protein, and DNA content with an increase in cell density. By 24 weeks, only rats subjected to early restriction showed persistent deficit which was similar for all four parameters, indicating normal cell density. Protein/DNA ratios decreased after 16 weeks in experimental and control rats. At the height of deprivation both groups had a normal BMR per body weight, organ weight, and protein content, but the BMR per mg organ DNA was low. This reflects a low cellular metabolic rate which evidently offset the effect of increased cell density on the BMR per body weight and organ weight and protein content. The BMR of normal rats showed a positive linear correlation with DNA, despite marked changes in body composition which occurred between 3 and 32 weeks of age. By contrast, the correlations between BMR and body weight, organ weight, and organ protein content were curvilinear. Absolute BMR values (calories per day) failed to increase after 10 weeks of age despite continued weight gain because cell multiplication ceased at that time.

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Preterm infants
respiratory distress syndrome
triiodothyronine

Postnatal Triiodothyronine Concentrations in Healthy Preterm Infants and in Infants with Respiratory Distress Syndrome

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Summary

Postnatal changes in triiodothyronine (T_3) concentration were investigated in 12 preterm infants of 26-34 weeks of gestational age. Blood for measurement of T_3 was obtained from the cord at delivery and from infants at 1 day of age and at weekly intervals for 4 weeks. Seven of the babies suffered from respiratory distress syndrome (RDS) and five were considered healthy. Gestational ages and body weight were comparable in both groups. In preterm infants with RDS, cord blood T_3 concentration was significantly lower than that in cord blood of babies without RDS (22 ± 2.6 versus 36 ± 5 ng/dl, $P < 0.05$). There was no significant rise in T_3 concentration of RDS babies at 24 hr of age (22 ± 2.6 versus 34.0 ± 8 ng/dl, $P > 0.05$), and hypotriiodothyroninemia persisted for 3 weeks. At 4 weeks of age, T_3 concentration in babies with RDS, although within the

normal range (80-190 ng/dl), was significantly lower than that in the healthy preterm infants (110 ± 10 versus 165 ± 11 ng/dl, $P < 0.05$). Postnatal T_3 changes in healthy preterm infants were characterized by the absence of the initial hypertriiodothyroninemia and by a gradual rise within the first month of life. The noted difference in the pattern of postnatal T_3 changes in healthy preterm infants compared to full term infants may reflect thyroid immaturity. The mechanism and the significance of the neonatal hypotriiodothyroninemia in RDS and its long term effects on the development of these babies remain to be investigated.

Speculation

Triiodo and tetraiodo hypothyroninemia seem to have been established as a concomitant of the respiratory distress syndrome. The significance of these findings in the pathophysiology

of RDS remains unclear at this point. The existing evidence of thyroid deficiency before clinical onset of RDS and the experimental data in favor of a significant role of thyroid hormones in the maturation of lung surfactant suggest a causal relationship.

Significant postnatal changes in thyrotropin (TSH), thyroxine (T_4), and T_3 concentrations of full term infants have been described. Serum TSH concentration rapidly increases in the early minutes of postnatal life (6, 9). A gradual rise in T_4 concentration is followed by peak levels at 24–48 hr (1, 8). T_3 concentration, in the hypothyroid range in cord blood, increases to thyrotoxic levels by 24 hr of age (1, 8). The elevated levels of thyroid hormones and TSH gradually decline and stabilize within the first month of life. Neither the physiologic significance nor the exact mechanism of the postnatal changes in thyroid function have been fully recognized. To investigate the dependency of the postnatal alterations in T_3 concentration on gestational age, a study of the postnatal T_3 changes in preterm infants was undertaken.

MATERIALS AND METHODS

Twelve preterm infants of gestational ages 24–35 weeks were studied. Blood was obtained from the cord at delivery and at 24 hr from the infants for measurements of T_3 , T_4 , and TSH concentrations. Sampling the blood at weekly intervals continued for 4 weeks in some of the babies.

Retrospectively, the 12 preterm infants could be divided into two groups. *Group I* comprised five relatively healthy babies and *group II* included seven sick infants with RDS. One of the babies in *group II* died before 24 hr of age. Two of the babies in *group I* and one in *group II* were delivered by cesarean section. Gestational age was determined by the criteria of Dubowitz *et al.* (7). The diagnosis of RDS was based on clinical, radiologic, and biochemical findings. T_3 and TSH were determined by radioimmunoassays described previously (14, 17). T_4 was measured by the competitive protein binding method (16). Informed and written consent was obtained.

RESULTS

Mean gestational age and body weight of the two groups of preterm infants were comparable and are shown in Table 1. Cord blood T_3 concentration (mean $\pm$ SE) in sick preterm infants was significantly lower than cord blood T_3 concentration in the healthy group (22.0 ± 2.6 versus 36 ± 5 ng/dl, $P < 0.025$). At 24 hr of age a minimal T_3 rise was observed in three of the sick babies, in two there was no rise, in one the sample was not obtained and mean T_3 concentration did not differ significantly from the cord value (34 ± 8 versus 22 ± 2.6 ng/dl, $P > 0.1$). In healthy preterm infants there was a significant increase in T_3 concentration at 24 hr of age (115 ± 12 ng/dl, $P < 0.001$). However, the T_3 rise was not as dramatic as in full term infants and remained in the low normal range (80–190 ng/dl).

During the 4-week follow-up of healthy preterm infants a gradual but steady rise in T_3 concentration was observed and at 4 weeks of age T_3 concentration was significantly greater than that at 24 hr of age (16 ± 11 versus 115 ± 12 ng/dl, $P < 0.05$). The weekly sampling in *group II* preterm infants was not complete because of the unfavorable condition of the babies. The observations made, however, are interesting and presented in Figure 1. Despite a gradual rise, T_3 levels remained in the hypothyroid range in three babies at 2 weeks and in one at 3 weeks of age. At 4 weeks of age, T_3 concentration in these babies was significantly lower than that in healthy preterm infants (110 ± 10 versus 165 ± 11 ng/dl, $P < 0.05$). The postnatal changes of T_3 in both healthy and sick preterm infants are shown in Figure 1. The possibility of congenital hypothyroidism in infants with low T_3 was ruled out by demonstration of gestational age appropriate cord blood TSH and T_4 concentrations. Cord blood T_4 and TSH

Table 1. Gestational age (GA), body weight, and mode of delivery (vaginal, vag; cesarean section, C/S) in healthy and sick preterm infants

	GA weeks (mean $\pm$ SE)	Body wt. g (mean $\pm$ SE)	Delivery (vag-C/S)
Healthy preterm (5) ¹	32.9 $\pm$ 0.5	1,816 $\pm$ 98	3 2
Sick preterm (7) ¹	31.1 $\pm$ 1	1,546 $\pm$ 260	6 1
P	>0.2	>0.4	

¹ Number of infants.

Fig. 1. Postnatal triiodothyronine (T_3) changes in healthy and sick preterm infants. Each point represents mean $\pm$ SE of two to seven determinations.

concentrations in the healthy group were not significantly different from those in the sick group (7.8 ± 0.2 versus 6.6 ± 0.6 μ g/dl, and 9.4 ± 2 versus 7.2 ± 2 μ u/ml, respectively).

DISCUSSION

The maturation of thyroid function in human fetus is a continuous and gestational age-dependent process. Fetal blood concentration of T_4 gradually increases to levels within the normal range at about the 34 weeks of gestational age (12, 15), and to levels equal to maternal concentration at term (10, 11). A further increase in T_4 concentration is noted 24–48 hr after birth (1, 8). T_3 concentration in fetal circulation is low and a state of hypotriiodothyroninemia exists throughout gestation, presumably because of preferential monodeiodination of T_4 to reverse T_3 (rT_3) (4). Within 24 hr of birth T_3 increases significantly to levels considered toxic beyond the neonatal period. A gradual decline to normal values follows within the first month of life (1, 8). Other than a possible role in neonatal nonshivering thermogenesis the significance of the postnatal thyroid hyperactivity has not been fully appreciated (8).

The low levels of T_3 observed in RDS babies could be attributed to a decrease in peripheral monodeiodination of T_4 to T_3 , as has been described in older sick individuals (2, 3). The possibility of a primary thyroid deficiency in RDS has been supported by the observations of several investigators. Redding and Pereira⁽¹⁸⁾ found significantly lower T_4 concentrations at birth and at 2 days of age in premature babies with RDS as compared to premature babies without RDS. Recently Cuestas, Lindall, and Engel⁽¹⁹⁾ have also reported significantly lower cord blood T_3 and T_4 concentrations, but higher TSH concentration in premature babies with RDS. Therefore, our observations of prolonged hypotriiodothyroninemia in RDS may reflect reduced T_3 production on the basis of a primary thyroid deficiency as well as decreased peripheral conversion from T_4 . Further investigation including determinations of TSH and rT_3 concentrations is required to clarify this issue.

The stimulating effects of thyroid hormones on several enzymatic functions have been recognized (13). Whether they play a major role in the maturation of the enzymatic apparatus of lung surfactant remains to be demonstrated. Therefore, an etiologic role of thyroid deficiency in RDS cannot be considered and the association may be regarded as coincidental or possibly consequential. A deficiency of thyroid hormones, albeit relative and transient, may produce adverse consequences in a critical period of cerebral maturation. At present, however, the extent and the nature of such possibility remains conjectural. From the observations of T_3 changes in healthy preterm infants it appears that the birth-triggered increase in peripheral monodeiodination of T_4 to T_3 requires a gestational age-dependent maturational process. These limited observations emphasize the need for further evaluation of the role of thyroid hormones in RDS and in the early postnatal development of preterm infants.

CONCLUSION

A significant difference in the postnatal T_3 concentrations of healthy preterm infants compared to full term infants has been described. In preterm infants with RDS the immediate postnatal T_3 rise is lacking and abnormally low levels of T_3 persist up to 3 weeks of age. The difference in the postnatal T_3 concentration of healthy preterm infants from the pattern observed in healthy full term infants can be explained on the basis of thyroid immaturity but the mechanism of the prolonged hypotriiodothyroninemia in babies with RDS remains to be elucidated.

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Amino acids intestinal development
carbohydrates maternal nutrition
diet neonatal development

Effect of Maternal Protein Deprivation on the Development of Neonatal Intestinal Function in Rats

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Summary

The developmental pattern of *in vitro* intracellular accumulation (IA) was studied in the small intestine of the offspring of females fed a 27% protein diet (normal) (NPD animals) and the offspring of females fed an 8% protein diet (low) (LPD animals).

At 2 days of age, the IA of L-leucine (Leu) and D-galactose (Gal) was significantly reduced in the intestines of the LPD animals as compared to the NPD animals at initial velocities (75% and 81%) and under steady state conditions (82% and 84%). The IA of both compounds in the intestines of the LPD animals increased relative to the NPD animals until at weaning