	116	543	437	535	505

*Number of hours after the beginning of the infusion.

0.20, –0.28 ± 0.19, and –0.35 ± 0.18, and in the normal individuals, the decrements were –0.16 ± 0.14, –0.17 ± 0.10, and –0.20 ± 0.14. The difference between the placebo and prednisolone infusion periods with respect to the changes in $\frac{C_{CR}}{C_{IN}}$ were highly significant (Fig. 3, *A* and *B*).

Effective renal plasma flow. The variations in C_{PAH} pursued a course similar to that in C_{IN} and C_{CR}. During the placebo infusion in the patients, C_{PAH} values were equal to: 99 ± 15, 106 ± 28, and 113 ± 29 per cent and in the normal individuals, 107 ± 12, 107 ± 16, and 110 ± 17 per cent of the preinfusion control values, whereas following prednisolone infusion, the C_{PAH} values in the patients were 83 ± 12, 84 ± 19, and 86 ± 23 per cent and in the normal individuals, 87 ± 9, 85 ± 7, and 91 ± 3 per cent of the preinfusion control clearances (Fig. 4, *A* and *B*). The average decreases in C_{PAH} after prednisolone infusion (using the values after placebo infusion as reference points) were: in the patients, 16, 20, and 27 per cent and in the normal individuals, 20, 18, and 19 per cent of control.

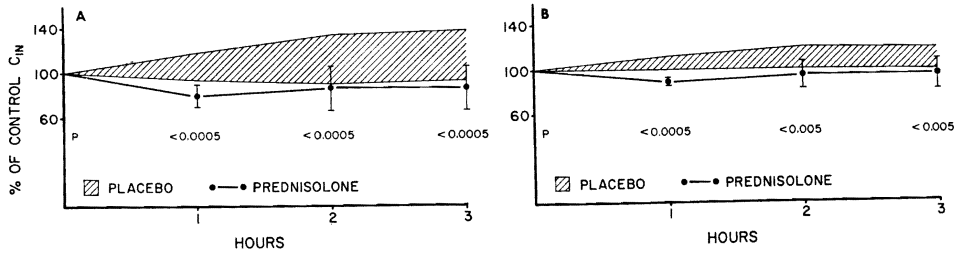

Fig. 1. Changes in inulin clearances (C_{IN}) during 3 one-hour periods following prednisolone and placebo infusions. The results are presented as per cents of control clearances. The values shown are mean ± S.D. for (*A*) all patients and (*B*) all normal subjects.

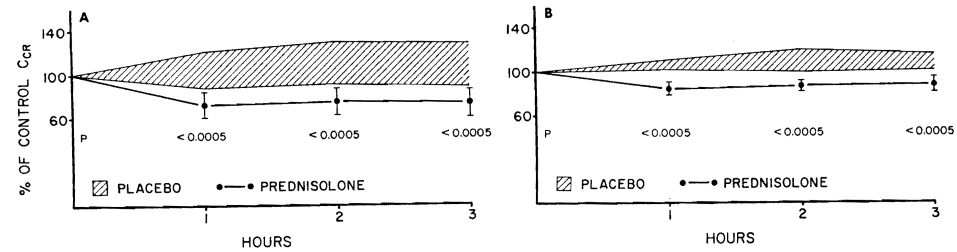

Fig. 2. Changes in creatinine clearances (C_{CR}) during 3 one-hour periods following prednisolone and placebo infusions. The results are presented as per cents of control clearances. The values shown are mean ± S.D. for (*A*) all patients and (*B*) all normal subjects.

Fractional excretion of sodium. The alterations in renal handling of Na followed a biphasic pattern: $\frac{C_{Na}}{C_{IN}}$ increased during the first hour, returned to the control baseline value during the second hour, and decreased during the third hour. These changes were seen both in the patients and in the normal individuals; however, in the latter they were less prominent (Table IV).

Fractional excretion of potassium. In both groups, a decline in $\frac{C_K}{C_{IN}}$ was noticed following placebo infusion. After prednisolone infusion, $\frac{C_K}{C_{IN}}$ increased progressively during the postinfusion hours (Table IV). When the variations in $\frac{C_K}{C_{IN}}$ were plotted against those in $\frac{C_{Na}}{C_{IN}}$ for each pair of individual periods and for all periods together, the relationships were not significant. The serum concentrations of K showed no significant change during the placebo and the prednisolone infusion in all 3 periods, both in the patients and in the normal individuals.

Fractional excretion of ultrafiltrable calcium. In the normal individuals there was a significant decrement in $\frac{C_{Ca}}{C_{IN}}$ during the first and second hours following prednisolone infusion (Table IV). The alterations in ultrafiltrable serum Ca levels in both groups were not significant (Table IV).

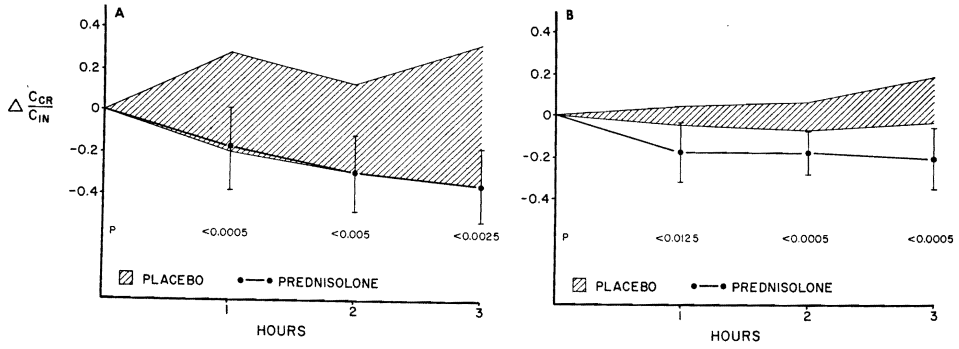

Fig. 3. Changes in fractional excretions of creatinine $\left(\frac{C_{CR}}{C_{IN}}\right)$ during 3 one-hour periods following prednisolone and placebo infusions. The results are presented as the difference between the preinfusion and postinfusion values for (*A*) patients and (*B*) normal subjects.

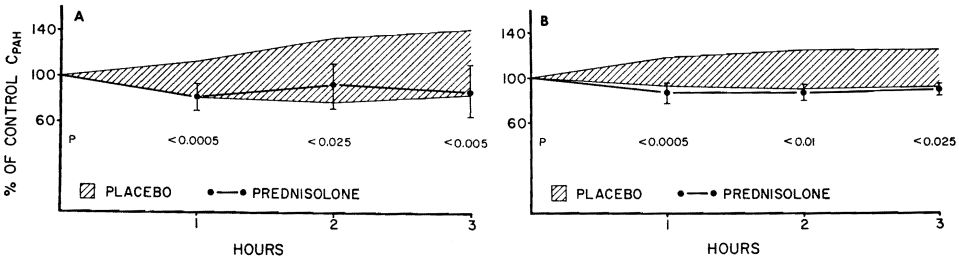

Fig. 4. Changes in *p*-aminohippurate clearances (C_{PAH}) during 3 one-hour periods following prednisolone and placebo infusions. The results are presented as per cents of control clearances. The values shown are mean ± S.D. for (*A*) all patients and (*B*) all normal subjects.

Fractional excretion of ultrafiltrable magnesium. Following placebo infusion, $\frac{C_{Mg}}{C_{IN}}$ decreased in the patients and increased in the normal individuals. $\frac{C_{Mg}}{C_{IN}}$ was not affected significantly by prednisolone infusion in the patients (first and second hours), whereas a significant decrement was noticed in the normal individuals (Table IV). No significant changes in the ultrafiltrable serum Mg levels were seen in both groups.

Fractional excretion of phosphorus. Following placebo infusion, the variations in $\frac{C_P}{C_{IN}}$ were minimal in both groups. Significant increments in $\frac{C_P}{C_{IN}}$ were noticed in the patients during the first hour and in the normal individuals during the first and second hours following prednisolone infusion (Table IV). The serum levels of P remained unchanged in the patients, whereas small but significant decrements were noticed in the normal subjects during the second (–0.4 ± 0.5 mg. per 100 ml.) and third (–0.7 ± 0.5 mg. per 100 ml.) postinfusion periods.

Table IV. Changes in fractional excretions of sodium $\left(\frac{C_{Na}}{C_{IN}}\right)$, potassium $\left(\frac{C_K}{C_{IN}}\right)$, calcium $\left(\frac{C_{Ca}}{C_{IN}}\right)$, magnesium $\left(\frac{C_{Mg}}{C_{IN}}\right)$, and phosphous $\left(\frac{C_P}{C_{IN}}\right)$ (mean ± S.D.) after placebo and prednisolone infusions

	Infusion	*Patients*			*Control subjects*		
		*1**	*2*	*3*	*1**	*2*	*3*
$\Delta\dagger \frac{C_{Na}}{C_{IN}}$	Placebo	-0.002 ±0.044	-0.002 ±0.016	-0.001 ±0.010	-0.001 ±0.004	-0.005 ±0.005	-0.002 ±0.004
	Prednisolone	+0.010 ±0.024	-0.004 ±0.010	-0.010 ±0.019	+0.001 ±0.002	-0.002 ±0.002	-0.004 ±0.003
	P	< 0.025	NS‡	< 0.0005	< 0.05	NS	< 0.05
$\Delta \frac{C_K}{C_{IN}}$	Placebo	-0.009 ±0.130	-0.075 ±0.150	-0.110 ±0.180	-0.050 ±0.100	-0.097 ±0.112	-0.110 ±0.080
	Prednisolone	+0.090 ±0.140	+0.168 ±0.183	+0.218 ±0.271	+0.006 ±0.010	+0.095 ±0.200	+0.160 ±0.270
	P	< 0.0005	< 0.0005	< 0.0005	< 0.0005	< 0.01	< 0.010
$\Delta \frac{C_{Ca}}{C_{IN}}$	Placebo	+0.002 ±0.026	-0.015 ±0.022	-0.033 ±0.032	+0.005 ±0.007	+0.001 ±0.010	+0.003 ±0.007
	Prednisolone	-0.008 ±0.036	-0.010 ±0.033	-0.010 ±0.030	-0.007 ±0.014	-0.013 ±0.019	-0.005 ±0.022
	P	NS	NS	NS	< 0.05	< 0.05	< 0.05
$\Delta \frac{C_{Mg}}{C_{IN}}$	Placebo	-0.038 ±0.150	-0.044 ±0.130	-0.036 ±0.045	+0.020 ±0.030	+0.024 ±0.036	+0.015 ±0.028
	Prednisolone	-0.006 ±0.051	+0.015 ±0.093	+0.010 ±0.093	-0.001 ±0.039	-0.010 ±0.044	-0.026 ±0.047
	P	NS	NS	< 0.005	< 0.05	< 0.0025	< 0.005
$\Delta \frac{C_P}{C_{IN}}$	Placebo	-0.013 ±0.110	-0.012 ±0.187	+0.030 ±0.250	+0.001 ±0.053	-0.025 ±0.065	-0.034 ±0.072
	Prednisolone	+0.065 ±0.081	+0.009 ±0.109	+0.028 ±0.134	+0.061 ±0.052	+0.064 ±0.007	-0.020 ±0.031
	P	< 0.0025	NS	NS	< 0.05	< 0.001	NS

*Number of hours after the beginning of the infusion.
†(Δ) Change from control values (increment or decrement).
‡Not significant.

Discussion

The present study demonstrated a significant effect of large intravenous doses of prednisolone on certain aspects of renal function. The most striking finding was prompt reduction in GFR (C_{IN}), effective renal plasma flow (C_{PAH}), and creatinine clearance (C_{CR}). The present observations were limited to the immediate action of the large dose of prednisolone, whereas evaluation of the clinical

consequences of this treatment, which might require longer follow-up studies, was obviously beyond the scope of the present investigation.

In previously reported studies, glomerular filtration did not vary considerably following acute administration of glucocorticoids to normal subjects.[10-14] However, acute increase in filtration rate was observed in states of glucocorticoid deficiency and/or salt depletion.[12, 15-17] Evidently the acute suppression of renal function observed in the present study was not specific to transplanted kidneys, but seemingly it represents general renal response to large doses of glucocorticoids.

The fall in C_{PAH} could be due to one or several different mechanisms: (1) decrease in total renal plasma flow, (2) redistribution of renal plasma flow without changes in its total rate, (3) markedly decreased PAH extraction, and actual increase in total renal plasma flow with a decrease in GFR due to an efferent arteriolar dilatation, and (4) interference with tubular transport of PAH. Total renal plasma flow was not measured in our study; neither were PAH extraction ratios and Tm_{PAH} measured. In the absence of the above measurements, the interpretation of the observed changes in C_{PAH} is difficult. The available information regarding acute effect of glucocorticoids on renal plasma flow is scarce. Acute administration of glucocorticoids (hydrocortisone 10 mg. per kilogram) failed to alter total renal vascular resistance in experimental animals.[18] Solu-Medrol (40 mg.), injected directly into one renal artery of a dog, had a negligible effect on renal vascular tone, both in renal autografts and homografts.[13] Glucocorticoids have not been shown to affect tubular transport of PAH directly.[20] However, studies with kidney slices in vitro showed inhibition of PAH uptake by 9-alpha-fluorohydrocortisone.[21]

The discrepancy between C_{CR} and C_{IN} after prednisolone infusion leading to a significant decrease in $\frac{C_{CR}}{C_{IN}}$ could be secondary to interference with tubular transport of creatinine. This observation emphasizes the fact that changes in C_{CR} associated with the administration of large doses of glucocorticoids do not reflect necessarily the true variation in GFR. Several substances are known to inhibit tubular secretion of creatinine (PAH in high doses and carinamide[22]), however, glucorticoids have not been known to have a similar effect.

The changes in urinary excretion of Na following acute administration of glucocorticoids in normal subjects have been reported to be minimal when compared with those following the administration of mineralcorticoids.[14, 23] In many instances, the observed increase in Na excretion following glucocorticoids was associated with an increase in GFR and was attributed to the resulting increase in the filtered load of Na.[24-27] However, in other studies, significant changes in Na excretion were not associated with appreciable changes in GFR.[11-12]

The comparison of our data with those reported by others is difficult for several reasons. The doses of glucocorticoids used in other studies were considerably smaller. The clearance determinations were not made at comparable time intervals to ours, and, occasionally, the first hour was excluded from the study.[28]

In this study, the changes in fractional excretion of Na $\left(\frac{C_{Na}}{C_{IN}}\right)$ were significant

and followed a biphasic curve: initial increase and late decrease. The initial increase in $\frac{C_{Na}}{C_{IN}}$ cannot be explained on the basis of increased filtered load of Na as GFR decreased during the first hour and serum Na concentration did not change. It seems unlikely also that prednisolone could affect the aldosterone-controlled tubular handling of Na in that short time. It appears, therefore, that factors other than GFR and aldosterone were involved.

Variations in extracellular fluid volume play an important role in the regulation of tubular Na reabsorption.[29] Glucocorticoids have been shown to increase acutely extracellular fluid volume in dehydrated dogs, probably by a shift of salt and water from intracellular to extracellular compartments.[30] However, no information is available regarding the acute effect of glucocorticoids on extracellular volume in human beings. Intravenous administration of glucocorticoids[31] to normal subjects induced an acute increase in cardiac output and decrease in peripheral vascular resistance. Increase in cardiac output, even without noticeable changes in GFR and renal plasma flow, may increase renal excretion of Na.[32] Another possibility could be that glucocorticoids depress tubular reabsorption of Na directly, leading to an early increase in $\frac{C_{Na}}{C_{IN}}$. The delayed decrease in $\frac{C_{Na}}{C_{IN}}$ (during the third postinfusion hour) could result from enhanced Na reabsorption in the distal tubule. Recent micropuncture studies provide evidence which supports the above possibility.[33]

The striking increase in fractional excretion of K $\left(\frac{C_K}{C_{IN}}\right)$, both in normal subjects and in patients, was similar to that reported by others.[11, 14, 34-36] Like others, we also noticed dissociation between the variation in Na and K excretory patterns.[35, 36] The reported observation[37] that Na retention following glucocorticoids administration could be blocked by spironolactone, but the latter failed to affect K excretion is consistent with the notion that the glucocorticoid-induced kaliuresis is not determined solely by Na^+-K^+ exchange mechanism.

Several authors have maintained that the increased excretion of K following the administration of glucocorticoids was secondary to an attendant increase in serum K^+ concentration possibly due to a release of K^+ from the intracellular space.[35, 36] In the present study, we were unable to observe any significant changes in serum K levels.

The observed rise in $\frac{C_P}{C_{IN}}$ in the present study was minimal and of short duration. The reports on acute effect of glucorcorticoids on renal handling of P are controversial. Mills and Thomas[38] noticed an acute decrease in P excretion accompanied by a decrease in serum P concentration. The latter was attributed by the authors to an increased cellular uptake of P. Others reported an acute decrease in Tmp both in animals and humans, following acute administration of glucocorticoids.[39-41] Hydrocortisone produced phosphaturia in intact rats but not in parathyroidectomized animals. However, large doses of hydrocortisone induced phosphaturia also in absence of parathyroid glands.[42]

Renal handling of Ca and Mg has not been shown to be altered by acute administration of glucocorticoids.[28, 34] However, recent study demonstrated that the presence of excess glucocorticoids, either from exogenous or from endogenous source, decreased the calciuretic response to Ca infusion.[43] Small but significant decreases in fractional excretions of Ca and Mg were noticed in our study only in the normal individuals. These changes were not associated with significantly altered ultrafiltrable serum fractions of Ca and Mg; however, because of the decrease in GFR, the filtered loads of Ca and Mg were reduced as well. The above changes in the fractional excretions of Ca and Mg were absent in the patients despite comparable decreases in GFR. It is possible, therefore, that the pre-existing effect of maintenance glucocorticoids in the patients precluded further response to intravenous prednisolone.

REFERENCES

1. Starzl, T. E.: Experience in hepatic transplantation, Philadelphia, 1963, W. B. Saunders Company, p. 359.
2. Kountz, L. K., and Cohn, R.: Initial treatment of renal allografts with large intrarenal doses of immunosuppressive drugs, Lancet **1**: 338, 1969.
3. Lucas, Z. J., Palmer, J. H., Payne, R., Kountz, L. K., and Cohn, R. B.: Renal allotransplantation in humans. I. Systemic immunosuppressive therapy, Arch. Surg. **100**: 113, 1970.
4. Coburg, A. J., Gray, S. H., Katz, F. H., Penn, I., Halgrimson, C., and Starzl, T. E.: Disappearance rates and immunosuppression of intermittent intravenous prednisolone in rabbits and in humans, Surg. Gynec. Obstet. **131**: 933, 1970.
5. Galli, A.: Colorimetric determination of inulin in blood and in urine, Path. Biol. **14**: 911, 1966.
6. AutoAnalyzer Methodology. File N-11a, Technicon Instruments Corporation, Chauncey, N. Y., 1963.
7. Harvey, R. B., and Brothers, A. N.: Renal extraction of *p*-aminohippurate and creatinine measured by continuous in vivo sampling of arterial and venous blood, Ann. N. Y. Acad. Sci. **102**: 46, 1962.
8. Toribara, T. Y., Terepka, A. R., and Dewey, R. A.: Ultrafiltration methods and normal values, J. Clin. Invest. **36**: 738, 1957.
9. Kuby, S. A.: Determination of inorganic phosphorus, J. Biol. Chem. **235**: 2830, 1960.
10. Mills, J. N., and Thomas, S.: The acute effects of cortisone and cortisol upon renal function in man, J. Endocr. **17**: 41, 1958.
11. Mills, J. N., Thomas, S., and Williamson, R. S.: The acute effect of hydrocortisone, desoxycorticosterone, and aldosterone upon the excretion of sodium potassium and acid by the human kidney, J. Physiol. **151**: 312, 1960.
12. Dingman, J. F., Finkenstaedt, J. T., Laidlaw, J. C., Reinold, A. E., Jenkins, D., Merrill, J. P., and Thorn, G. W.: Influence of intravenously administered adrenal steroids on sodium and water excretion in normal and Addisonian subjects, Metabolism **7**: 608, 1958.
13. Jick, J., Snyder, J. G., Finkelstein, E. M., Cohen, J. W., Moore, E. W., and Morrison, R. S.: On the renal site and mode of action of glucocorticoid in cirrhosis, J. Clin. Invest. **42**: 1561, 1963.
14. Yunis, S. L., Berkovitch, D. D., Stein, R. M., Levitt, M. F., and Goldstein, M. H.: Renal tubular effects of hydrocortisone and aldosterone in normal hydropenic man: comment on sites of action, J. Clin. Invest. **43**: 8, 1964.
15. Raisz, L. G., McNeely, W. F., Saxon, L., and Rosenbaum, J. D.: The effects of cortisone and hydrocortisone on water diuresis and renal function in man, J. Clin. Invest. **36**: 767, 1957.
16. Kleeman, C. R., Maxwell, M. H., and Rockney, R. E.: Mechanisms of impaired water

excretion in adrenal and pituitary insufficiency. I. The role of altered glomerular filtration rate and solute excretion, J. Clin. Invest. **37**: 1799, 1958.

17. Gill, J. R., Gann, S. S., and Bartter, F. C.: Restoration of water diuresis in Addisonian patients by expansion of the volume of extracellular fluid, J. Clin. Invest. **41**: 1078, 1962.
18. Kadowitz, P. J., and Yard, A. C.: Circulatory effects of hydrocortisone and protection against endotoxin shock in cats, Europ. J. Pharmacol. **9**: 311, 1970.
19. Hollenberg, N. K., Retik, A. B., Rosen, S. M., Murray, J. E., and Merrill, J. P.: The role of vasoconstriction in the ischemia of renal allograft rejection, Transplantation **6**: 59, 1968.
20. Burnett, C. H.: Actions of ACTH and cortisone on renal function in man, New York: Trans. Conf. on Renal Function, Josiah Macy, Jr., Found., 106, 1950.
21. Foulkes, E. C., and Miller, B. F.: Steps in *p*-aminohippurate transport by kidney slices, Amer. J. Physiol. **196**: 86, 1959.
22. Brod, J., and Sirota, J. J.: The renal clearance of "endogenous" creatinine in man, J. Clin. Invest. **27**: 654, 1948.
23. Mills, J. N., Thomas, S., and Williamson, K. S.: The effects of intravenous aldosterone and hydrocortisone on the urinary electrolytes of the recumbent human subject, J. Physiol. **156**: 415, 1961.
24. Finkenstaedt, J. T., Dingman, J. F., Jenkins, D., Laidlaw, J. C., and Merrill, J. P.: The effect of intravenous hydrocortisone and corticosterone on the diurnal rhythm in renal function and electrolyte equilibrium in normal and Addisonian subjects, J. Clin. Invest. **33**: 933, 1954.
25. Laidlaw, J. C., Dingman, J. F., Arons, W. L., Finkenstaedt, J. T., and Thorn, G. W.: Comparison of the metabolic effects of cortisone and hydrocortisone in man, Ann. N. Y. Acad. Sci. **61**: 315, 1955.
26. Garrod, O., Davies, S. A., and Cahill, G.: The action of cortisone and desoxycorticosterone acetate on glomerular filtration rate and sodium and water exchange in the adrenalectomized dog, J. Clin. Invest. **34**: 761, 1955.
27. Davis, J. O., and Howell, D. S.: Comparative effect of ACTH, cortisone, and DCA on renal function electrolyte excretion and water exchange in normal dogs, Endocrinology **52**: 245, 1953.
28. Lemann, J., Biering, W. F., and Lennon, E. J.: Studies of the acute effects of aldosterone and cortisol on the interrelationship between renal sodium calcium and magnesium excretion in normal man, Nephron **7**: 117, 1970.
29. Wardener, H. E., De Mills, I. H., Clapham, W. F., and Hayter, C. J.: Studies on the efferent mechanism of the sodium diuresis which follows the administration of intravenous saline in the dog, Clin. Sci. **21**: 249, 1961.
30. Swingle, W. W., Parkins, W. M., Taylor, A. R., and Hays, H. W.: Relation of serum sodium chloride levels to alterations of body water in the intact and adrenalectomized dog, and the influence of adrenal corticol hormone upon fluid distribution, Amer. J. Physiol. **116**: 438, 1936.
31. Sambhi, M. P., Weil, M. H., and Udhoji, V. N.: Acute pharmacodynamic effects of glucocorticoids. Cardiac output and related hemodynamic changes in normal subjects and patients in shock, Circulation **31**: 523, 1965.
32. Alestig, K., Bojs, G., and Larson, St.: Renal function during cardiac pacemaking, Acta Med. Scand. **184**: 45, 1968.
33. Hierholzer, K.: Intrarenal action of steroid hormones on sodium transport, *in* Thurau, K., and Jahrmarker, H., editors: Renal transport and diuretics, International symposium, Faldsting, 1968, Berlin, 1969, Springer-Verlag.
34. Fourman, P., Bartter, F. C., Albright, F., Demsey, E., Carroll, E., and Alexander, J.: Effects of 17-hydrocorticosterone (compound F) in man, J. Clin. Invest. **29**: 1462, 1950.
35. Knight, R. P., Kornfield, D. S., Glaser, C. H., and Bondy, P. K.: Effect of intravenous hydrocortisone on electrolytes of serum and urine in man, J. Clin. Endocr. **15**: 176, 1955.
36. Bartter, F. C., and Fourman, P.: The different effects of aldosterone-like steroids and

hydrocortisone-like steroids on urinary excretion of potassium and acid, Metabolism **11**: 6, 1962.

37. Mills, J. N., Thomas, S., and Williamson, K. S.: The blocking by spironolactones of the actions of aldosterone and cortisol upon the human kidney, J. Endocr. **23**: 357, 1962.
38. Mills, J. N., and Thomas, S.: The influence of adrenal corticoids on phosphate and glucose exchange in muscle and liver in man, J. Physiol. **148**: 227, 1959.
39. Roberts, K. E., and Pitts, R. F.: The effect of cortisone and desoxycorticosterone on the renal tubular reabsorption of phosphate and excretion of titratable acid and potassium in dogs, Endocrinology **52**: 324, 1953.
40. Roberts, K. E., and Randall, H. T.: The effect of adrenal steroids on renal mechanisms of electrolyte excretion, Ann. N. Y. Acad. Sci. **61**: 306, 1956.
41. Anderson, J., and Foster, J. B.: The effect of cortisone on urinary phosphate excretion in man, Clin. Sci. **18**: 437, 1959.
42. Arison, R., and Stoerk, H. C.: Mediation of phosphaturia in hydrocortisone-injected rats by parathormone, Fed. Proc. **19**: 159, 1960.
43. Wajchenberg, B. L.: Urinary calcium and phosphorus in hypercortisolism. I. Evaluation by means of calcium infusion test, J. Clin. Endocr. **31**: 260, 1970.