

Physiologic Variation Of Renal Function In Twins: Diuresis After Water Intake¹

Bertha M. Aschner, *M. D.* and Stanley M. Gartler, *Ph. D.*

It has been known for some time that there exists a rare hereditary form of diabetes insipidus which starts in infancy and lasts through the entire life span of otherwise healthy persons (10); it is genetically complex in that both autosomal dominant and sex-linked forms have been reported. It has always been suspected that such cases may be due to an anomaly of the target organ, the kidney itself rather than to a disorder of the pituitary gland or the vegetative nervous centers (2,3). Recently this form of diabetes insipidus has been called nephrogenic diabetes insipidus (4, 5). Williams and Henry (4) have studied very carefully such a family with apparently sex-linked inheritance of nephrogenic diabetes insipidus through five generations. Their cases as well as those of some other authors did not respond to pituitrin, a sign that the kidney cells were unable to react to the antidiuretic hormone in the normal manner and that they apparently were the primary site of the disorder. The authors conclude from their observations that their patients suffered from a congenital defect in the renal tubules, impairing reabsorption.

The occurrence of such a hereditary anomaly of tubular function gave us the idea that genetic factors might play a role in the normal regulation of water elimination through the kidneys, in particular, of the tubular reabsorption and its physiologic variations. In order to obtain some information on this question, we studied the comparative behavior of healthy one-egg and two-egg twin pairs by the Fishberg-Volhard test, i.e. measuring diuresis after rapid intake of a large amount of water.

H. Geyer (6) had done similar experiments in 1931. He studied the drinking test in twin pairs, measuring the urine output and its specific gravity one and two hours after drinking. He did not find any differences in the behavior of one-egg and two-egg twin pairs with regard to the quantity and dilution of the urine. In addition, however, Geyer determined the hemoglobin concentration every half hour after drinking as a measure of the accompanying blood dilution. The maximum of decrease of the hemoglobin value — regardless as to how long after drinking it was reached — was found to be much more similar in monozygotic than in dizygotic twin partners. Geyer's mean value for the intrapair difference of hemoglobin di-

¹ This work was supported by a grant from the National Science Foundation.

Table 1 - Statistical analysis of urine flow at height of diuresis in monozygotic and dizygotic twin pairs

	Urine flow cc/minute		Intrapair Difference	Mean Intrapair Difference
	Twin A	Twin B		
Monozygotics	13.1	9.9	3.2	1.2
	10.3	9.5	0.8	
	14.7	14.3	0.4	
	10.3	12.3	2.0	
	8.8	9.7	0.9	
	10.3	10.3	0.0	
Dizygotics	5.5	15.9	10.4	3.6
	12.3	11.7	0.6	
	10.0	9.5	0.5	
	11.7	12.3	0.6	
	10.0	14.7	4.7	
	12.7	7.7	5.0	
Intrapair variance ratio dizygotics/monozygotics				9.9

lution in one-egg twins was 0.85 Gm%, in two-egg twins 1.78 Gm%. However, the data were not analyzed statistically, and consequently we know little about the significance of this difference.

This was a puzzling result inasmuch as we know that the processes of blood dilution and water elimination after drinking are intimately correlated, and it seems hardly comprehensible that the blood dilution would be controlled by genetic factors while such forces would have no influence on the diuresis. Therefore, we considered it worth while to give the problem renewed attention.

Method and material

Our own material consists of 6 one-egg and 6 two-egg twin pairs. Among the identical pairs were 5 male and one female pair while the fraternal pairs were equally divided into 3 male and 3 female pairs. Opposite sexed pairs were excluded from our examination. The twins were diagnosed for zygosity by a combination of various blood group systems, pigmentation, and dermatoglyphics.

Our tests were carried out in voluntary twin pairs, mostly college or university students between the ages of 15 and 25 years. Both twin partners were always examined simultaneously. They were given 1000 cc of water to drink within 12-15 minutes after an over-night fast. We carefully saw to it that the two individuals of each twin pair drank their fluid during exactly the same time. The tests were done under

continuous supervision of a member of our institute. In two cases the test persons were unable to drink the entire amount of fluid. In one of these instances each twin partner took only 870 cc. in the other one only 550 cc; in both these cases the two twin individuals were given exactly the same quantity during the same time, and in both cases the typical effect of the water drinking became evident in spite of the reduced intake.

The output of urine was followed every half hour for three hours. after the end of drinking. The quantity of the urine and its specific gravity were measured in each portion. During the first two hours the subjects were kept in a recumbent position.

Results and discussion

All our subjects showed an essentially normal response to water drinking. The ingested fluid was eliminated in about three hours by the excretion of a highly diluted urine which reached a specific gravity of 1000 to 1003 in all cases. In the detailed course of the diuresis, however, certain individual variations were found, which can be observed in figures 1 and 2 where the individual diuresis curves are given.

As can be seen there is marked variability among the individuals tested in all aspects of their diuretic response (total volume of urine excreted, time of onset of maximum urine flow, and the maximum rate of urine flow). It is also rather obvious that the diuretic curves for the monozygotic twin pairs are more similar than those for the dizygotic ones (note the marked intrapair differences in dizygotics Jo and St.).

The character exhibiting the greatest variability and the greatest similarity for identicals is the maximum rate of urine flow. In table 1 the data for this variable are given along with the intrapair differences and the statistical analysis of these differences. It appears from the table that the mean intrapair difference for the dizygotic twin pairs is three times as large as the mean intrapair difference for the monozygotic pairs. An analysis of variance of these data gives an F ratio of 9.9 for the intrapair variance of the dizygotics / intrapair variance of the monozygotics. This F ratio with 6,6 d.f. is significant at better than the 0.01 level. Although the intrapair differences for the total volume of urine excreted and the time of onset of maximum urine flow are greater for the dizygotics than for the monozygotics, these differences are not statistically significant.

In spite of the comparatively small material studied so far, the figures obtained are clear enough to permit the conclusion that the fluid output after rapid drinking of 1000 cc water, in particular the maximum rate of urine flow at the height of the diuresis is significantly more similar in one-egg twin partners. This fact shows that genetic factors must be operative in the elimination of ingested water by the normal kidney.

It is now generally believed that the main factor causing the diuresis after intake of large amounts of water is an inhibition of reabsorption in the distal tubules. According to Verney's (7) work, the release of the antidiuretic hormone by the neuro-

pituitary is suppressed under these test conditions. It is likely therefore that the observed variations in urine flow at the height of diuresis are not related to any differences in the anti-diuretic response of the neuro-pituitary or to differences in the sensitivity of the distal tubular cells to the antidiuretic hormone. This might indicate the possibility that genetic forces control distal tubular cell reabsorption activities

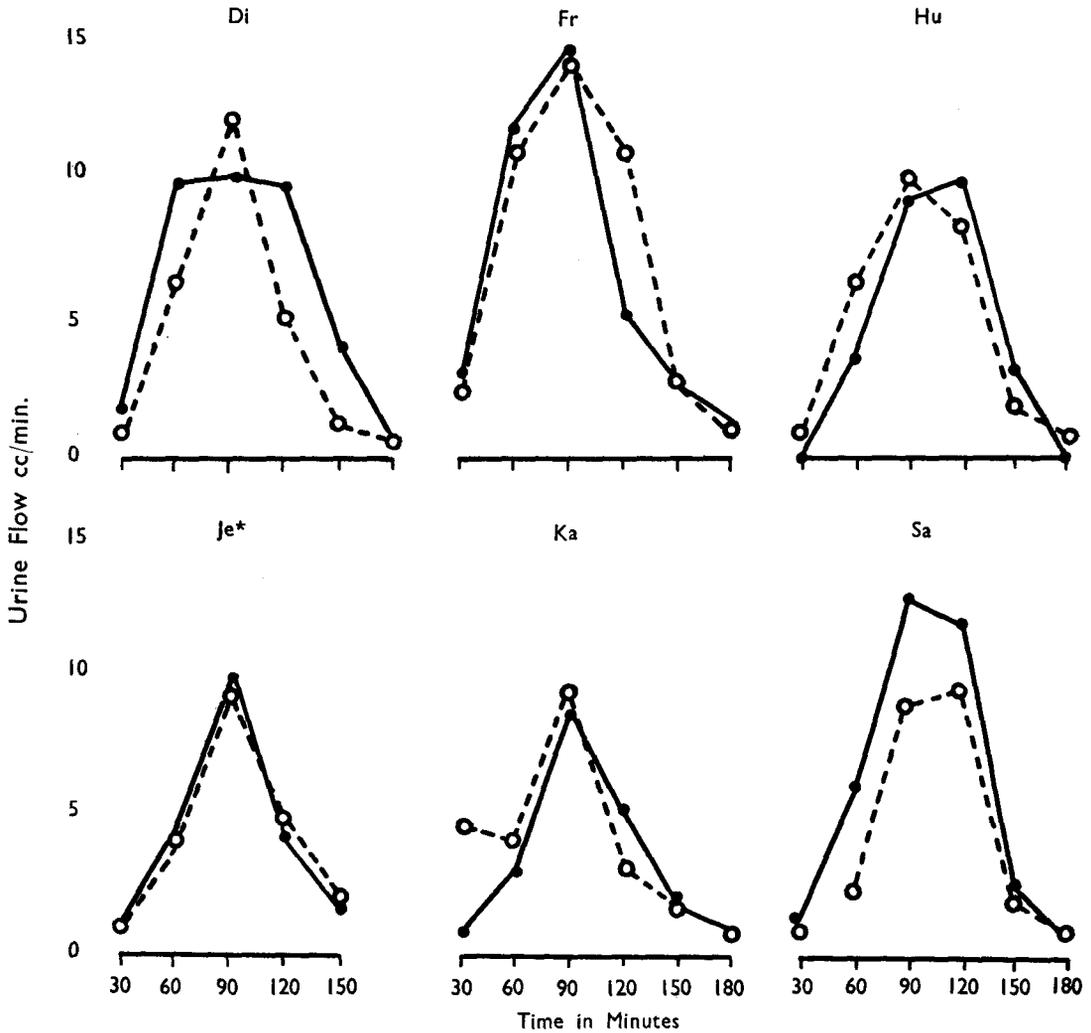


Figure 1. Diuresis curves for monozygotic twin pairs after the rapid ingestion of 1000 cc of water.
 * Ingested only 870 cc of water.

directly. Such a concept would be in good agreement with the observations on hereditary nephrogenic diabetes insipidus. We have to keep in mind, on the other hand, that the normal kidney function is a highly complicated mechanism and that various physiological forces acting independently or in combination may be responsible for the observed differences in reactive diuresis.

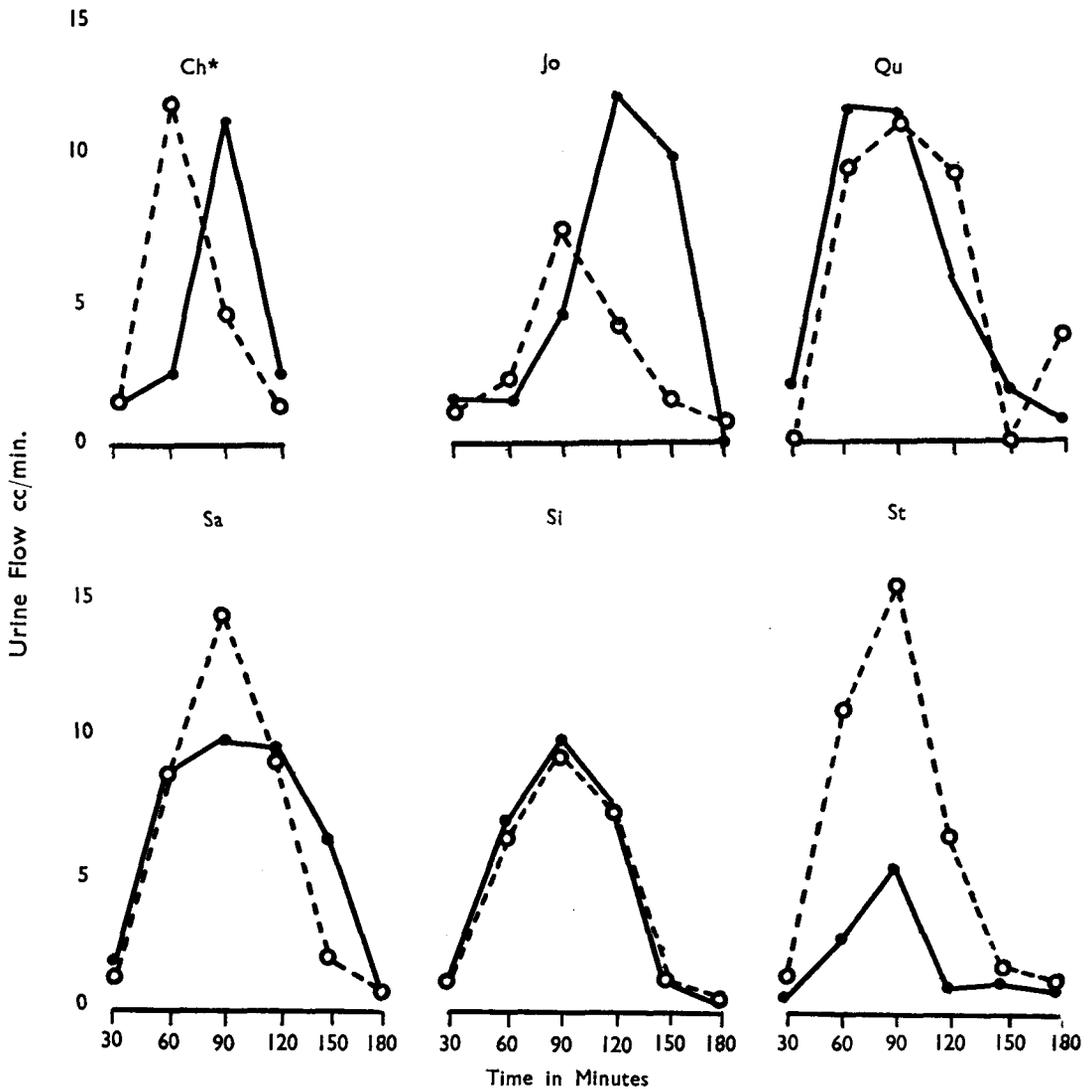


Figure 2. Diuresis curves for dizygotic twins after the rapid ingestion of 1000 cc of water.
 * Ingested only 550 cc of water.

Summary

In six monozygotic and six dizygotic healthy twin pairs the urine elimination after rapid drinking of 1000 cc of water (Fishberg-Volhard test) was studied. Considerable variation was observed in the diuretic response of these individuals, particularly in the maximum rate of the reactive diuresis. The minute volumes of urine during the half-hour period of the largest output were compared between the partners of each twin pair. It was found that the difference of the maximum rate of urine flow was significantly (0.01 level) smaller between one-egg than between two-egg twins under otherwise equal conditions. The concept of genetic factors controlling the function of the renal tubular cells is discussed.

References

1. WEIL, A., JUN.: *Deutsch. Arch. f. klin. Med.*, 93: 180, 1908.
2. BAUER, J.: *Differential Diagnosis of Internal Diseases*. 2nd Ed. Grune & Stratton, New York, 1955.
3. —, and ASCHNER, B.: *Wien. Arch. inn. Med.*, 1: 297, 1920.
4. WILLIAMS, R.H., and HENRY, C.: Nephrogenic diabetes insipidus; transmitted by females and appearing during infancy in males. *Ann. int. Med.*, 27: 84, 1947.
5. WELT, L.G.: The influence of diseases on the renal excretion of water. *Yale Jour. Biol. Med.*: 29: 299, 1956.
6. GEYER, H.: Der Trinkversuch bei eineiigen und zweieiigen Zwillingen. *Klin. Wochenschr.*, 10: 1488, 1931.
7. VERNEY, E.B.: Croonian Lecture: The antidiuretic hormone and the facts which determine its release. *Proc. Roy. Soc., Ser. B*, 135: 25, 1947.

RIASSUNTO

Fu studiata l'eliminazione dell'orina, dopo aver bevuto velocemente 1000 cc. d'acqua, in sei paia di gemelli uniovulari e sei paia di biovulari. Variazioni considerevoli della reazione diuretica furono osservate in questi individui, specialmente nella forza massima della diuresi reattiva. Abbiamo comparato i volumi dell'orina per minuto durante la mezz'ora di massima eliminazione fra i co-gemelli di ogni paio. Abbiamo trovato che la differenza nella forza massima della diuresi era significativamente (livello di 0,01) più piccola fra gemelli unovulari che fra biovulari sotto condizioni altrimenti uguali. Si discute il concetto d'un controllo genetico della funzione cellulare dei tubuli renali.

ZUSAMMENFASSUNG

An sechs eineiigen und sechs zweieiigen Zwillingspaaren wurde die Diurese nach einem Wasserstoss (Volhards Probe) von 1000 cc verfolgt. Diese Versuchspersonen zeigten beträchtliche Variationen ihrer diuretischen Reaktion, insbesondere in der maximalen Intensität ihrer reaktiven Diurese. Das Minutenvolumen des Harns während der halben Stunde intensivster Ausscheidung wurde zwischen den Partnern jedes einzelnen Paares verglichen. Es ergab sich, dass die Differenz der maximalen Intensität der Harnflut unter sonst gleichen Versuchsbedingungen zwischen eineiigen Zwillingen bedeutend kleiner war als zwischen zweieiigen. Dieser Unterschied lag weit ausserhalb der statistischen Fehlergrenzen. Die Annahme einer genetischen Kontrolle der Zellfunktion der Nierentubuli wird besprochen.