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THE RENAL FUNCTION OF NEWBORN INFANTS

By H. HELLER, *From the Department of Pharmacology, University of Bristol*

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In a recent paper McCance & Young [1941] have shown that normal infants aged 7–14 days excrete a urine which is persistently more dilute than that of adults. They have found that in premature and full-term infants the urea and mineral clearances are always low by adult standards [Young, Hallum & McCance, 1941] and that almost all the electrolytes filtered off in the glomeruli of many infants must be re-absorbed by the tubules. This may be one of the reasons why infants are unable to increase the concentration of urinary solutes in the way adults do when the output of urine falls. However, a detailed analysis of the process of elaboration of urine at low minute volumes in newborn children would seem to suggest that the low mineral clearances of the infantile kidney are unlikely to be the only factor which operates for the excretion of a persistently dilute urine. McCance & Young's work supplies evidence for the view that the proximal tubule of the infantile kidney is capable of reabsorbing 'threshold' substances at a rate which, favoured by the low filtration rate characteristic for the glomerulus of the newborn infant, is at least equal to the reabsorptive capacity of the adult tubule. It seems therefore permissible to assume that, just as in the adult kidney, a blood isotonic [Walker, Bott, Oliver & MacDowell, 1941] or more likely a blood hypotonic [Shannon, 1942*a*] fluid is formed in the proximal renal tubule of the infant. A fluid of such a composition and flowing at such low velocity would invariably be highly concentrated when passing through the distal tubules of a normal adult kidney. The excretion by the kidney of the newborn of a dilute urine at low minute volumes suggests, therefore, that the distal tubules of the newborn infant function in a manner different from that of the adult.

The possibility that several factors may be involved in the process of water reabsorption by the distal tubule has recently been postulated [Shannon, 1942*a*]. However, there is so far no evidence against regarding the posterior pituitary antidiuretic principle as the major determinant of the final concentration of the urine at low minute volumes. The question arises therefore whether the persistently high dilution of the urine of newborn infants might be due to some inadequacy of the posterior pituitary-renal mechanism. It was realized that such an inadequacy might be connected with one or several of the following possibilities: (1) Lack of response of the infantile kidney cells to the

circulating antidiuretic hormone. (The question of the developmental state of the human tubules at birth, as discussed by Gersh [1937], Gruenwald & Popper [1940] and McCance & Young [1941] should here be considered.) (2) Insufficient production of the antidiuretic factor by the posterior pituitary lobe of the newborn infant. (3) Insufficient development of the mechanism which integrates the production and liberation of the antidiuretic hormone with the functional state of the tubular epithelium. The aim of the present paper was an attempt to investigate the first of these possibilities. An investigation of the urinary concentration of infants during the first 6 days of extra-uterine life and its relation to fluid intake were subsidiary subjects.

Methods

Specimens of urine were obtained from twenty-three normal, full-term infants aged 8–135 hr. Male children only were investigated. The urine samples were collected in small test-tubes attached by elastic strapping. The movements of the children were not restrained. Twelve healthy men aged from 21 to 37 years served as adult controls. Urine samples were put on ice immediately after collection.

Urinary freezing-point depressions (Δ) were estimated with a Beckmann apparatus for small quantities of fluid. Δ values were converted into milli-osmolar concentration by the usual formula: C (in milli-osM.) $= \Delta/1{\cdot}86 \times 1000$. Corrections for the sediment which forms on cooling were obtained by the following procedure: the volume of the urine sample was measured at room temperature, the sample cooled to $-0{\cdot}5°$ C., centrifuged, the supernatant fluid decanted, the sediment dissolved in twice the original volume of distilled water and the freezing-point depression of this solution determined. The figure so obtained was multiplied by two and added to the Δ of the supernatant fluid.

Heller's [1941] apparatus was used for the determinations of specific gravity. The pituitary (posterior lobe) preparation employed was B.D.H. posterior pituitary extract.

Results

The effect of posterior pituitary extract on the urinary secretion of newborn infants

An assessment of the action of posterior pituitary extract on the kidney of the newborn infant meets considerable technical difficulties. It is customary to estimate the response of the mammalian kidney to the antidiuretic hormone by the inhibitory effect of a given dose of posterior pituitary extract on a water diuresis. The inhibition in turn is measured by the decrease of urine flow in the unit time. This technique is hardly applicable to the newborn infant because (1) it is difficult to be sure that none of the urine voided has been lost, and (2) because newborn infants cannot be made to empty their bladder at regular

intervals. (It was felt that the use of a catheter was not permissible in an investigation on healthy infants.) The following method was therefore used

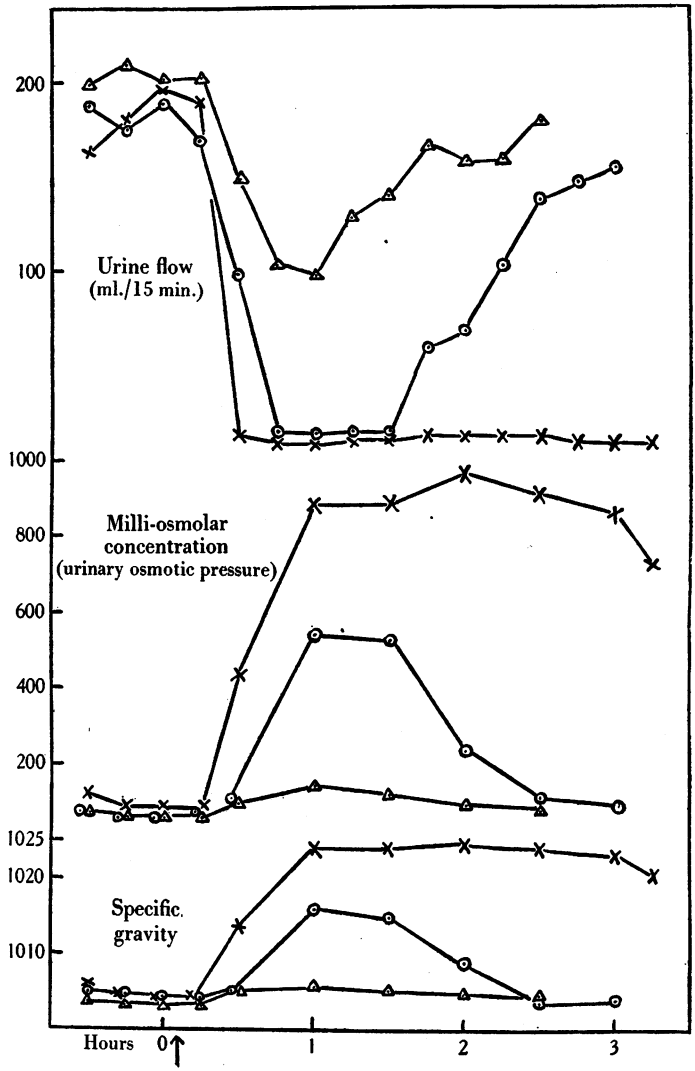

Fig. 1. The effect of intramuscular injections of posterior pituitary extract on urine flow, urinary osmotic pressure and urinary specific gravity of a normal adult subject. (H. ♂, 36, body surface 1·90 sq.m.) △——△ 12·5 mU. sq.m., ⊙——⊙ 25 mU. sq.m., ×——× 150 mU. sq.m. Injections at the time marked by arrow. The subject drank 100 ml. water per sq.m. body surface at intervals of 15 min. throughout the duration of the experiment.

to obtain evidence as to whether injections of posterior pituitary extract had an effect on the urinary secretion of the newborn child: Changes of urinary osmolar concentration (calculated from Δ) rather than changes of urinary

volume were used as criterion of the effect of the antidiuretic principle. Fig. 1 shows that this method of gauging the effect of an injection of posterior pituitary extract gives as faithful a picture of the action of the antidiuretic factor on the urinary secretion of the adult as measurements of changes of the urine volume. The possibility of a dissociation by the infantile kidney of the effect of the antidiuretic factor on the urinary volume and the urinary concentration cannot at present be discounted. However, such a dissociation has, to the author's knowledge, hitherto not been observed in normal subjects.

Estimations of concentration rather than volume obviate the necessity of quantitative collections of urine. The elimination of the second difficulty, viz. the collection of urine specimens of newborn infants at specified times, was attempted by the use of the following procedure: (1) A urine specimen from a newborn child was collected and a given dose of posterior pituitary extract injected intramuscularly. (2) Samples of urine voided spontaneously at the two following occasions were then taken and the Δ of all specimens determined. (3) In order to compare the effect of the antidiuretic principle on the urinary secretion of the newborn child with that on the adult, an equivalent amount of posterior pituitary extract was injected into adults who drank 100 ml. water per sq.m. body surface at intervals of 15 min. throughout the duration of the experiment. (4) Urine samples of adults were collected at exactly the same times as those at which the infants had emptied their bladders spontaneously.

Fig. 2 illustrates such experiments. It is clear that the analysis of urine samples collected at such irregular times and at such comparatively long intervals cannot give an accurate picture of the effect of the posterior pituitary extract. However, it will be noticed that in the case of the newborn infant the first urine collected after the injection was somewhat more concentrated than the urine obtained before the injection was made. The second sample after the injection shows a return to the pre-injection level. This slight rise of urinary concentration and the subsequent return to the normal occurred regularly in experiments of this type and is unlikely to have been accidental ($t = 3{\cdot}06$, $P < 0{\cdot}05 > 0{\cdot}02$). It may therefore be taken as indicating that posterior pituitary extract may have some slight effect on the kidney of the newborn, though a comparison of this effect with the effect of an equivalent dose on the urinary concentration of an adult subject (Fig. 2) suggests a high degree of insensitivity of the renal tubules of the newborn child to the antidiuretic hormone.

It will be noted that the concentration of the urine samples taken immediately before the injection of the posterior pituitary extract are much the same for newborn infants and adults. It was to achieve this that the adult controls drank large quantities of water before an injection of posterior pituitary extract was made. The subsequent doses of 100 ml. water per

sq.m. body surface taken every 15 min. were sufficient to maintain their urinary concentration at a level comparable to that of infants aged over 4 days (Fig. 3). It will be shown later that children aged 1–4 days were usually found

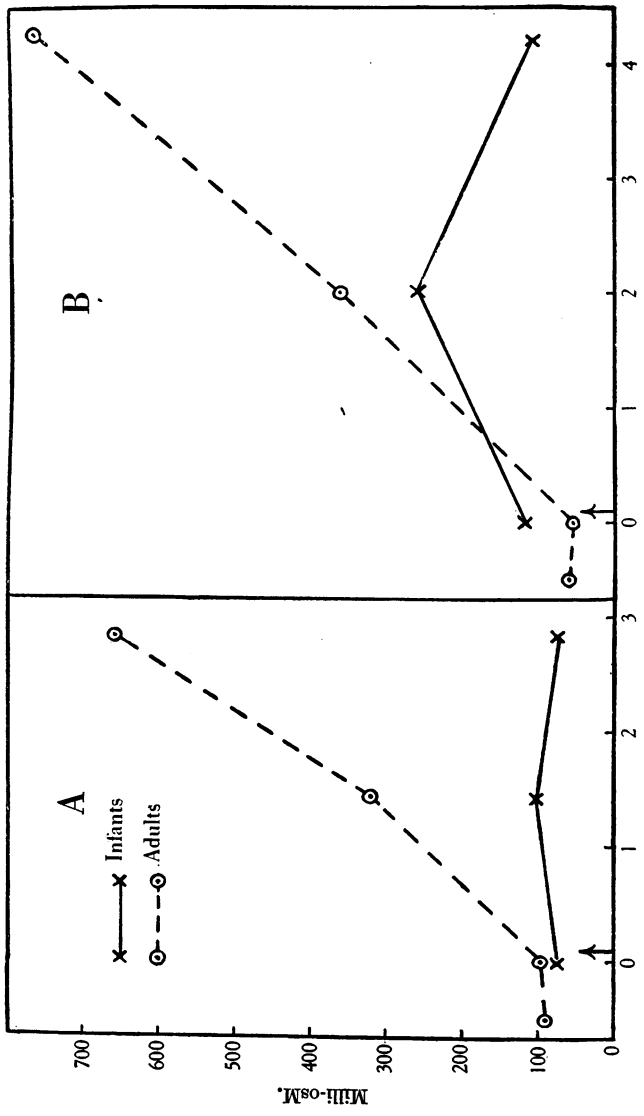

Fig. 2. A comparison of the effect of equivalent doses of posterior pituitary extract on the urinary osmotic pressure (in terms of milli-osmolar equivalents) of newborn infants and of adults. (A) At the time marked by arrow intramuscular injection of 125 mU. sq.m. into the infant Sh. (5th day of extra-uterine life) and the adult subject Pa. Absolute doses: 25 mU. and 210 mU. respectively. (B) At the time marked by arrow intramuscular injection of 250 mU. sq.m. into the infant Ma. (5th day of life) and the adult subject Du. Absolute doses: 50 mU. and 500 mU. respectively.

to excrete a considerably more concentrated urine. Two such children (baby Cap. aged 84 hr. and baby Car. aged 90·5 hr.) were injected with 150 mU. posterior pituitary extract per sq.m. Urine samples collected before the injection gave a concentration of 664 and 462 milli-osM. respectively. The first sample after the injection (obtained after 50 min. in the case of baby Cap.

and after 86 min. in that of baby Car.) yielded values of 643 and of 441 milliosM. respectively. It will be seen that the slight increase of urinary concentration after the injection of posterior pituitary extract which was regularly noticed in infants who secreted a strongly hypotonic urine (Fig. 2) was not observed in these cases.

The means by which 'equivalent' doses for newborn infants and for adults had been established have still to be discussed. The doses used (Fig. 2) were based on the relative areas of body surface, since it appears that rates of urinary output at all ages are correlated most accurately with the body surface [Adolph, 1933]. Following McCance & Young [1941] the average ratio of adult to infantile surface area has been taken as 8·25, and the doses of posterior pituitary extract injected were calculated accordingly. McCance & Young point out that in the newborn infant body surface area, though proportional to the output of urine, is not proportional to basal metabolic rate and kidney weight. The use of the surface area as a basis for the calculation of doses of posterior pituitary extract is therefore less acceptable for infants than for adults. However, it will be noticed (Fig. 2A) that 125 mU. posterior pituitary extract per sq.m. had been chosen as the standard dose. Several other experiments gave essentially similar results when 250 mU. per sq.m. had been injected (Fig. 2B). This means, as Fig. 1 shows, that the adult controls received 5 or respectively 10 times the minimum effective dose of the antidiuretic hormone. The use of such large doses makes it *a priori* unlikely that the choice of another basis for the calculation of equivalent doses would have influenced the results significantly. It should also be pointed out that the absolute dose injected into infants receiving 250 mU. posterior pituitary extract per sq.m. amounted to as much as 50 mU. This is a dose which, injected into an healthy adult, produces a marked inhibition of a water diuresis (Fig. 1). The choice of the basis of comparison was thus of comparatively little importance.

The osmolar concentration of urines of infants aged 8–135 *hr.*

McCance & Young [1941] furnished data for the osmolar concentration of urines of normal children aged 7–14 days. The infants investigated in the present series were younger than those of McCance & Young, and the data are therefore complementary to the figures of these authors. Urinary osmotic pressures were assessed by determining freezing-point depressions. Where possible the first urine voided after birth was analysed and the investigation prolonged to the 6th day of life. Children of this age were chosen for two reasons. First, fluid intake during the first week of life is much more variable than during the second. Secondly, clinical disturbances of the water balance are more frequent during the first days of life.

Fig. 3 shows results obtained from a series of twenty-three infants. It will be seen that most infants excreted a comparatively concentrated urine during

the first 2 days after birth. The average concentration decreased rapidly during the 3rd day. Urines voided on the 4th, 5th and 6th days were, with few exceptions, very dilute. McCance & Young's findings suggest that they remain so for at least another week. Facilities to obtain blood samples from the infants investigated in this series were not available. To obtain some information about the serum/urine osmotic pressure ratio it was, therefore, unavoidable to rely on published data for values of the average serum osmotic pressure of

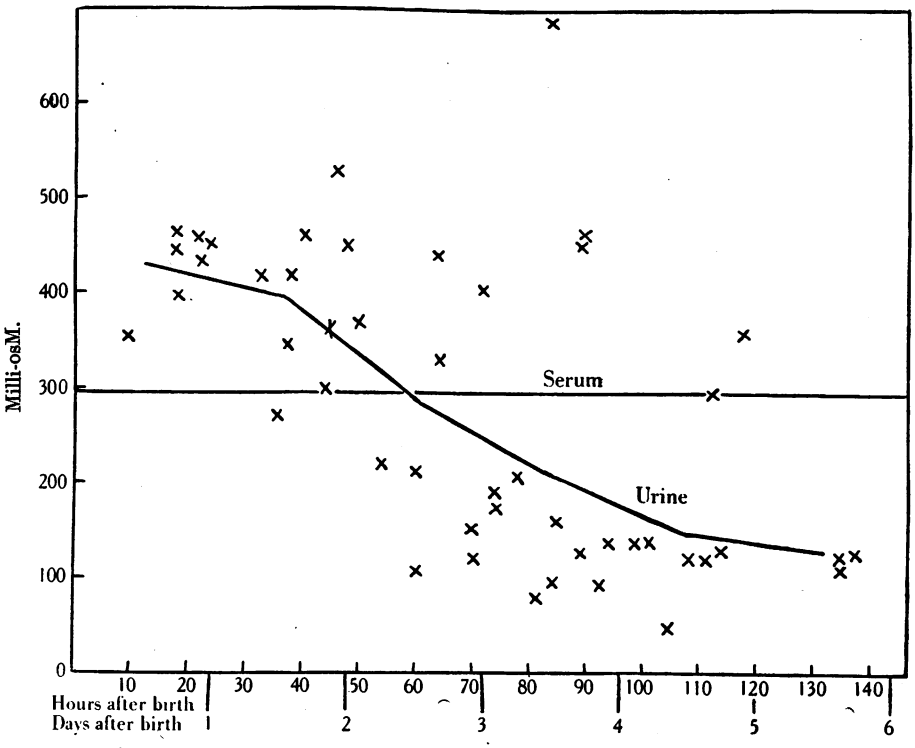

Fig. 3. Urinary osmotic pressures (in terms of milli-osmolar equivalents) of a series of newborn infants.

infants. Füth & Wirz [1929] who determined the freezing-point depression of serum samples taken during the first hour after birth found a serum osmotic pressure equivalent to 295·8 ± 8·72 milli-osM. (recalculated). This figure would seem to be in agreement with the data of McCance & Young [1941] who, using a different method, obtained a serum osmotic pressure equivalent to approximately 310·9 ± 14·7 milli-osM. for infants aged 7–14 days. These figures make it very likely that the infants on which the data of Fig. 3 are based, excreted a slightly hypertonic urine during the first 2 days after birth.

However, it should be emphasized that even these comparatively high concentrations were still much below the average concentrations of urines ex-

creted by a group of normal adults (Fig. 4), and this in spite of the fact that the subjects chosen were having their full complement of fluids (including a minimum of six cups of strong tea per day), whereas the fluid intake of infants during the first and second days of life was much restricted (Fig. 5). The average values of 'day' and 'night' urines of our adult series agree well with Koranyi's [1897] figures. In an investigation on four normal men he found

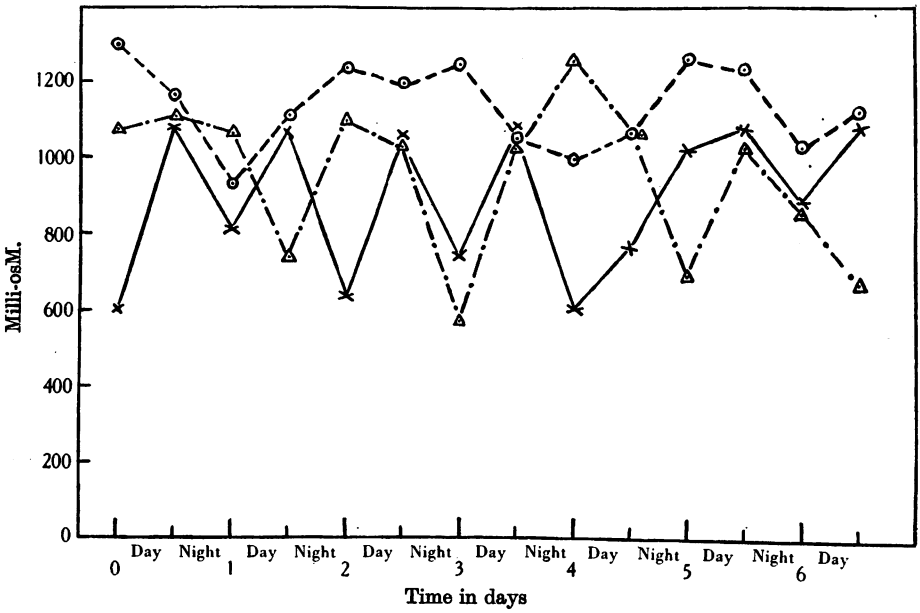

Fig. 4. Urinary osmotic pressure ε(in terms of milli-osmolar equivalents) of three normal adults. ×——× subject H., ⊙---⊙ subject P., △-·-·-△ subject R. 'Night' urines collected between 10 p.m. and 10 a.m., 'day' urines collected between 10 a.m. and 6 p.m. *Note.* The scale is different from that of Fig. 3.

the following milli-osmolar concentrations (recalculated from freezing-point depressions) for urines collected during 4 hr. periods: 7 a.m. to 11 a.m.: $1121 \pm 76{\cdot}6$; 11 a.m. to 3 p.m.: $1205 \pm 108{\cdot}6$; 3 p.m. to 7 p.m.: $1208 \pm 128{\cdot}1$; 7 p.m. to 11 p.m.: $1052 \pm 251{\cdot}8$; 11 p.m. to 3 a.m.: $1226 \pm 136{\cdot}4$; and 3 a.m. to 7 a.m.: $1260 \pm 90{\cdot}9$.

The influence of the daily fluid intake on the urinary concentration of newborn children

A number of factors may be involved in the comparatively sudden decrease of urinary concentration observed in infants during the third day of extra-uterine life (Fig. 3). Metabolic changes resulting from adaptations to extra-uterine life and hormonal changes resulting from the separation from the maternal organism may be considered. Further investigations will be needed

to establish their possible significance in connexion with the metabolism of water and with kidney function. However, one factor possibly concerned with the urinary concentration of newborn infants has, to some extent, been investigated. This factor is the influence of the daily fluid intake. If 24-hourly fluid intakes are plotted against urinary osmotic pressure (in terms of milli-osmolar equivalents) it will be seen (Fig. 5) that the urinary concentrations

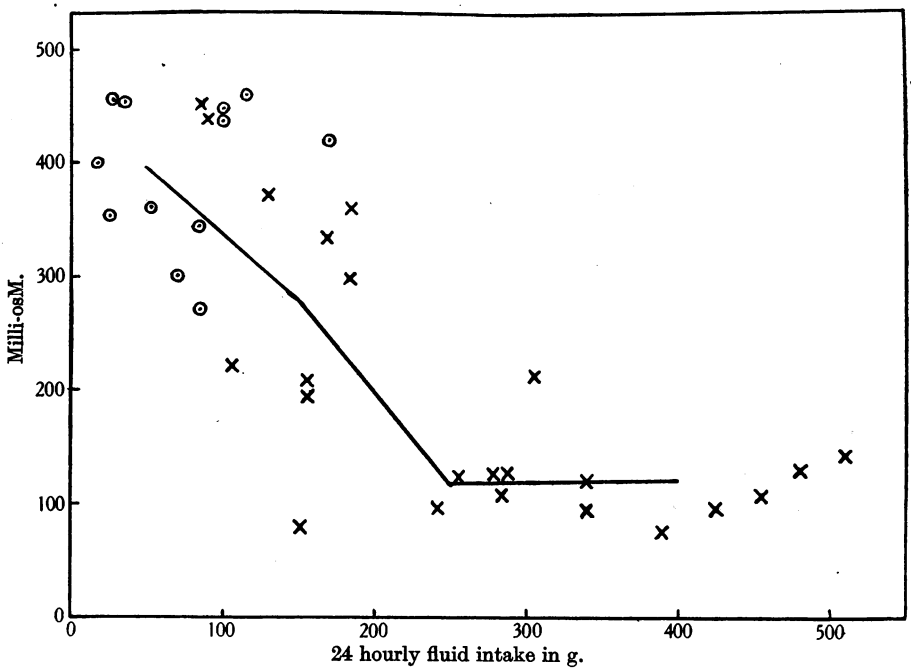

Fig. 5. Relation between fluid intake and urinary osmotic pressure (in terms of milli-osmolar equivalents) of a series of newborn infants. ⊙ infants aged 8–48 hr., × infants aged 49–135 hr.

fall as the daily fluid intake increases. The correlation coefficient for the data represented on Fig. 5 is highly significant ($r = -0{\cdot}78$, $P < 0{\cdot}001$), and a relationship between fluid intake and urinary concentration is, therefore, very probable. However, in view of the possible involvement of other, hitherto uninvestigated, factors, it would be rash to assess the degree of causal connexion between the two variants.

Discussion

To what extent do the results of this investigation support the hypothesis that one of the factors responsible for the difference in the function between the kidney of the newborn infant and that of the adult is an inadequacy of the posterior pituitary regulatory mechanism? It has been shown that a dose of posterior pituitary extract which had a pronounced inhibitory effect on the

water diuresis of adults had very little effect on the urinary concentration of newborn children. The question arises whether we are entitled to compare the water diuresis of the adult with the 'normal' urinary secretion of the newborn infant ingesting adequate amounts of milk at four hourly intervals. The two states are well comparable in so far as the average osmotic pressures of the respective urines are concerned, but they differ in that very low urinary osmotic pressures comparable to those which are maintained for days and very likely weeks by newborn infants, seem to be linked invariably with a relatively much higher minute volume in the adult. To produce such low urinary osmotic pressures in adult healthy mammals a water diuresis has to be instituted. A dissimilarity of the urinary minute volumes can, therefore, hardly be avoided if normal adults should be used for the purpose of comparison.

However, there are conditions in which adult mammals excrete a urine of low concentration at a comparatively low rate. This may occur in cases of abnormal pituitary function such as diabetes insipidus. For example: Shannon [1942*a*, Table II] mentions a dog with experimental diabetes insipidus which excreted a urine of $\Delta = -0{\cdot}22°$; the corresponding rate of urine flow was 1·57 ml./min. This may be compared with a normal dog of similar body weight which excreted a urine of similarly low concentration ($\Delta = -0{\cdot}26°$), but in this case at a rate of 10·00 ml./min. [Shannon, 1942*b*, Table III]. When the urine flow of the latter animal was decreased to a value comparable to that of the diabetes insipidus dog, i.e. to a rate of 1·52 ml./min. by an infusion of small amounts of pituitrin, the urinary concentration rose to $\Delta = -1{\cdot}64°$. The similarity in the behaviour of the minute volume/concentration ratio between an organism suffering from diabetes insipidus and the newborn infant suggests the possibility of a posterior pituitary inadequacy in the latter. Are there any other resemblances between the renal function of the newborn child and that of cases of diabetes insipidus? McCance & Young [1941] have shown that the newborn infant's clearances of sodium, chloride and potassium are significantly lower than those of adults. The influence of such factors as the glomerular filtration rate on the clearance value of these threshold substances must not be discounted, but it should be remembered that an increase of the reabsorptive capacity of the proximal tubule for sodium (and chloride) is held to be one of the fundamental derangements in diabetes insipidus [Shannon, 1942 *a*, *b*]. It appears thus possible that the low sodium and chloride clearances of newborn infants may partly be due to an insufficient control of the tubular electrolyte reabsorption by the posterior pituitary lobe. Moreover, the findings of Stehle [1927] and others suggest that the renal excretion of potassium as well as that of other ions is influenced by the posterior pituitary hormones.

The foregoing considerations suggest that the nephron of a well-hydrated infant may be pictured as functioning in some such manner as the following:

The insufficiently developed glomerulus delivers its filtrate to the proximal tubule at a low rate [Barnett, 1940; McCance & Young, 1941]. Owing to the low velocity of flow and possibly to the lack of posterior pituitary control, electrolyte reabsorption is higher than in the adult, and a hypotonic fluid reaches the distal site of the action of the antidiuretic hormone. The low velocity of flow in conjunction with the low tonicity of the tubular fluid constitute highly favourable conditions for the action of the antidiuretic hormone, but owing to an insufficiency of the posterior pituitary-renal mechanism little water reabsorption occurs, with the result that at relatively low filtration rates a small volume of a urine of low osmotic pressure is elaborated.

Assuming then that the renal function of newborn infants resembles in some points that of an adult subject suffering from total or partial diabetes insipidus, is there any justification in suggesting that newborn children suffer from a state of 'physiological' diabetes insipidus?

(A) The comparison would seem to apply in so far as the results of the present investigation suggest that the posterior pituitary-renal mechanism works imperfectly in the newborn child. Certain clinical evidence may be added to this. It is generally agreed that the function of the posterior pituitary antidiuretic hormone in the adult mammal is the conservation of body water especially under conditions of stress. There is evidence that it is difficult for some newborn infants, at least, to conserve body water. Infants aged 2–4 days are liable to a febrile disturbance (inanition or desiccation fever) which coincides with the period of the lowest fluid intake (Figs. 3, 5) [Faber, 1922; Kaufmann & Bickel, 1931]. This pyrexia has been shown to be accompanied by a diminution of the plasma water content [Bakwin, 1922]. Normal body temperature is quickly restored by an increase of fluid intake. The correlation between body hydration and temperature regulation is too well known to require comment [Herrington & Gagge, 1943], but further data on the water metabolism of newborn infants suffering from inanition fever are needed to make the supposition acceptable, that the rise in temperature is due, or partly due, to an inability to conserve water in the adult fashion, i.e. by the elaboration of a sufficiently concentrated urine. However, attention may be drawn to the similarity between the 'inanition' fever of the newborn child and the febrile response of cases of diabetes insipidus to water restriction [McGavack, Boyd & Gelvin, 1942].

(B) It should be pointed out that the comparison between the state of the water metabolism of the newborn infant and that obtaining in cases of experimental and clinical diabetes insipidus is not applicable in so far as the results of this investigation merely suggest that, compared with the normal adult, the renal tubules of the newborn infant are less sensitive to posterior pituitary extracts, whereas diabetes insipidus has been shown to be due to a deficiency of the posterior pituitary antidiuretic hormone. It appears quite possible that

in the newborn mammal such a hormonal deficiency coexists with the insensitivity of the renal tubules to the antidiuretic principle but experimental evidence on this point is lacking.

Summary

1. Intramuscular doses of posterior pituitary extract which produced a pronounced inhibition of a water diuresis in adults had only a very slight and fleeting effect on the urinary concentration of newborn infants excreting a markedly hypotonic urine (Fig. 2). A low sensitivity of the renal tubules of the newborn children to the posterior pituitary antidiuretic hormone is thus indicated.

2. Freezing-point determinations of urine samples obtained from a series of infants aged 8 hr. to 6 days showed that these children excreted a comparatively concentrated urine during the first 2 days of extra-uterine life (Fig. 3). However, even these, most likely hypertonic, urines were still much below the average concentration of urines excreted by a group of normal adults (Fig. 4). Urinary concentrations were found to decrease rapidly during the 3rd day of life. Urine samples collected during the 4th, 5th and 6th days of life were, with few exceptions, markedly hypotonic.

3. The relation between the daily fluid intake and the concentration of urine samples obtained from the same group of newborn children (Fig. 5) suggests that the former may be an important determinant for the latter.

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