the relationship in control neonates or older children. In the face of low cord blood C-LDL, nearly all of the total plasma cholesterol variation was accounted for by C-HDL. The inverse C-HDL to C-LDL correlation was not significant.

In hyperalphalipoproteinemic neonates, C-LDL but not C-HDL correlated significantly with total plasma cholesterol. Nearly all of the total plasma cholesterol variation was accounted for by C-LDL. The inverse C-HDL to C-LDL relationship was not significant.

Whatever factors contribute to both the overall and to the extremes of the C-HDL and C-LDL frequency distributions at birth, C-HDL and C-LDL in neonates appear to be under independent metabolic control.

It might be interesting to follow into later infancy and childhood neonates at the extreme of the C-LDL and C-HDL distributions to determine whether or when, with the inevitable ascendence of C-LDL as the predominant cholesterol carrying lipoprotein (1–4), significant inverse C-HDL to C-LDL relationships will appear.

CONCLUSION

In 117 unselected neonates the correlation coefficients for C-HDL to total cholesterol ($r = 0.63$), and C-LDL to total cholesterol ($r = 0.76$) were very similar to those reported for older children. However, in contrast to school children, the C-HDL to C-LDL relationship in the unselected neonates was not significant ($r = -0.002$). In 63 hypobetalipoproteinemic neonates, C-LDL failed to correlate with total plasma cholesterol levels ($r = 0.07$), but C-HDL was closely related to total cholesterol ($r = 0.98$). The inverse C-HDL to C-LDL correlation was not significant. In 58 hyperalphalipoproteinemic neonates C-LDL ($r = 0.88$), but not C-HDL ($r = 0.22$), correlated significantly with total plasma cholesterol. Nearly all of the total plasma cholesterol variation was accounted for by C-LDL. The inverse C-HDL to C-LDL relationship ($r = -0.18$) was not significant. Whatever factors contribute to both the overall and to the extremes of the C-HDL and C-LDL frequency distributions at birth, C-HDL and C-LDL in neonates appear to be under independent metabolic control.

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Extrauterine life glomerular filtration rate
gestational age inulin clearance

Glomerular Filtration Rate during the Period of Adaptation to Extrauterine Life

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Summary

Inulin clearance (C_{in}) was measured in 20 infants of 27–43 weeks of gestation during the first 24 hr of their extrauterine life. C_{in} ranged from 0.7–4.7 ml/min and correlated with gestational age ($P < 0.05$). In 18 infants of similar gestational ages studied after 2–3 days of extrauterine adaptation, the C_{in} ranged from 1.1–17.9 ml/min and also correlated with gestational age ($P < 0.01$). By day 2–3, the infants of near term gestational age achieved a greater increase in C_{in} than did the markedly preterm infants, as reflected by a significantly different slope of the regression line for C_{in} and gestational age for the infants studied at 1 vs. 2–3 days of age ($P < 0.001$).

Speculation

Although gestational age does affect glomerular filtration rate (GFR) in the first day of life, additional factors influencing glomerular filtration rate during this period may be adjustments in extrarenal hemodynamics, renal blood flow, and extracellular volume. We have shown previously that high rates of infusion of fluid result in an increase in glomerular filtration rate in the preterm infant. It is possible that the limitation noted in glomerular filtration rate during the first few days of life is partly related to decreasing extracellular fluid.

The exteriorized lamb has been used as a model to study function of the mammalian metanephric kidney. Robillard *et al.* (11) reported a direct correlation between fetal lamb glomerular filtration rate and gestational age. Alexander and Nixon (1) reported *in utero* inulin clearances (C_{in}) of 0.4 and 1.7 ml/min in lamb fetuses of 89–119 and 121–140 days, respectively (1). By full term, fetal lambs achieved a C_{in} of 4.3 ml/min; by 1 day of age their C_{in} doubled to 9 ml/min.

Oh *et al.* (10) have described a C_{in} of 20 ml/min/1.73 m^2 for healthy, 1–12-hr-old infants of 38–42 weeks' gestation. When measured at 2–3 days of age, C_{in} is proportional to gestational age, and to conceptual age (gestational age and postnatal age) when measured during the first months of life (8). Few data are available, however, for the C_{in} of premature infants during the first day of life (5). Thus, during this period, fluids, electrolytes, and drugs excreted by glomerular filtration have been administered in an empiric manner.

This study reports the C_{in} of infants of various gestational ages during the first day of extrauterine life. The data are compared to 18 infants studied 2–3 days after birth at a time when postnatal hemodynamic adjustment would have been largely accomplished.

MATERIALS AND METHODS

The study protocol was approved by the Harbor General Hospital Human Subjects Committee. After obtaining informed parental consent, 20 healthy, appropriate for gestational age newborn infants less than 24 hr of age were selected for study. Birth weight ranged from 580 to 3500 g (Table 1). Eighteen similar, 2–3-day-old infants were studied in an identical manner (Table 2). Thirty-one infants had received glucose at a rate of 6 mg/kg/min from birth; seven infants were receiving milk-based formula (1–2 ounces every 4 hr).

The studies were performed with the infant having fasted for at least 3 hr. An intravenous solution of dextrose water was administered at a rate of 6 mg/kg/min. A baseline serum inulin concentration was obtained. A priming dose of 50 mg/kg body weight of inulin, 10% solution, (purified inulin solution, Stone-Arnar Company, Mt. Prospect, Ill.) was infused intravenously over a 1-min period. A sustaining dose of 0.1 mg/kg/min inulin and glucose was administered by means of a constant infusion pump for 1–3 hr using a mixture of 0.13% inulin and 5% glucose.

Serial inulin samples were obtained by heel puncture every 30–60 min and at the time of each voiding. The infusate concentration of inulin was measured and the pump infusion speed was determined at appropriate intervals. All infants included in the study achieved steady plasma inulin levels. Inulin determinations were performed by the resorcinol method (12). A standard curve for inulin, 5% glucose, and serum blank were run with each determination.

The inulin clearance was calculated on the basis of a constant infusion principle (2, 8, 9) with the following formula

$$\text{Inulin clearance} = \frac{\text{inulin concentration in infusate (mg/ml)} \times \text{rate of inulin infusion (ml/min)}}{\text{plasma inulin (mg/ml)}}$$

RESULTS

Gestational ages, determined by menstrual history and by Dubowitz scoring (4), varied from 27–43 weeks (Table 1). Mean postnatal age at study was 17 hr for the 20 infants studied early. The 18 infants studied at 2–3 days of life were of similar gestational ages and weights (Table 2); mean age at study was 74 hr.

All infants were healthy at the time of study except for three patients with mild meconium aspiration and two with mild respiratory distress syndrome. None required ventilatory assistance.

Table 1 shows the data for the individual infants less than 24 hr of age. Inulin clearance (C_{in}) for these infants ranged from 0.7–4.7 ml/min. The C_{in} for the infants studied at 2–3 days of age, seen in Table 2, ranged from 1.1 to 17.9 ml/min. Figure 1 shows that C_{in} measured at less than 24 hr of age and at 2–3 days

Table 1. *Inulin clearance in first 24 hr*

Patient	Condition at study	Gestational age, weeks	Birth wt, g	Age at study, hr	C_{in}, ml/min
1	Healthy	27	580	24	0.8
2	Healthy	29	800	22	1.6
3	Healthy	38	2800	19	4.7
4	Mild meconium aspiration	43	2600	12	3.2
5	Healthy	28	885	19	1.4
6	Healthy	34	1760	20	0.7
7	Healthy	27	990	12	1.6
8	Healthy	30	710	18	0.9
9	Healthy	30	975	18	1.1
10	Healthy	41	3500	24	3.9
11	Mild meconium aspiration	41	3470	22	2.7
12	Healthy	41	2810	19	2.8
13	Mild respiratory distress syndrome	30	1180	17	2.0
14	Healthy	34	2320	18	4.1
15	Healthy	38	2520	2	1.1
16	Healthy	38	2520	24	1.0
17	Healthy	33	1760	18	0.7
18	Healthy	35	2183	16	0.9
19	Healthy	39	2300	7	1.3
20	Healthy	35	1985	15	1.6
Mean ± SEM		34.6 ± 1.2	1932 ± 205	17.3	1.9 ± 0.3

Table 2. *Inulin clearance at age 2–3 days*

Patient	Condition at study	Gestational age, weeks	Birth wt, g	Days at study	C_{in}, ml/min
1	Healthy	30	1070	2	2.5
2	Healthy	41	3740	3	17.9
3	Healthy	34	1570	2	2.6
4	Healthy	34	1340	2	2.5
5	Healthy	32	1420	3	3.5
6	Healthy	38	3000	3	8.1
7	Healthy	29	1080	3	2.5
8	Healthy	34	1928	3	4.7
9	Healthy	40	3500	2	6.0
10	Healthy	34	1710	3	3.9
11	Healthy	30	1160	3	2.4
12	Mild meconium aspiration	42	2800	2	7.9
13	Healthy	29	1130	3	1.1
14	Mild respiratory distress syndrome	27	1050	2	1.3
15	Healthy	34	1820	2	2.5
16	Healthy	40	3280	3	9.1
17	Healthy	38	3005	3	3.7
18	Healthy	40	2620	3	6.3
Mean ± SEM		34.8 ± 1.1	2069 ± 221		4.9 ± 0.9

was proportional to gestational age ($P < 0.05$). The slope of the regression line for infants less than 24 hr of age was significantly different from that for infants of similar gestational age studied at 2–3 days of age ($P < 0.001$). There was a significant difference between C_{in} in the first 24 hr of life in the preterm (< 37 weeks) and full term infants (mean = 1.5 vs. 2.6 ml/min; $P < 0.05$).

DISCUSSION

Neonatal adaptations influencing renal function occurring at the time the fetus begins extrauterine life include dramatic sequential changes in blood pressure, vascular resistance, and blood flow. These are accompanied by changes in body fluid composition. Extracellular water decreases from 45% to approximately 39% of body weight by 7 days of age (7). In addition, the degree of placental transfusion, the presence or absence of a patent ductus arteriosus diverting blood from the kidney, and varying colloid osmotic pressures may also influence renal function during the first day of life. Thus, measurements of GFR during the first day of life at any gestational age may reflect a transitory state of renal function in which the major influences may be adaptive processes rather than total glomerular functional potential.

The GFR as reflected by the C_{in} is proportional to gestational age when measured either in the first 24 hr or at 2–3 days. In addition, the inulin clearance measured after 2–3 days is proportional to conceptual age (8). In the infants studied at 2–3 days, C_{in} may more nearly reflect actual renal maturation rather than the functional changes occurring during the first few days following birth. This concept is supported by the fact that the functional acceleration in C_{in} seen over the first few days of life is greater in infants of greater gestational age who presumably have more mature kidneys.

Although the data from this study are similar to the values reported by Guignard (5) for four infants on the first day of life, this series represents the first report of inulin clearance for the markedly preterm infants of less than 24 hr of age. Values for the premature infants in this series are significantly lower than those previously reported in full term subjects less than 24 hr of age (10). This may represent an anatomic limitation to renal function since the full glomerular complement is not present until after 36 weeks' gestation. It is likely that the hemodynamic and body composition changes occurring over the first few days also affect glomerular filtration. In contrast to the values presented here for our basically healthy infants, inulin clearance is markedly reduced by various pathologic processes common in sick preterm infants (3, 6).

Figure 1 shows the inulin clearance data as a function of gestational age. The direct implications of this study are that renal function is proportional to gestational age in infants before and after a period of extrauterine adaptation. There is also a significant difference between the inulin clearance of the preterm and the full term infants. Furthermore, the absolute magnitude of the adaptive increase in GFR over the first few days of extrauterine life is greater in term infants than in preterm infants.

Our data support the concept that the dosage for substances excreted by glomerular filtration should, during the first day of life, be calculated utilizing the volume of drug distribution predominantly. After 2–3 days of age a correction should be made for changes in glomerular filtration rate related to gestational age.

CONCLUSION

The inulin clearance rates (C_{in}) of 38 infants varying in gestational age from 27–43 weeks were studied at less than 24 hr of age or 2–3 days of age. Inulin clearance varied from 0.7–4.7 ml/min in the younger infants and 1.1–17.9 ml/min in the older

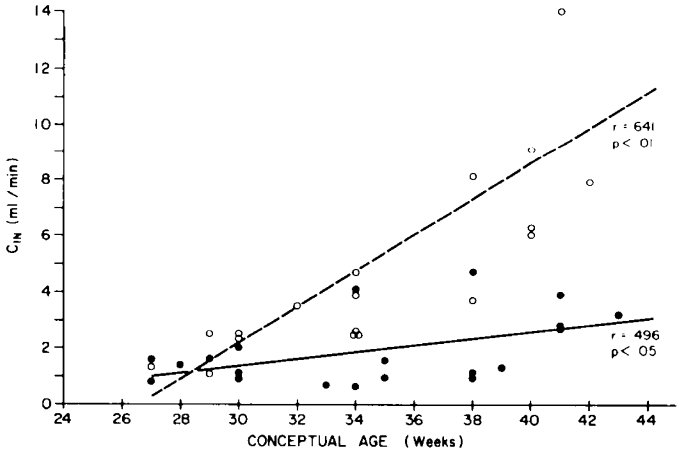

Fig. 1. Insulin clearance of infants studied at less than 24 hr (——) and at 2–3 days of age (– – –). Infants 2–3 days of age: $C_{in} = 2.2 + 0.1187 \times$ age. Infants <24 hr of age: $C_{in} = 17.36 + 0.6406 \times$ age.

infants. During both study periods inulin clearance was proportional to gestational age. The slopes of the regression lines for C_{in} vs. gestational age were significantly different. The absolute increases in C_{in} following 2–3 days of extrauterine adaptation were greater for the near term infants than for the markedly preterm ones.

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Energy homeostasis
glucagon
glucose
insulin
neonate
somatostatin

Effects of Somatostatin (SRIF) Infusion on Glucose Homeostasis in Newborn Lambs: Evidence for a Significant Role of Glucagon

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Summary

In order to investigate the significance and relative contribution of glucagon (IRG) and insulin (IRI) to neonatal glucose homeostasis, studies were conducted utilizing somatostatin (SRIF) in newborn fasting lambs aged 1–3 days. A priming dose followed by constant infusion of SRIF was maintained for 2 hr. During the first hour, SRIF alone was infused (period A); during the second hour, glucagon or insulin were additionally infused (period B); recovery was assessed 30 min after cessation of infusions (period C). During period A, a rapid and sustained suppression in the plasma concentrations of IRG and IRI occurred ($P < 0.01$), accompanied by a fall in plasma glucose significant at 60 min. Reinfusion of glucagon (5 ng/kg/min) during period B raised IRG by 342 ± 92 pg/ml (mean ± SEM, $P < 0.01$). Despite ongoing SRIF, plasma IRI also rose by 19.7 ± 7 μU/ml ($P < 0.05$) and was not accountable by contamination of the infused glucagon with insulin. Plasma glucose rose modestly, perhaps as a result of the antagonistic effects of glucagon and insulin. After cessation of SRIF and glucagon infusions (period C) plasma IRG fell, plasma IRI rose, and plasma glucose fell significantly (16.5 ± 4 mg/dl, $P < 0.01$). When insulin (0.1 units/kg/hr) was infused in period B, plasma IRI rose to approximately 70 μU/ml, plasma IRG remained suppressed and plasma glucose fell profoundly, recovering during period C as plasma IRI fell and plasma IRG rose. When, during period B, glucagon was infused at 10 times the original dose, plasma glucose concentration doubled despite a plasma IRI concentration of 100 μU/ml.

These results demonstrate that: (*1*) SRIF effectively inhibits IRI and IRG secretion in newborn lambs; (*2*) glucose falls when both hormones are acutely suppressed, suggesting that glucagon is a major hormone for maintaining blood glucose concentration during short term fasting; a rise in glucose, as occurs in insulin-deficient diabetes, would be expected if insulin were the dominant hormone; (*3*) both insulin and glucagon and acute changes in the effective ratio of these hormones modulate glucose homeostasis; and (*4*) at physiologic concentrations glucagon can overcome the suppressive effects of SRIF on insulin secretion in newborn lambs.

Speculation

In the lamb, insulin and glucagon are both important for neonatal glucose homeostasis. Acute changes in the ratio of these two hormones can effectively modulate plasma glucose concentration presumably through governing hepatic glucose output and/or peripheral glucose utilization. Extrapolation,