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Analysis of Various Renal Functions in the Korean*

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ABSTRACT

Various renal functions were studied in 45 young Koreans, 41 males and 4 females. The glomerular filtration rate, the renal plasma and blood flows and the filtration fraction were comparable to those in the occidental. The renal diluting capacity, as judged by the value of positive free water clearance (C_{H2O}), was also comparable to that in the occidental. However, the renal concentrating ability, as judged by values of both the maximum urine osmolality induced by pitressin injection or during dehydration and the maximum negative free water clearance ($T^c_{mH_2O}$) during mannitol diuresis, was somewhat low in the Korean. The tubular reabsorptive capacity of glucose (T_{mG}) was significantly low in the Korean while the tubular secretory capacity of PAH (T_{mPAH}) was not altered. The urea clearance and its ratio with the inulin clearance were generally low. Moreover, the normal osmolar composition of urine indicated that urea is responsible for only 20 to 30%, while salt accounts for nearly 2/3 of the total urine osmolality. In view of the fact that the Korean is chronically maintained on a low or poor protein diet, these results are discussed in the light of this peculiar dietary habit of the Korean. Although the reduction of both the renal concentrating ability and the urea clearance could be reasonably attributed to a low protein intake, the observed low value of Tmc could not be explained thus at present.

Knowledge of the physiology of the kidney has shown remarkable progress in the past, and thus many renal function tests have now been developed by many investigators. However, some of these tests have been developed rather recently and by preclinical investigators, and thus they are still impractical from the clinical point of view. As a result, these function tests have not been widely applied to clinical practice and, hence, certain important renal functions are not well established to date, especially for the Korean.

According to a nutritional survey on Koreans, it has been indicated that the Korean people are living on a low-protein or a low-quality protein diet (Lee et al., 1962) and that they seem to consume a slightly larger amount of sodium chloride than the people in other countries (Lee, unpublished data). In view of the reports by other investigators (Epstein et al., 1957a) that the amount of protein intake is important in determining the extent of the renal concentrating operation, it seemed conceivable to the authors that certain renal functions of the Korean may be different from those of the occidental.

Therefore, this investigation was undertaken to study various renal functions of the Korean as thoroughly as possible by means of all the known tests. In making the final analysis, results were compared with those obtained in other countries, and attempts have been made to explain the differences between Koreans and others.

METHODS

Studies were carried out mainly on healthy young men whose ages ranged from 18 to 37 years old. In all, 41 men and 4 women were employed for the various

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studies. Prior to the experiments, each subject was carefully examined in order to rule out those with disease.

On the day of each experiment, the subject was instructed to come to the laboratory by 9 a. m. without breakfast and, upon arrival at the laboratory, was put on a bed-rest for 30 min. The urinary bladder was then catheterized, and urine was recovered from the urinary bladder and quantitatively ascertained.

The renal functions were determined by the various renal function tests as follows:

A. Renal hemodynamics:
  a. Glomerular filtration rate (GFR)
  b. Renal plasma flow (RPF)
  c. Filtration fraction (FF)
  d. Renal blood flow (RBF)
B. Renal diluting capacity:
C. Renal concentrating capacity:
  a. Pitressin-induced
  b. Dehydration-induced
  c. Maximum free water reabsorption during mannitol diuresis ($T^c_{mH_2O}$)
D. Tubular reabsorptive capacity of glucose (T_{mG}):
E. Tubular secretory capacity of PAH (T_{mPAH}):
F. Tubular reabsorption of urea:

Each test will be described in detail under "RESULTS". All the numerical figures indicating various renal functions were recalculated by the formula for the body surface area of 1.73m^2, and the mean value as well as the standard deviation (S.D.) were computed for each function.

The concentration of inulin was determined by the method of Roe et al. as modified by Schreiner (1950), while PAH was determined by Bratton and Marshall's method as modified by Smith et al. (1945). The osmolality was calculated from the freezing point depress. on as determined by a Beckmann thermometer. Glucose and urea were determined by Folin-Wu's method (as described by Hawk et al., 1947) and by Van Slyke and Cullen's method (1916), respectively. Chloride was determined by the methods of Schales and Schales (1941) and of Asper et al. (1947).

RESULTS

A. Renal Hemodynamics:

Inulin and PAH clearances were determined on the majority of subjects as indices of GFR and RPF,

Table 1. Overall summary of inulin clearance, PAH clearance, and filtration fraction on individual subjects

Subject No.	C_{IN}(ml/min.)	C_{PAH}(ml/min.)	FF
1	151	969	0.16
2	120	742	0.16
3	110	763	0.15
4	185	740	0.25
5	100	623	0.16
6	102	769	0.13
7	152	637	0.24
8	126	614	0.21
9	97	734	0.13
10	95	757	0.12
11	70	519	0·14
12	113	646	0.18
13	109	—	—
14	86	877	0.10
15	88	518	0.17
16	125	864	0.14
17	110	974	0.11
18	119	—	—
19	107	888	0.12
20	95	462	0.21
21	141	1135	0.12
22	134	909	0.15
23	89	—	—
24	127	—	—
25	113	—	—
26	115	668	0.17
27	112	617	0.18
28	135	673	0.20
29	123	639	0.19
30	112	514	0.20
31	126	685	0.18
32	130	628	0.20
33	142	621	0.22
34	118	753	0.16
35	98	581	0.17
36	131	661	0.20
37	135	—	—
M	117	716	0.17
S.D.	22	151	0.04

respectively, on the basis of the constant infusion method outlined by Smith (1956). Both clearance values were determined every 15 min for a period of 1 hr and the averages calculated for each subject. In Table 1, values of C_{IN} and C_{PAH} for individual subjects are shown along with the corresponding values of FF.

The values of C_{IN} ranged from 70 to 185 ml/min. with an average of 117±22 ml/min., and the values of C_{PAH} ranged from 462 to 1135 ml/min. with an average of 716±151 ml/min. The calculated values of FF ranged from 0.10 to 0.25 with an average of 0.17±0.04.

Table 2. Summary of hematocrit ratio, PAH clearance and the calculated renal blood flow (RBF).

Subject No.	Hct (%)	C_{PAH}(ml/min)	RBF(ml/min)
26	46	668	1229
27	40	617	1023
28	48	673	1294
29	44	639	1141
30	52	514	1071
31	40	685	1125
32	47	628	1184
33	45	621	1129
M	45	630	1133
S.D.	4	53	85

In 8 subjects, the hematocrit ratio was determined simultaneously with the determination of C_{PAH}, in order to calculate the RBF (Table 2). It can be seen that the hematocrit ratio ranged from 40 to 52% with an average of 45±4%; thus the calculated values of the RBF for the individual subjects ranged from 1093 to 1294 ml/min. with an average of 1133 ±85 ml/min.

B. Renal Diluting Capacity:

In 6 subjects, 1000 ml of distilled water was administered orally at zero time, and the amount of water excreted every 20 min. was replaced at the end of each period. When the urine flow became steady at the maximal level, both urine and blood samples were taken every 15 min. for a period of 1 hr. These samples were analyzed for osmolality and chloride as well as for inulin and PAH, both of which were administered throughout the entire experimental period. From these values, Cosm and C_{H_2O} were calculated for each clearance period, and average values were obtained for individual subjects (Table 3).

The maximum urine flow (V) was 20.0±3.7 ml/min., while the osmolality of these maximally diluted urine samples (U_{osm}) was 105±12 mOsm/kg. The calculated values of C_{osm} averaged 6.8±1.6 ml/min., and thus the maximum positive free water clearance (C_{H_2O}) averaged 13.2±2.2 ml/min. It may be noticed that the chloride concentration was maintained at as low as 26±7 mEq/L. Both C_{IN} and C_{PAH} did not show any significant variation during this experimental period.

C. Renal Concentrating Capacity:

a). Pitressin-induced test: In 4 hydrated subjects, 200 mu of pitressin was administered intravenously as a priming dose, following which 4 mu was infused per minute during the experimental period. Both inulin and PAH clearances were also determined

Table 3. Various renal functions obtained during dilution tests

Subject No.	V (ml/min.)	U_{Cl} (mEq/L)	U_{osm} (mOsm/kg)	C_{IN} (ml/min.)	C_{PAH} (ml/min.)	C_{osm} (ml/min.)	C_{H_2O} (ml/min.)
1	22.3	22	118	151	969	8.8	13.5
2	24.9	28	102	120	742	8.5	16.4
3	16.7	20	99	110	763	5.1	11.6
4	16.2	31	118	185	740	6.3	9.9
5	19.4	20	85	100	623	5.1	14.3
6	20.4	37	105	102	769	7.1	13.4
M	20.0	26	105	128	768	6.8	13.2
S.D.	3.7	7	12	33	93	1.6	2.2

throughout the experimental period. When the urine flow became steady at the lowest level, both urine and blood samples were obtained every 15 min for a period of 1 hr.

The various renal functions studied in this series are summarized in Table 4, where average values for individual subjects are listed. The lowest urine flow (V) averaged 2.7±0.7 ml/min., and the highest urine osmolality (U_{osm}) was 630±146 mOsm/kg. Since C_{osm} was 5.9±1.5 ml/min., the free water clearance became negative ($T^c_{H_2O}$) amounting to 3.2±0.6 ml/min. Neither C_{IN} nor C_{PAH} showed any significant variation over the experimental period.

b). Dehydration-induced test: In four male and female subjects who had been dehydrated for 12 hrs., both urine and blood samples were collected every 30 min for a period of 4 hrs. and the concentrations of chloride and of total osmotic substances were determined in these samples. Since samples were found to be concentrated to a similar extent for each subject, average values for individual subjects are summarized in Table 5 along with the corresponding C_{osm} and $T^c_{H_2O}$.

The urine flow was, on the average, as low as 0.35±0.05 ml/min., while the maximum U_{osm} was 1172±266 mOsm/kg and the maximum U/P osmolal ratio was 3.84±0.83. The calculated values of C_{osm} and of $T^c_{H_2O}$ were 1.24±0.67 and −0.89±0.47 ml/min., respectively.

c). Maximum free water reabsorption during mannitol diuresis ($T^c_{mH_2O}$): In five subjects, 200 mu of pitressin was given intravenously at zero time, following which a sustaining dose (4 mu/min.) was continuously administered while 20% mannitol solution was being infused as fast as possible. Proper doses of both inulin and PAH were also being administered in order that respective clearances could be calculated. Both urine and blood samples were

Table 4. Various renal functions obtained during ADH-induced concentration tests

Subject No.	V (ml/min.)	U_{Cl} (mEq/L)	U_{osm} (mOsm/kg)	C_{IN} (ml/min.)	C_{PAH} (ml/min.)	C_{osm} (ml/min.)	$T^c_{H_2O}$ (ml/min.)
7	3.4	141	432	152	637	7.0	3.6
8	3.4	169	610	126	614	7.0	3.6
11	1.6	264	762	70	519	3.9	2.3
12	2.5	265	715	113	646	5.7	3.2
M	2.7	210	630	110	604	5.9	3.2
S.D.	0.7	64	146	34	61	1.5	0.6

Table 5. Various renal functions in dehydrated human subjects

Subject No.	Plasma		Urine					U/P_{osm}
	P_{osm} (mOsm/L)	P_{Cl} (mEq/L)	V (ml/min).	U_{Cl} (mEq/L)	U_{osm} (mOsm/kg)	C_{osm} (ml/min.)	T_{H_2O} (ml/min.)	
38 (M)	334	114	0.55	284	801	1.32	0.77	2.40
39 (M)	303	104	0.20	345	1258	0.83	0.63	4.15
40 (M)	296	110	0.13	210	937	0.44	0.31	3.28
41 (M)	280	114	0.40	347	1210	1.75	1.33	4.32
42 (F)	290	24	0.24	287	980	0.80	0.56	3.36
43 (F)	348	102	0.60	410	1359	2.17	1.57	3.61
44 (F)	280	107	0.29	350	1343	1.39	1.10	4.49
45 (F)	303	120	0.39	356	1455	1.20	0.81	4.48
M	304	112	0.35	312	1172	1.24	0.89	3.84
S.D.	24	7	0.05	84	266	0.67	0.47	0.83

(M) and (F) denote male and female, respectively.

Table 6. Various renal functions obtained during mannitol-induced concentration tests

Subject No.	V (ml/min.)	U_{osm} (mOsm/kg)	C_{IN} (ml/min.)	C_{PAH} (ml/min.)	C_{osm} (ml/min.)	$T^c_{mH_2O}$ (ml/min.)
13	17.5	446	109	—	21.0	3.5
14	14.4	426	86	877	17.7	3.3
15	19.0	407	88	518	22.1	3.1
16	21.1	420	125	864	27.4	6.3
17	15.0	542	110	974	19.8	4.8
M	17.4	448	103	808	21.6	4.2
S.D.	2.8	54	16	199	3.5	1.3

obtained every 10 to 15 min. for a period of 1.5 hrs. From an analysis of these samples, the $T^c_{H_2O}$ was calculated for each period. Values of $T^c_{H_2O}$ usually increased as time elapsed and eventually reached a peak (i.e. $T^c_{mH_2O}$) in 30 to 40 min. Therefore, various renal functions obtained during this period of maximum free water reabsorption were measured, and averages for each subject are summarized in Table 6.

The urine flow (V) was, on the average, 17.4± 2.8 ml/min., while C_{osm} was 21.6±3.5 ml/min., and hence the calculated $T^c_{mH_2O}$ was −4.2±1.3 ml/min. Neither C_{IN} nor C_{PAH} showed any significant change during the experimental period.

D. Tubular Reabsorptive Capacity of Glucose (T_{mG}):

In five subjects, 125gm of glucose in 50% solution was administered intravenously at zero time as a priming dose, following which a sustaining dose of glucose was infused at a rate of 150 mg/min. during the experimental period. After allowing 20 min for equilibration, both urine and blood samples were obtained every 10 min. for a period of 1 hr. These subjects were, at the same time, given inulin so that the C_{IN} could be determined for the calculation of T_{mG}. Average values of the plasma concentration of glucose (P_G), C_{IN} and T_{mG} for each subject are summarized in Table 7.

Table 7. Maximal tubular reabsorption of glucose (T_{mG})

Subject No.	P_G (mg%)	C_{IN} (ml/min.)	T_{mG} (mg/min.)
29	502	123	323
30	489	112	217
31	717	126	299
32	545	130	263
33	868	142	297
M	623	126	280
S.D.	160	10	41

The P_G value varied greatly from one subject to another, with an average of 623±160 mg%. Although the P_G seemed to be somewhat low in some cases, the values of T_{mG} were fairly uniform in all subjects and averaged 280±41 mg/min.

E. Tubular Secretory Capacity of PAH (T_{mPAH}):

In five subjects, T_{mPAH} was determined on the basis of the method outlined by Smith (1956), and the data are summarized in Table 8.

Table 8. Maximal tubular secretion of PAH (T_{mPAH})

Subject No.	P_{PAH} (mg%)	C_{IN} (ml/min.)	T_{mPAH} (mg/min.)
23	48.5	89	123
24	16.5	127	77
25	25.5	113	62
26	35.0	115	89
27	25.6	112	116
M	30.2	111	93
S.D.	12.3	13	25

The plasma concentration of PAH (P_{PAH}) ranged from 16.5 to 48.5 mg%, with an average of 30.2± 12.3 mg%. However, the calculated values of T_{mPAH} were independent of the P_{PAH} values encountered in this investigation and ranged from 62 to 123 mg/min., with an average of 93±25 mg/min.

F. Tubular Reabsorption of Urea:

In six hydrated subjects, the urea clearance (C_{urea}) was determined along with the C_{IN}; the data are summarized in Table 9. Although the urine flow

is not indicated in the table, it was maintained at a level above 10 ml/min.

Table 9. Urea clearance and urea and inulin clearance ratio

Subject No.	C_{urea} (ml/min.)	C_{IN} (ml/min.)	C_{urea}/C_{IN}
26	36	115	0.31
28	61	135	0.45
29	51	123	0.41
31	50	126	0.40
32	62	130	0.48
33	49	142	0.35
M	51	128	0.40
S.D.	9	9	0.06

The values of C_{urea} ranged from 36 to 62 ml/min., and the C_{urea}/C_{IN} ratio from 0.30 to 0.48, with an average of 0.40±0.06. In order to illustrate the relationship between the C_{urea}/C_{IN} ratio and the urine flow, the former was plotted as a function of the urine/plasma inulin concentration ratio (U/P inulin) in Fig. 1. In this figure, the line whi h was taken

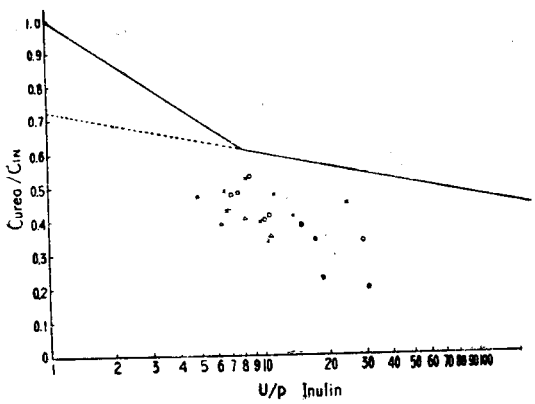

Fig. 1. Urea/inulin clearance ratios as a function of urine/plasma inulin concentration ratio.
The line representing the normal range in the occidental was obtained from the data of Chasis and Smith (1938).

from the data of Chasis and Smith (1948) is indicated as a reference.

DISCUSSION

In the following discussion, the various renal functions in the Korean as obtained in the present investigation will be compared with corresponding values obtained in other countries. Attempts will also be made to account for certain differences which exist between the Korean and the peoples in other countries.

A. Renal Hemodynamics: The average values of GFR, RPF, FF and RBF are virtually identical with those reported in otehr countries (Smith, 1956; Ueda, 1958; Smith et al., 1948).

B. Renal Diluting Capacity: The average value of C_{H_2O}, which is the best indicator of the renal diluting capacity, was also quite similar to those obtained in the U.S.A. (Boylan and Antkowiak, 1959; Smith, 1956).

C. Renal Concentrating Capacity: The maximum U_{osm} induced by the injection of pitressin was lower than any values reported by other investigators (Epstein et al., 1957 and 1957a; de Wardener and Herxheimer, 1957) who administered a similar dose of pitressin, suggesting that the pitressin induced concentrating capacity is perhaps low in the Korean. However, it was shown earlier in our laboratory (Yoon and Hong, 1961) that a group of Korean men given 5000 mu of pitressin intramuscularly concentrated the urine to as high as 904 mOsm/kg, a figure which is comparable to those reported in other countries. Therefore, it may be postulated that Koreans are less sensitive to pitressin as compared to people in other countries.

A comparison of the maximum U_{osm} as induced by dehydration also suggests that Koreans tend to concentrate the urine to a lesser extent than those in other countries (Adolph, 1923; McCance, 1945; Rapoport et al., 1949). The values of $T^c_{mH_2O}$ were also in the lower range as compared to others (Zak et al., 1954; Epstein et al., 1957 & 1957a).

Although the statistical significance of these differences might be somewhat doubtful because of the limited number of subjects in the present investigation, there is a clear trend in that all of three parameters for renal concentrating ability were distinctly lower than the corresponding figures obtained in the U.S.A. and in England. It is, therefore, postulated that Korean people are not able to concentrate urine as much as are occidentals. Possible

reasons for this lack of renal concentrating ability will be discussed later.

D. Renal Tubular Reabsorptive Capacity of Glucose (T_{mG}): The average T_{mG} value obtained in the present investigation was lower than that reported by Shannon (quoted by Smith, 1956) on Americans. Although the average plasma concentration of glucose was not as high as one would like to maintain in this type of experiment, it was sufficiently high in certain cases, and yet the values of T_{mG} were still lower than Shannon's figure. It is, therfore, concluded that, in the Korean, tubules are not able to reabsorb glucose as much as in Americans.

E. Renal Tubular Secretory Capacity of PAH (T_{mPAH}): Although the average T_{mPAH} obtained in this investigation was slightly higher than that in Americans as reported by Smith (1956) and Chasis et al. (1945), there was no statistically significant difference between them.

F. Tubular Reabsorption of Urea: It is shown in this investigation that C_{urea} or C_{urea}/C_{IN} for a given urine flow is significantly lower in the Korean than in the occidental(Chasis and Smith, 1938). It is, therefore, evident that a higher percent of the filtered urea is reabsorbed in the Korean as compared to others. Moreover, the urinary concentration of urea for a given urine osmolality was lower in the Korean than in occidentals (See Fig. 2). In order to find out the normal composition of urine, the osmolality of urine contributed by NaCl, as estimated by $2 \times U_{Cl}$, was plotted against U_{osm} in Fig. 2. It is clear from this figure that the urine osmolality contributed by NaCl is responsible for nearly 2/3 of the U_{osm}, suggesting that urea contributes at most 1/3 of the U_{osm}. Actual measurements of both urinary concentration of urea and U_{osm} indicated that, in the Korean, approximately 20 to 30 % of U_{osm} is due to urea (Yoon and Hong, 1961; Hong et al., 1961). This fact may be compared with that of occidentals in whom urea and NaCl are normally responsible for approximately 40 % and 30% of U_{osm}, respectively (McCance, 1945; Epstein et al., 1957a). However, the addition of 8 to 30 gm of salt to the usual diet brought about an increase in the urinary concentration of chloride to such an extent that $2 \times U_{Cl}$ was responsible for nearly 2/3 of the U_{osm} (McCance, 1945). On the other hand, when subjects were fed a low protein diet, the urea excretion was lowered, and approximately 25 % of U_{osm} could be accounted for by urea (Epstein et al., 1957a).

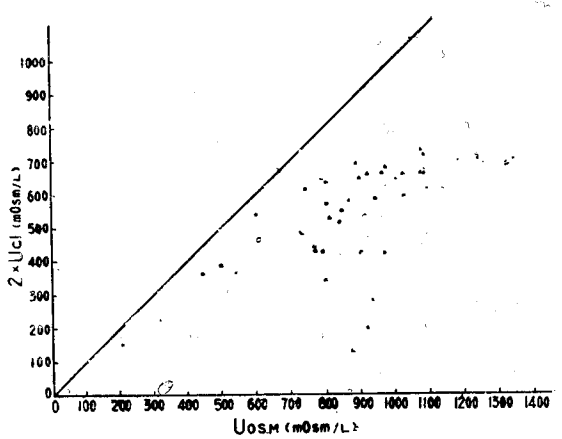

Fig. 2. Urinary concentration of NaCl (in mOsm/L) as estimated by $2 \times U_{Cl}$ as a function of the total urine osmolality. In the calculation of mOsm/L, the osmotic coefficient of urine was assumed to be 1.0. The straight line which has the slope of 1.0 s included as a reference.

On the basis of the above comparisons, it is evident that certain renal functions in the Korean seem to be significantly different from those in occidentals. Among the various renal functions studied, the reduction of renal concentrating ability and the lowering of the C_{urea}/C_{IN} ratio may be explained by the fact Korean people are commonly maintained on a low-protein or a low-quality protein diet. According to Lee et al. (1962), the average Korean farmor consumes 55 to 99 gm of protein per day depending upon the season, but nearly 2/3 of this protein is derived from cereals and less than 10 % from animal sources. It is therefore evident that although the actual amount of protein intake may seem to be sufficient, its biological value is extremely low, and thus the Koreans are essentially living on a poor or low protein diet. It was shown previously by several investigators that when animals or human subjects were given a low protein diet, the renal concentrating ability was lowered and the urea excretion reduced(Epstein et al, 1957; Dicker et al., 1933; Schmidt-Nielsen, 1958). However, there is no likely explanation why the value of T_{mG} was lowered

in the Korean. According to Moustgaard(quoted by Smith, 1951), the protein content of the diet did not alter the T_{mG}. Although a low-protein diet is also known to lower the GFR as well as the RPF, these values were not altered in the Korean. This may be attributed to the fact that the low-protein diet of the Korean is well supplemented by salt, which is known to abolish the effect of a low-protein diet on renal hemodynamics (Chasis et al., 1950; Weston et al., 1950). Although the T_{mPAH} was known to be elevated by increasing the protein intake (Pullman et al., 1954), it was not altered in the Korean.

Considering the fact that the ingestion of salt is higher in the Korean (Lee, unpublished data) than in the occidental, it may, as an alternate, be speculated that the poor renal concentrating ability as seen in the Korean could equally be due to an increased excretory burden which would augment the water excretion. However, this is unlikely, in view of the work by Epstein et al. (1957a), who showed that subjects maintained on a low-protein diet partially lost their renal concentrating ability regardless of the amount of salt ingested.

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