URINARY WATER EXCRETION AND NEUROHYPOPHYSIAL FUNCTION IN FULL TERM AND PREMATURE INFANTS SHORTLY AFTER BIRTH

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In recent years the intravenous administration of fluids has been recognized as desirable in the therapy of an increasing number of conditions in infants. It seems important to describe some of the limitations of the ability of young or premature infants to handle the water that is introduced into their extracellular fluid in this manner.

The inability of the kidney of young infants to conserve water by the production of a concentrated urine has been reported. Very little has been published concerning the capacity of the young infant to dilute his urine when excess fluid is present. Ohlmann gave a group of infants up to one year of age 200 cc. water by mouth after an overnight fast. He found that the oldest did excrete this dose of water in five hours but that infants under 3 months of age excreted approximately half as much. Lasch, giving a smaller dose of water to young infants, confirmed these findings. Recently Barnett and others reported on the limitations of the response of premature infants to the administration of excess water and dehydration. Their results indicate that although the kidneys of premature infants do not function at an adult level, the difference is less than previously thought. Similar results have been observed in newborn animals. Adolph working with puppies, Heller and McCance with rats and Dicker with guinea pigs found that little if any diuresis followed the administration of 5% of the body weight of water given to newborn animals; the water was excreted slowly over a long period.

Of prime importance in the urinary excretion of water is the antidiuretic hormone of the neurohypophysis. Heller attempted to explain some of the limitations of young infants' kidneys in terms of their inability to respond to antidiuretic hormone. He observed very little response to injections of large doses of antidiuretic hormone in young infants as compared with adults. His interpretation of these results are questioned since a diuresis was in progress in the adults but not in the infants when the hormone was administered. Barnett and his colleagues reported the comparative responses of a 6 day old infant to a 16 hour thirst and to 1 milliunit (m.u.) of pitressin per minute infused in 0.9% saline for approximately 30 minutes. Since the increase in urine concentration was greater in response to the period of thirst than to the large dose of hormone, it was concluded that the infant's kidney had responded inadequately to the exogenous hormone. Many factors which influence the kidney's response to antidiuretic hormone were not constant in the two periods compared in this infant. It is therefore difficult to interpret these results.

The investigation here reported represents an attempt to describe further the factors that limit water excretion in young full term and premature infants.

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METHODS

All infants in this study were from the newborn nursery in Sloane Hospital or from the premature unit in Babies Hospital. The infants were examined before each study and were considered to be in good condition. The older children were patients in Babies Hospital who had recovered from minimal infections or minor surgical procedures. The adults were normal healthy volunteers.

Urine samples from infants were collected through an in-dwelling catheter directly into cylinders graduated to 0.05 cc. The bladder was emptied by applying pressure to the suprapubic region following the introduction of 1 to 3 cc. air.

Water was given orally through a small plastic tube which fits a No. 23 needle. The tube was inserted into the infant's nose and then passed into the stomach. It was allowed to remain in place 1 to 3 hr. before the start of an experiment.

The antidiuretic assays were carried out by the method reported by Ames, Moore and van Dyke. A urine for assay was chilled and the pH adjusted to 4.0 until it was used. Assays were carried out within 12 hr. after collections were made. In every case in which antidiuretic activity of endogenous origin was present thioglucose inactivation was carried out in order to furnish further evidence for the identification of the antidiuretic substance as antidiuretic hormone.

The antidiuretic hormone used for injection was a special preparation of pitressin supplied by Parke, Davis and Co. which contained 80 pressor units and 3.8 oxytocic units/mg. powder.

Inulin clearances were carried out as described by Barnett et al. Schreiner's method was used for inulin determination. Creatinine was determined according to the Evelyn modification of the Folin-Wu method.

RESULTS

Excretion of Water by Full Term and Premature Infants

1. Oral Administration of water: The response of 67 infants to the oral administration of 30 cc. water/kg. body weight was observed. Urine samples were collected every 5 to 15 minutes for 3 hours and inulin or creatinine clearances were measured. The babies weighed between 1.2 and 5.7 kg. at the time the studies were carried out and they were from 3 hours to 92 days of age. Thirty-eight of them weighed between 0.8 and 2.0 kg. at birth. The graphic analysis of the data obtained is shown in chart 1.

In the first 24 hours of life less than 10% of the water given is excreted in 3 hours. At 3 days of age about 35% of the water given was excreted in 3 hours and at 7 days of age 50% or more was excreted in the same period. In infants under 3 days of age the urine flow increased slightly and the minute volume remained a little higher than the control level throughout the experiment. After one week of age a diuresis of varying degree occurred at some time during the 3 hours. The infants studied were in a state of euhydration or appeared clinically to be in the overhydrated state commonly found in infants in the first days of life. The studies were carried out approximately one hour after a feeding.

TABLE 1

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* Mean ± standard error.
Comparison of water excretion in different age and weight groups following oral administration of water 30 cc./kg. body weight at -15 min.

1 No. of patients in each group.

This group received 15 cc. water every 3 hr. for 12 hr. prior to study.

Comparison of water excreted by various age groups following intravenous administration of 2.5% glucose as 30 cc./kg. body weight given at approximately -10 to 0 min.

2 No. of patients in each group.

Eight infants less than 24 hours old were given 15 cc. water every 3 hours in the 12 hours prior to the administration of a water load. The total urine output in the 3 hours following the test load was greater than that excreted by 26 infants of the same age who received no added fluids before a similar water load. When a double dose of water was given at one time to six other infants of this same age the rate of urine flow did not increase appreciably. No true diuresis was observed in any of these infants.

Changes in the specific gravity of the urine excreted by the infants during the studies described above before and following a water load are summarized in table 1.

2. Intravenous Administration of Water (hypotonic glucose solution): A water load was induced in 42 infants by the intravenous administration of fluids. When water was given orally, the variables of the amount of water and the rate of its absorption by the stomach and intestines were present and a number of small infants had to be excluded from the study because they were unable to retain large doses of water. To avoid an osmotic diuresis caused by 5% glucose in water given intravenously a 2.5% solution was given in the experiments charted in chart 2. In this group of experiments 42 infants were studied, 18 of whom weighed less than 2.0 kg. at birth. Little diuresis followed the intravenous administration of fluids in infants under 24 hours old. The pattern of water excretion in the various age groups is similar to that observed after fluid had been given by mouth. The onset of diuresis when it occurred was approximately 15 to 20
minutes earlier following intravenous fluids but did not otherwise differ from that observed following oral fluids. The changes in specific gravity of the urine before and after water loads were given were similar in magnitude to those observed when water was given orally.

3. Water Excretion by Full Term and Premature Infants: In chart 1 the data obtained from premature infants under 2.0 kg. in weight at birth are charted separately from those derived from the larger premature and full term infants. It can be seen that immaturity apparently had little influence on the rate of development of this function. Although the comparative portions of the water load excreted in two hours are less at all ages, the difference between the means of the outputs of large and small infants is not significant (P = 0.1). Premature infants at 3 or 4 weeks of age can excrete water more efficiently than one week old full term infants even when the premature babies weigh considerably less and appear more immature in many other respects.

4. Water Excretion in Relation to Age: Ten infants whose birth weights were between 1.9 and 2.6 kg. were studied extensively over a 30 day period. Their response to 30 cc. of 2.5% glucose intravenously/kg. body weight was measured every few days. Average values from these data are summarized in chart 3. These data serve to demonstrate the relative ability to diurese at different ages. The volumes of urine excreted/minute as well as the inulin clearances are shown following glucose infusions. Very little if any diuresis can be said to occur under 3 days of age. At one month of age all the infants studied responded to the injection or ingestion of water with a definite rise in urine flow, over 85% of the water given being excreted at the end of 2 hours. The most rapid develop-

![Chart 3](chart3.png)

**Chart 3.** Mean response of 10 infants during first month of life to 2.5% glucose as 30 cc./kg. body weight given at approximately -10 to 0 min. Each curve represents average values from 10 infants who were studied repeatedly over 30 day period. Birth weights were between 1.9 and 2.6 kg. Curve for 60 days was drawn from data obtained from 10 similar infants.

*Absolute values for inulin clearances.*
ment of the ability to excrete a fluid load in a short period of time occurred in a premature infant whose birth weight was 1.2 kg. This baby was able to excrete 50% of an infused water load in 2 hours by the fourth day of life and 100% at the age of 12 days.

It was of interest to study the infants under 3 days of age further. Five infants whose birth weights were between 1.4 and 2.0 kg were placed on a metabolism frame in an incubator and 3 hour urine samples were collected for 24 hours on the second or third day of life. Near the end of a 24 hour period 30 cc. of 2.5 glucose/kg body weight were given intravenously. Urine samples were collected for a second 24 hour period. This same procedure was carried out at 8 to 10 days of age when the fluid intake and output of the infant were greater. A chart of the data obtained from one of these babies is shown in chart 4. Since it has been shown that painful or excitatory stimuli cause a release of antidiuretic hormone, precautions were taken to avoid exciting or causing discomfort to these infants. Inasmuch as they were small, only loose restraints were necessary which did not appear to cause much discomfort. They were given their regular formulae every three hours. Their only painful experience was the injection of the glucose solution and this was over in 5 to 10 minutes. Endogenous creatinine excretion was the only measurement of kidney function carried out. In those less than 3 days of age no significant diuresis was observed in any 3 hour period and there was merely an

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**Chart 4.** Urine flow (upper curve) and creatinine excretion (lower curve) of premature infant tested at 23 hr. and at 9 days of age. At A 30 cc./kg body weight of 2.5% glucose solution was injected intravenously during interval of less than 10 min.
increase in the total 24 hour urine specimen following fluid administration. On the other hand, at 8 to 10 days of age an increase in urine flow was observed in the same babies in the 3 hour period immediately following the glucose infusion.

It has been shown that in normal individuals endogenous creatinine clearances are very close to inulin clearances and probably measure glomerular filtration rates. A rise in creatinine clearance of between 5 and 12% was observed following fluid administration orally or intravenously in 26 of 37 infants studied under 3 days of age. In infants over 10 days of age the rise in creatinine clearance following a water load varied between 14 and 32% in 55 of 67 infants studied. No appreciable change in clearance rates was seen in 23 (22%) in a group of 104 infants at all ages. Changes in inulin clearances were of a magnitude similar to those observed with creatinine clearances in 16 infants.

Response to Exogenous Antidiuretic Hormone

It has been well substantiated that the antidiuretic effect of the neurohypophysial hormone can be demonstrated only when a water diuresis is in progress. Since a diuresis was not induced in infants in the first 3 days of life, attempts to demonstrate a response to the antidiuretic hormone should be unsuccessful. In the first weeks of life the response should be variable. This proved to be true. Studies were carried out in a manner similar to those described above. Fifty cubic centimeters of 2.5% glucose/kg. body weight were given intravenously to 20 infants under 3 days of age. No diuresis ensued and pitressin 0.5 to 5.0 m.u. given intravenously between 20 and 40 minutes after the fluid administration had little or no effect on the urinary output. When more than 1.0 m.u. pitressin was given there was transitory blanching of the skin, restlessness, flatus and the expulsion of feces with moderate force.

In infants over 3 days of age pitressin 0.5 m.u. injected intravenously always stopped a diuresis. The length of the period of low urine flow depended on the degree of diuresis in effect at the time the hormone was given and the amount of discomfort the infant suffered during and following its administration. For several reasons it is difficult
to assess the response to the hormone quantitatively and to compare the antidiuretic effect in the various age groups. Even in animals with diabetes insipidus the response to known amounts of ADH varies for the most part with the state of hydration of the animal and the solute load in the urine. In animals and humans with intact neurohypophyses there is always the possibility of the release of endogenous hormone caused by excitation or discomfort.\textsuperscript{16-18} When a procedure caused discomfort there frequently was a fall in urine flow. Chart 5 demonstrates such a response to the passage of a No. 10 French catheter through an infant's mouth. Thirty minutes prior to this, 65 cc. H\textsubscript{2}O had been passed through a small plastic tube which had been in place in the infant's nose. Urine collected during this period of antidiuretic effect was found to have antidiuretic activity equivalent to pitressin 0.75 m.u./cc. urine. The response to 0.5 m.u. pitressin is also summarized in this figure. The pitressin was added to an infusion which had been running into a wrist vein, and the infant slept throughout the entire procedure.

In spite of the variability of the responses to the hormone it can be said that when a diuresis was established an antidiuretic response was obtained in all infants over 3 days of age following either a painful stimulus or the administration of antidiuretic hormone. When pitressin 0.5 m.u. was given to 42 infants over 5 days of age, urine flow fell to less than 0.25 cc./minute as compared with an average flow before hormone administration of 2.8 cc./minute. The period of antidiuresis varied according to the amount of excitement which accompanied the injection. In 12 infants to whom a continuous infusion of 2.5% glucose was being administered and who could be given the hormone without the discomfort of an additional injection, the period of antidiuresis was over in 30 to 40 minutes. The difficulty of avoiding psychic effects was greater in the older infants and children for whom restraints were necessary for any injection or infusion. Transient and apparently spontaneous falls in urine flow were even more frequent in the older children. As far as comparison was possible between infants and older children the response to exogenous hormone (0.5 to 2.5 m.u.) could not be said to be different.

Secretion of Antidiuretic Hormone in Young Infants: Since no response to antidiuretic hormone could be demonstrated in infants under 3 days of age, evidence of a functioning neurohypophysis was sought. Fluids were withheld from 23 infants under 3 days of age for 6 to 8 hours. Urines were collected in the last 30 minutes without disturbing the infant. These urines were found to contain an antidiuretic activity which was equivalent to 1.25 ± 0.25 m.u. pitressin/cc. urine. This activity was abolished by alkali, heat and reduction with thioglycollate,\textsuperscript{14} effects which are characteristic of the activity of neurohypophysial hormone. Six children aged 2 to 12 years had no detectable antidiuretic activity in their urine after 6 hours of thirst. Eight adults who were thirsted 12 hours had inactive urines, but following a 24 hour thirst there was 0.25 m.u./cc. in 2 specimens. The presence of hormone in the urines of the young babies probably means either that there is excessive liberation of hormone, or decreased destruction or inactivation, or that the hormone passes through the infant's glomeruli more readily than through adult glomeruli. It is also possible that the young infant loses more water/kg./minute and therefore is more depleted after a 6 hour thirst.

There are no available observations suggesting which of these factors is most important. Nevertheless, the presence of the hormone in the infant's urine is good evidence of a functioning neurohypophysis.
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DISCUSSION

It is apparent from the results obtained in these studies that the ability of the newborn infant to excrete a water load develops gradually in the first month of life. In the first 3 days of life it is difficult to be certain that the large doses of fluid administered in the course of these observations were associated with any change in renal function. These young infants are apparently unable to respond with a diuresis after an increase in body water. The rate of development of the ability to excrete a water load is little influenced by the maturity of the infant at birth as judged by body weight and period of gestation.

The cause of the early inability to excrete large doses of fluids is not clear from the evidence at hand. Three organs are chiefly involved in the urinary excretion of water; the kidney, the adrenals, and the neurohypophysis. We know that the kidney of the young infant is immature at birth. It has been shown by others that the glomerular filtration rates of premature and full term infants are half those of adults when compared on the basis of surface area. The adult levels are not reached until the end of the first year or, according to others, by the end of the second year. Tubular function in young infants as measured by diodrast and p-amino-hippuric acid clearances has also been found to be lower than in adults. Adult levels of tubular function are not reached until the end of the first year. The relatively low level of both glomerular and tubular functions at birth accounts in part for the early inability to excrete large doses of water. Yet some other deficiency must play a far more important role, since the infant is able to excrete a water load in a mature manner as early as at the age of one month rather than at 1 or 2 years.

It has been shown that patients with adrenal cortical insufficiency do not respond to water loads in the usual manner. No sudden diuresis ensues following the administration of a large dose of fluid but there is a gradual excretion of the excess water over a long period of time. This resembles the performance observed in young infants under 3 days of age. Our knowledge of the capacity of the adrenals in newborn infants to respond to stress of any kind is meager. Jailer found that the adrenals of newborn rats did respond to ACTH but that there was no evidence of ACTH release from the pituitary after stress. Venning et al. demonstrated an increased excretion of glucocorticoids in newborn human infants following trauma. This has been interpreted to mean that the anterior pituitary does respond to stress and in turn stimulates the adrenals in the human infant. How soon the adrenal cortex is able to function at an adult level is not known. However at present we have no evidence to support the hypothesis that adrenal hypofunction can account for the inability of the young infant to excrete a water load rapidly.

The neurohypophysis is of the utmost importance in the conservation of water. During water diuresis the release of ADH is suppressed. When diuresis occurs, exogenous as well as endogenous antidiuretic hormone, released in response to discomfort or excitation, can produce an antidiuretic effect in older infants and adults. Whether the effect is less in infants remains a question since it is difficult to evaluate quantitatively a response to a known dose of hormone in the presence of an intact neurohypophysis. Antidiuretic activity was present in the urines of young infants after thirsting. Since the substance responsible for this activity had several of the characteristics of pituitary ADH, we assume that the neurohypophysis is functioning in this group at an early age. In the absence of a functioning neurohypophysis in the adult, diuresis in response to an increased water load is not impaired and the kidneys respond to exogenous antidiuretic hormone. The very young
infant is unable to vary his urine flow to any great extent when his fluid intake changes, and no response to exogenous antidiuretic hormone can be demonstrated. Therefore, the immature responses of the very young infant do not imply neurohypophysial dysfunction. By exclusion, the low level of kidney function and a possible adrenal insufficiency remain as probable factors accounting for the deficient excretion of water in the first weeks of life.

It is perhaps not unexpected that additional hydration facilitates the excretion of water even in the very young infant. This was demonstrated in the 8 infants under 24 hours old who were given 60 cc. water in 12 hours prior to a large dose of water. Their ability to excrete the water load was much greater than that of infants of the same age receiving only the single large dose of water, although no real diuresis was observed in any of these infants under 3 days of age.

**Summary**

In infants studied in the first month of life there was a gradual development of the ability to excrete excess water in a short period of time. When a water load was given according to body weight, orally or intravenously, no diuresis was observed in infants under 3 days of age. In comparison, all individuals tested over 3 days of age responded with a definite increase in water excretion. As early as 2 weeks of age and in all infants over one month of age the entire water load of 3 to 5% of their body weight was excreted in a three hour period following the administration of fluid. No difference in the diuretic response to a water load was apparent in full term and premature infants of comparable postpartum age.

Antidiuretic hormone whether produced endogenously following thirst, excitation or pain, or injected in the form of exogenous antidiuretic principle, caused a decrease in urine output only in infants who received a water load and who were responding to it with a diuresis.

When diuresis followed a water load, the degree of the renal response to antidiuretic hormone could not be compared in the various age groups studied, because of the inability to control a sudden release of endogenous hormone provoked by excitatory stimuli.

The hormone was detectable in the urines of infants under 3 days of age after fluid deprivation; this is assumed to be evidence of a functioning neurohypophysis.

**References**

URINARY EXCRETION AND NEUROHYPOPHYSIAL FUNCTION


SPANISH ABSTRACT

La Excreción Urinaria de Agua y la Función Neurohipofisaria en Niños a Término y Prematuros

El uso de la vía venosa para la introducción de soluciones a lactantes con diversos padecimientos a fin de realizar una terapéutica mejor y más rápida, ha dado interés al estudio de las limitaciones que lactantes a término y prematuros puedan tener para regular el agua agregada por dicha vía al contenido líquido extracelular. Este trabajo tiende a analizar algunos factores que limitan la excreción acuosa en estos seres. Los niños aquí estudiados fueron considerados normales; se les proporcionó agua por vía oral y por vía intravenosa (para ésta se empleó solución glucosada hipotónica); la orina se recolectó por cateterización; la acción antidiurética se analizó con el método de Ames, More y Van Dyke; la hormona antidiurética de origen exógeno fue una preparación especial de pitresina de Parke Davis y Co.; por último las pruebas de la inulina se realizaron de acuerdo con el método de Barnett y colaboradores, la determinación de inulina por de Schreiner y la creatinina por el de Evelin modificando el de Folin-Wu.

Los estudios realizados por estos autores sugieren que la capacidad de los recién nacidos para eliminar una sobrecarga hídrica se desarrolla gradualmente en el primer mes de edad y que en los primeros tres días de la vida, no se puede acharcar la escasa eliminación exclusivamente a una alteración de la función renal. La madurez del niño al nacer, juzgada por su peso y por duración de su vida intrauterina, tampoco parece influir sobre el desarrollo de la capacidad excretora.

La causa de la incapacidad a esta edad no es clara; los tres órganos que intervienen en la excreción urinaria son el riñón, las suprarrenales y la neurohipófisis. La inmadurez del riñón, aceptada para los dos primeros años de vida, no impide que al mes el niño elimine el exceso de agua; entonces, se supone que haya alguna otra deficiencia que intervenga en la defectuosa eliminación de los primeros tres días de edad. La insuficiencia suprarrenal se considera como un factor al

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respecto en los adultos; pero poco sabemos de la función de las adrenales en el recién nacido y por lo tanto no podemos sostener la hipótesis de que la hipofunción de esta glándula sea la responsable de la incapacidad del lactante para eliminar los excesos acuosos. Asimismo se conoce la importancia de la neurohipófisis en la conservación del agua; tanto en niños mayores como en adultos hay supresión de la hormona antidiurética durante la diuresis de agua, y viceversa, pero no se sabe si lo mismo sucede en lactantes.

Los autores concluyen que existe un desarrollo gradual de la capacidad excretora de agua durante el primer mes de la vida. En los tres primeros días, no se observa diuresis con un exceso de agua de acuerdo con el peso del niño, empleando bien la vía oral o la intravenosa; después de estos tres días de edad hay aumento definido en la excreción acuosa; desde las dos semanas de edad y en todos los niños después del mes de edad, la sobrecarga acuosa que alcance del 3 al 5% del peso corporal, se excreta en las tres horas siguientes a la administración del líquido, sin que se observe diferencia de la respuesta diurética entre niños a término y prematuros de edad semejante después del nacimiento.

La hormona antidiurética, tanto de producción endógena por sed, excitación o dolor, como inyectada, produjo un descenso en la excreción urinaria sólo en aquellos niños que recibieron la sobrecarga acuosa y estaban respondiendo con diuresis. Cuando se presentó la diuresis por la sobrecarga acuosa no se pudo comparar la respuesta renal a la hormona antidiurética en los diferentes grupos de edades estudiados, por la imposibilidad de controlar las descargas bruscas de hormona endógena provocada por las excitaciones. La hormona logró aislarse en la orina de niños menores de tres días de edad tras un ayuno de agua; su presencia se acepta como prueba de actividad de la neurohipófisis.

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