

# ENDEMIC GOITER AND CRETINISM: CONTINUING THREATS TO WORLD HEALTH

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## IODINE DEFICIENCY AND THE MATERNAL-FETAL RELATIONSHIP<sup>1</sup>

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Dietary deficiency of iodine, with its consequence, endemic goiter, continues to be one of the most extensive problems of human malnutrition in the world. In 17 of 26 Latin American countries, endemic goiter has long been recognized as a severe public health problem, with the most affected areas being the Andean region of Ecuador (1), Peru (2, 3), and Bolivia (4). Nevertheless, little attention has been paid to the implementation of effective programs for prophylaxis and treatment—indeed, the prevalence of endemic goiter may have worsened during the past decades. Even the World Health Organization has assigned endemic goiter a relatively low priority for urgent attention, chiefly because the effects of this disease on development in the fetal and newborn periods have not been well documented.

The association of endemic cretinism with endemic goiter is well recognized. Cretinism increases the importance of endemic goiter because it has adverse effects on the development of the community. The infant mortality rate among cretins may be quite high. Those who survive into adulthood display variable degrees of physical or mental incapacity, which severely limits their value to their families and to the community.

Querido has strongly advanced the hypothesis that the prevalence of cretinism is related to the severity of iodine deficiency (5). This is

supported by the classic observations in Switzerland and more recent studies in Yugoslavia (6), New Guinea (7), and Ecuador (8), which have shown that the administration of iodine to women of childbearing age appears to prevent cretinism. However, other genetic, environmental, or dietary factors (9) may also play an important role in the pathogenesis of this disorder.

That thyroid hormones are intimately involved in the endocrine regulation of reproduction and the normal course of pregnancy is well documented. Perhaps of even greater importance, however, is the role they play during fetal development. It has been established that lack of thyroid hormones during intrauterine and early postnatal life produces irreversible damage to the central nervous system (10). There is virtually no published information, however, on maternal and fetal thyroid function in endemic goiter. The present studies were undertaken to gain information on the pathogenesis of endemic cretinism and its relationship to maternal and fetal thyroid function. In this presentation we will discuss our studies on: 1) the effects of chronic dietary iodine deficiency on thyroid hormone synthesis in pregnant women; 2) the possible effects of maternal thyroid hormone levels on fetal thyroid function, on intrauterine and postnatal development, and on the irreversible changes in the cretin's central nervous system; and 3) the effects of iodine administration to women of childbearing years on the prevention of cretinism.

### GENERAL EPIDEMIOLOGIC AND METHODOLOGIC CONSIDERATIONS

Our studies were conducted in three Andean villages with high incidences of goiter. These

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villages were chosen for a pilot investigation of the prophylactic effects of iodized-oil administration on endemic goiter and cretinism. General data on the population in these three villages are given in Table 1. A full description of baseline studies has been published elsewhere (2). The visible goiter rate was 58 per cent and was higher in women than in men. Among children under 5 years of age, 50 per cent were already goitrous. Cretinism and its associated defects occurred in from 1 to 3.6 per cent of the population. The main cause of the endemia was a severe deficiency of iodine, as demonstrated by urinary excretion of iodine (UEI) of 17 micrograms per 24 hours.

The pilot study was begun in October 1966, and follow-up data are available for seven years. Summaries have already been published (11). Of a total of 3,183 subjects injected either with iodized oil or a placebo, 747 were women of childbearing age who, according to the injection program, were classified into one of two groups: iodine-deficient (GR-D) or iodine-treated (GR-T).

Pregnancies occurring in the population were registered and followed until delivery by a physician appointed to the area. Many of the pregnant patients were admitted to a nearby hospital shortly before delivery. Serial or individual blood and urine samples were collected during pregnancy, at the time of delivery, and in some instances three to four days after birth in the newborn and six or more weeks postpartum in the mother.

In addition, a normal group from Lima (GR-N) was studied, and data on  $T_3$  and TSH from normal pregnant patients in the United States (12) have also been used, for comparative purposes.

Total and free thyroxine ("T-T<sub>4</sub>" and "free T<sub>4</sub>", respectively), total and protein-bound serum iodine, thyroxine binding proteins, and UEI were determined in our laboratory in Lima, according to procedures previously described (13). Triiodothyronine ( $T_3$ ) and thyrotrophin (TSH) were analyzed by radioimmunoassay methods (12,14).

TABLE 1. General data on the endemic populations.

	Tapo	Huasahuasi	Ataquero	Total
Altitude (m)	3,311	3,531,	3,100	
Urban population	1,830	1,934	400	4,164
Visible goiter (%)	52	53	59	
Palpable goiter (%)	84	84	78	
Cretinism* (%)	3.1	1.0	3.6	
<i>Injected subjects</i>				
Iodized oil (GR-T)	768	1,157	67	1,992
Placebo (GR-D)	466	660	65	1,191
Total	1,234	1,817	132	3,183
<i>Women of child-bearing age</i>				
(GR-T)	163	233	19	415
(GR-D)	133	179	20	332
Total	296	412	39	747
<i>Births recorded</i>				
(GR-T)	85	172	—	257
(GR-D)	61	127	—	188
Total	146	299	—	445

\* Includes all defective persons.

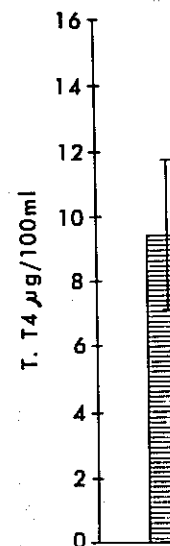
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### Serum Thyroxine

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FIGURE 1. Values are means



RESULTS

Urinary Iodine

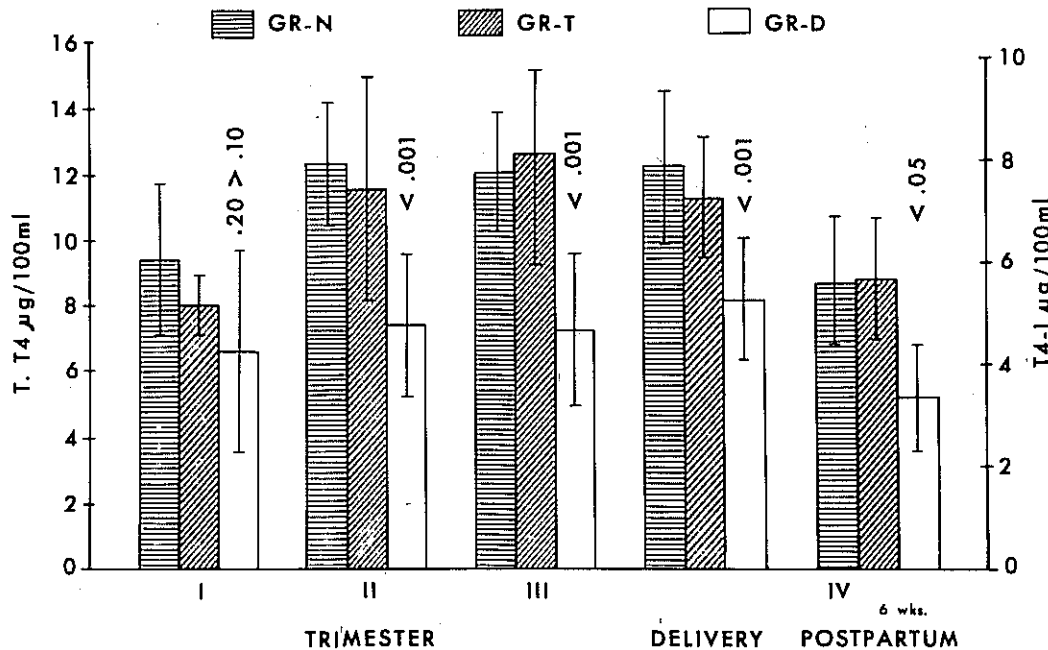
The mean daily urinary excretion of iodine during pregnancy was 543 micrograms in the treated group, 25 micrograms in the untreated group, and 182 micrograms in the normal group. At the time of delivery these values were, respectively, 238, 31, and 173 micrograms for the three groups.

Serum Thyroxine Levels

One hundred and eighty-five individual samples for thyroxine were obtained from pregnant women of the three groups; 61 of the samples were from iodine-deficient subjects. While 90 per cent of those in the normal and treated groups fell within normal limits for pregnancy (15), 67 per cent of the values in the iodine-deficient group were below the normal range and practically all of the remainder from this group were below the mean value.

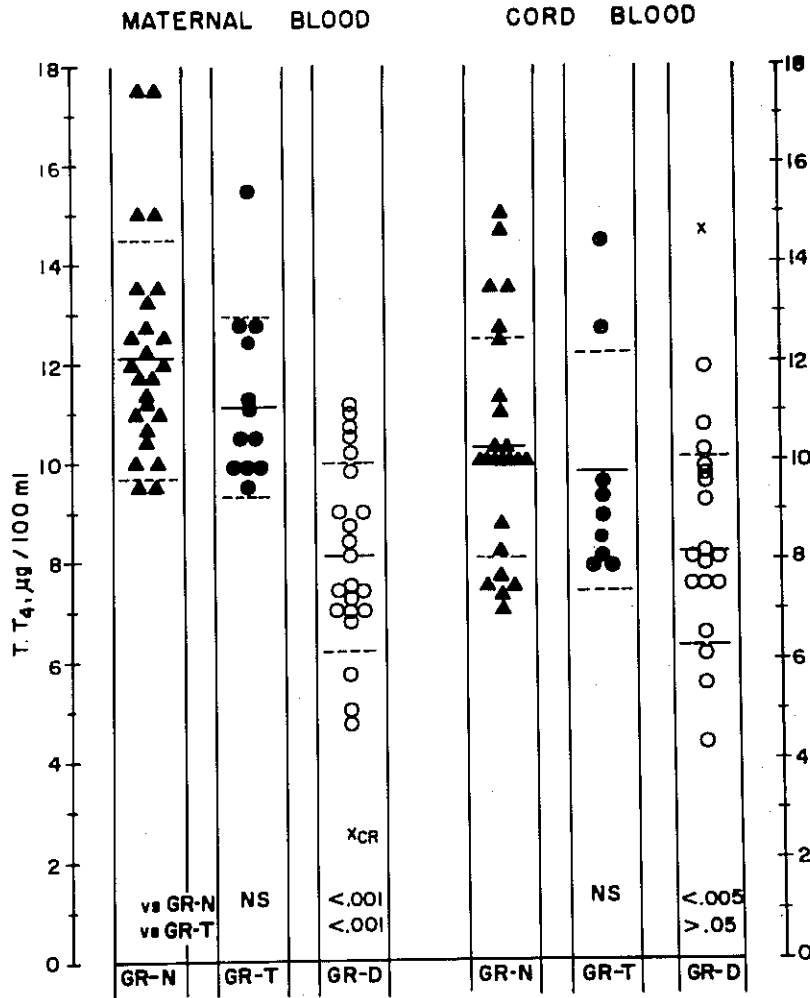
The changes occurring during pregnancy are shown in detail in Figure 1. There was an early increase in serum thyroxine in all three groups, and this reached a plateau around the 12th week of pregnancy at values significantly higher than those later observed postpartum. However, the iodine-deficient group had significantly lower values than the normal group throughout pregnancy. As shown in Figure 2, both the maternal and the cord thyroxine levels in the treated group were essentially the same as those found in the normal group at delivery, and the maternal values were significantly higher than those of the fetus, as has been observed in other series. In the iodine-deficient group, on the other hand, the maternal and fetal values were the same, and in both the mean values were significantly lower than normal. The differences between the iodine-deficient group and the two control groups are less marked for the fetal values than for those of the mothers. Thus, in the iodine-deficient pair, 73 per cent of the maternal values were below the range of the two control groups, whereas only 22 per cent

FIGURE 1. Changes in serum thyroxine levels during pregnancy, at delivery, and during postpartum. Values are means  $\pm$  standard deviation.



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FIGURE 2. Maternal and fetal serum thyroxine levels at delivery.



of the fetal values were below the range of their controls. Also, it should be noted that two of the extremely low fetal values corresponded to very low maternal values.

Results of determinations of free thyroxine are shown in Table 2. When the dialyzable fraction was expressed as a per cent of total thyroxine in the maternal and cord serum, the iodine-deficient group was similar to the control. However, absolute values for free thyroxine were significantly lower in the iodine-deficient group. Although this effect was noted

in both mother and fetus, the fetal values were significantly higher than the maternal values.

*Serum Triiodothyronine*

Figure 3 shows that the concentration of triiodothyronine in the serum of iodine-deficient pregnant women was similar to that observed in the treated group. In both groups almost 50 per cent of the individual values were below the range shown by the normal group (GR-N). The reason for this is not clear, since in

	Dialy
	Pre
GR-N	1.72
GR-T	2.00
GR-D	1.54

P values:  
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*Thyroxine B*

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TABLE 2. Values for dialyzable fraction of serum thyroxine and for calculated free thyroxine during pregnancy and at delivery.

	Dialyzable fraction (% of total serum T <sub>4</sub> )				Free T <sub>4</sub> (ng/100 ml)			
	Mean ± SD		p*		Mean ± SD		p	
	Pregnant	Mother	Fetus	p*	Pregnant	Mother	Fetus	p
GR-N	1.72 ± .35 (10)	1.63 ± .19 (11)	2.02 ± .31 (11)	.001	2.04 ± .66	1.99 ± .44	2.05 ± .42	.1
GR-T	2.00 ± .31 (15)				1.93 ± .56			
GR-D	1.54 ± .22 (18)	1.69 ± .26 (13)	1.95 ± .27 (11)	.001	1.08 ± .35	1.41 ± .49	1.66 ± .49	NS
P values:								
GR-T vs GR-N	.05				NS			
GR-D vs GR-N	NS	NS	NS		.001	.01	.001	
GR-D vs GR-T	.001				.001			

( ) Number.

\*p value in paired samples (mother and fetus).

the treated group iodine supplementation was adequate and the serum T<sub>4</sub> values were normal. Perhaps the finding reflects altered production of T<sub>3</sub> relative to T<sub>4</sub> in the iodine-deficient group, or perhaps an increased turnover of T<sub>3</sub> is a contributing factor.

As shown in the lower part of Figure 3, three single determinations of cord T<sub>3</sub> in the iodine-deficient group were slightly higher than normal, while two determinations in the treated group were similar to levels obtained in normals.

A high maternal-fetal gradient for T<sub>3</sub> was apparent, in agreement with previous reports (12, 16), and this might suggest that T<sub>3</sub> does not easily cross the placental barrier. When T<sub>3</sub> values were plotted as a function of serum T<sub>4</sub> concentrations, there appeared to be no correlation whatsoever in either group. This finding differs from those reported by others on nonpregnant goitrous subjects (17), but it is similar to observations made on normal pregnant women.

#### Thyroxine Binding Proteins

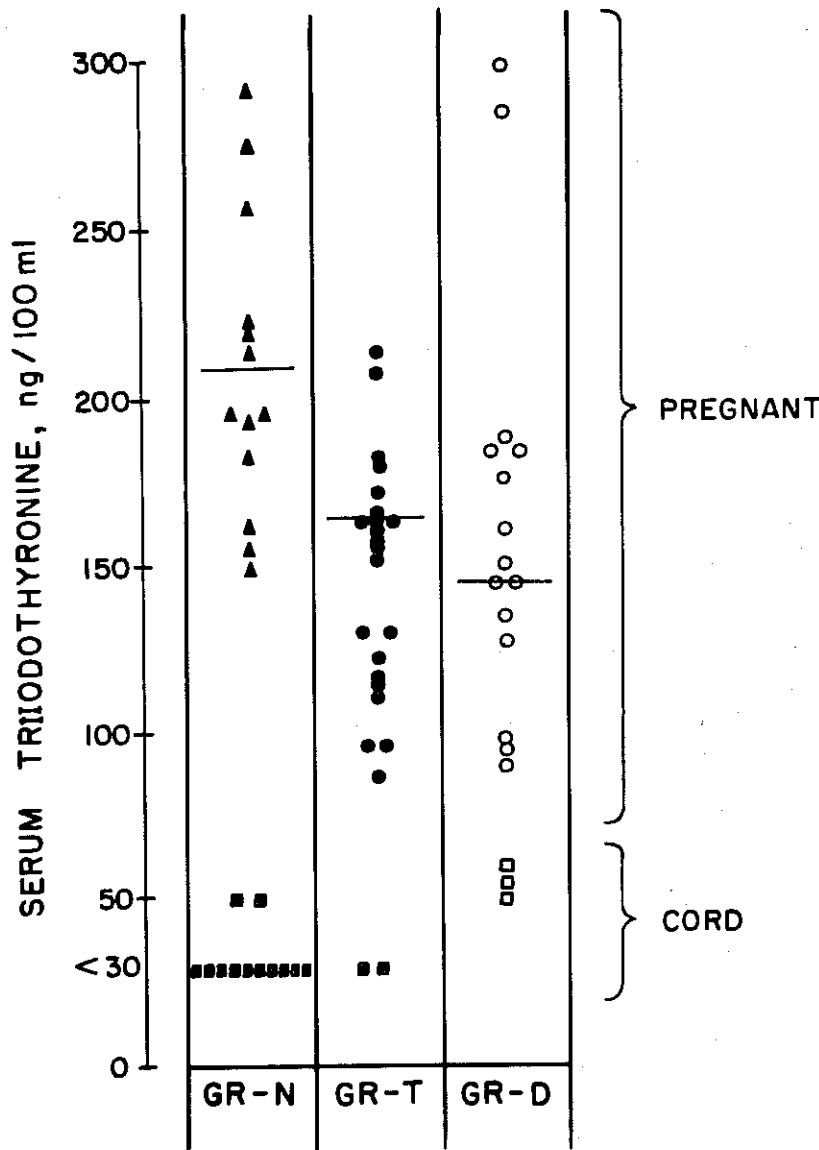
We evaluated thyroxine binding proteins to

exclude the possibility that impairment in binding proteins might cause low serum hormone values in the iodine-deficient women.

As Table 3 indicates, the two groups showed a similar distribution of thyroxine among binding proteins in the serum and also a similar capacity for thyroxine binding. Changes in binding proteins, resulting from elevated levels of circulating estrogen during pregnancy, are apparent in both groups by comparison with the postpartum values. There was a substantial increase in the amount of thyroxine binding globulin in both groups, while the amounts of thyroxine binding prealbumin were decreased. These findings suggest that the failure of thyroxine to rise in iodine-deficient pregnant women is caused by the iodine deficiency and not by a lack of thyroxine binding globulin. Support for this conclusion is provided by Figure 4. Here, if it is assumed that urinary iodine excretion represents the daily intake of iodine, it can be seen that there is a significant correlation between urinary iodine excretion and serum thyroxine levels when iodine intake is below 50 micrograms. Thus, extremely low dietary iodine may result in extremely low serum thyroxine values. A similar observation

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FIGURE 3. Serum triiodothyronine levels during pregnancy and in cord blood at delivery. The GR-N values in this figure are from normal subjects in the U.S.A. (12).



was made by Querido and his collaborators in New Guinea (18).

*TSH Levels*

As shown in Figure 5, there was a tendency toward higher values of serum TSH in iodine-deficient subjects than in those who were treated with iodine, although these differences

were not significant. It is of interest to note that in the iodine-deficient group the TSH values tended to be increased during pregnancy when compared with postpartum values. A possible source for this finding might be changes in the serum free thyroxine levels, since these are important determinants of TSH secretion and the serum free thyroxine has already been shown to be low during pregnancy in

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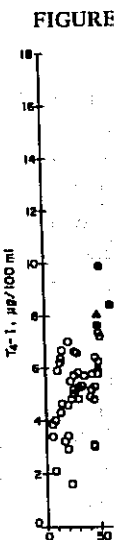


TABLE 3. Thyroxine binding proteins and thyroxine binding capacity.

		Endogenous distribution*			T <sub>4</sub> binding capacity*	
		TBG	ALB	TBPA	TBG	TBPA
I. DEFICIENT GROUP	Pregnancy	83 ± 2	6 ± 1	11 ± 2	43 ± 5	113 ± 31
	Delivery	83 ± 4	7 ± 2	11 ± 3	38 ± 6	107 ± 36
	Postpartum	66 ± 6	9 ± 2	25 ± 5	22 ± 5	153 ± 32
II. TREATED GROUP	Pregnancy	81 ± 3	6 ± 2	12 ± 2	44 ± 9	126 ± 22
	Delivery †	85	5	9	48	108
	Postpartum †	67	8	25	23	155
p value	Pregnancy vs postpartum	.001	.02	.001	.001	.05

\*Mean ± SD.  
 †Only two subjects.

iodine-deficient women. The increase in TSH, in turn, would help to maintain the high prevalence of goiter among adult women.

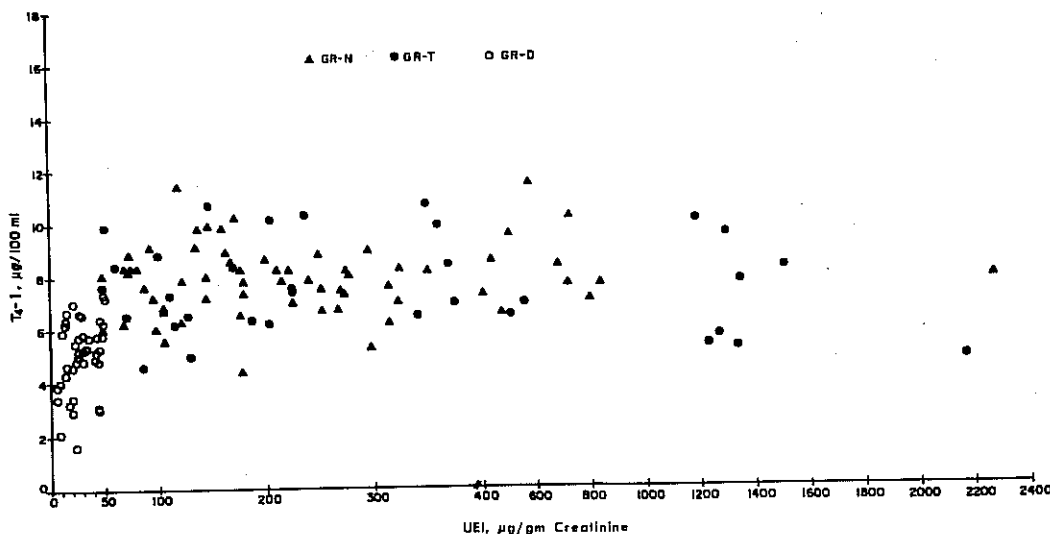
Figure 6 compares TSH levels in maternal and cord blood samples. On the maternal side, iodine deficiency resulted in a tendency toward higher levels of TSH, while there were no significant changes in the normal and treated groups. Except for one instance, the TSH values from children of iodine-deficient mothers were within the normal range reported by Lieblich and Utiger (12) and did not differ from the

levels found in children of iodine-treated mothers. TSH values were higher in most, but not all, of the cord blood samples when compared with maternal blood, a finding which has also been made in nonendemic populations.

MATERNAL-FETAL RELATIONSHIPS

A question of special interest in pregnant women with iodine deficiency is the effect that their low thyroid hormone levels have on fetal hormone levels. Under normal conditions, fetal

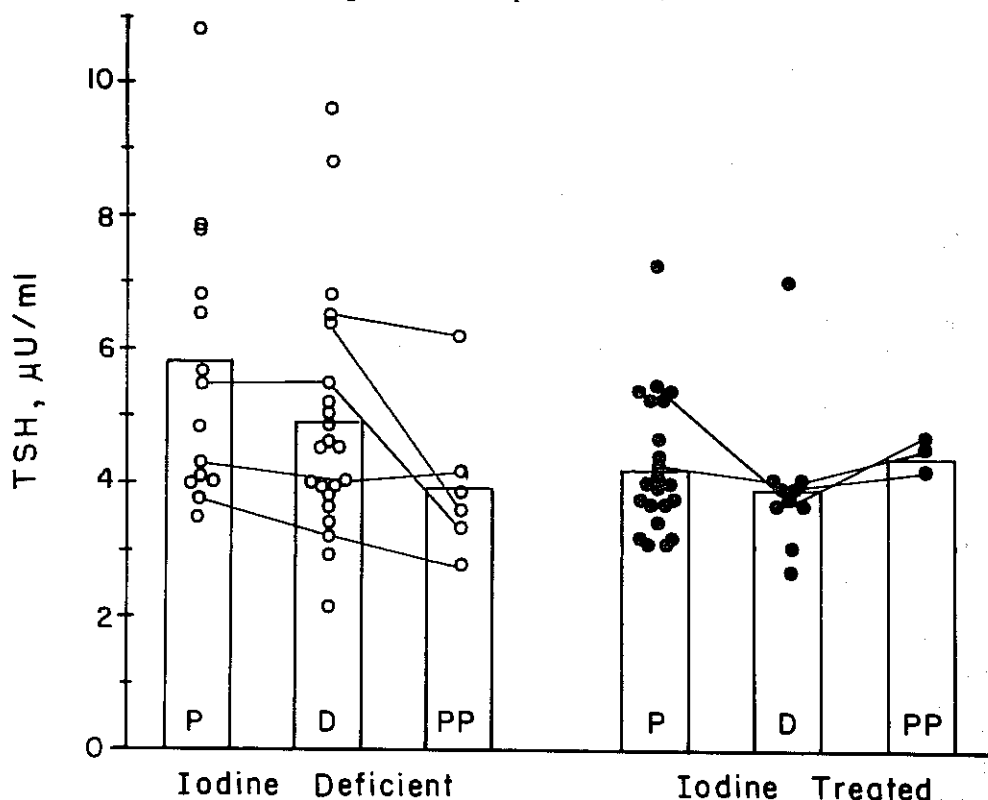
FIGURE 4. Correlation between the serum thyroxine levels and the urinary excretion of iodine.



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FIGURE 5. Thyrotropin levels during pregnancy (P), at delivery (D), and six or more weeks post-partum (PP). A few cases with a longitudinal follow-up are illustrated.



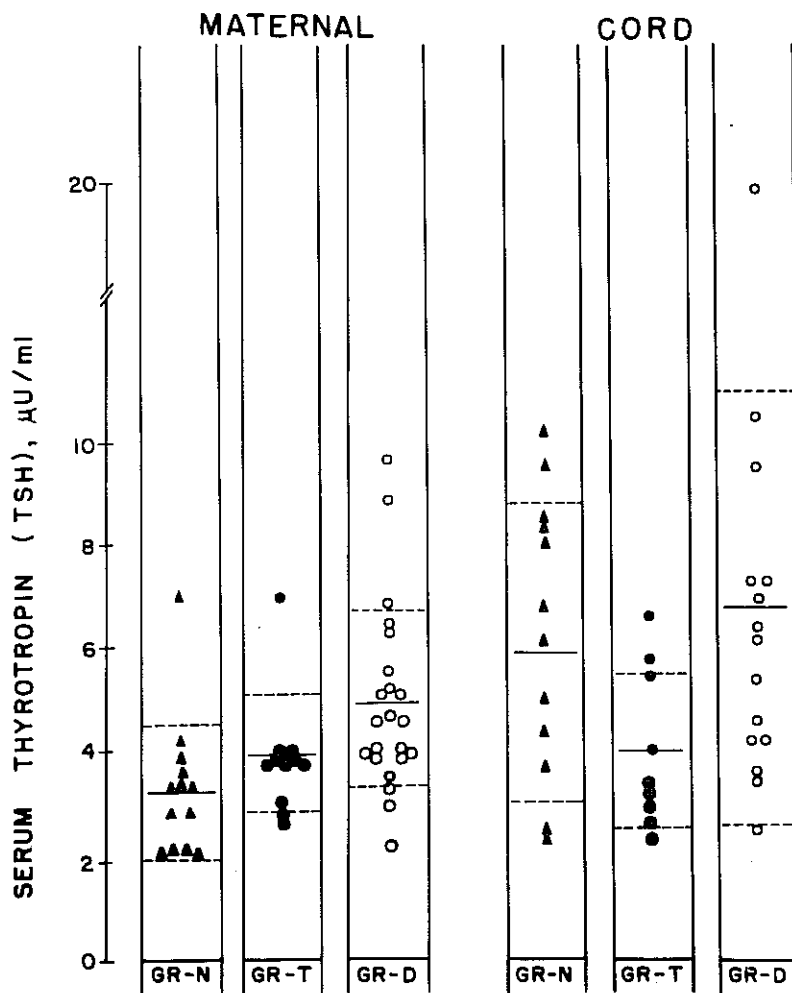
thyroid hormone synthesis begins by the 11th week of pregnancy, and the serum concentration of thyroxine increases in linear manner until the end of gestation (19). This implies that the mother must supply all the fetal hormone requirements early in pregnancy and very little or none at all by the end of intrauterine life. However, the role of the placenta in the regulation of hormonal transport has not been well established, nor is it known how it may vary under normal and pathological conditions. In any case, observations in humans suggest that the placental transfer of hormone from the mother to the fetus is, at best, very small, being limited to the free fraction of hormone. Observations in sheep (20) show there is little permeability of the placenta to thyroid hormones, pointing to an independent fetal and maternal thyroid hor-

mony synthesis. The same situation is suggested by our studies, as shown in Figure 7, in which the maternal  $T_4$  values are not correlated with those of the fetus. However, it is important to note that there were individual cases in which very low fetal values corresponded to low maternal values. Perhaps these represent cases in which iodine supplementation to the mother was extremely low. The correlation between maternal and fetal TSH values was also very poor; this is not surprising, since TSH does not cross the placental barrier (21).

Figure 8 shows a significant negative correlation between TSH and  $T_4$  values in both the maternal and the fetal circulation. This again points to an independence of these two circulations as regards thyroid hormones, and it demonstrates a normal hypothalamic-pituitary-thyroid axis in the iodine-deficient fetus.

The relative concentration of thyroid hormone in the fetus in iodine deficiency is illustrated in Figure 9. Since the maternal thyroid hormone concentration is significantly higher than the fetal concentration, the relative concentration of thyroid hormone in the fetus is significantly lower than in the mother.

FIGURE 6. TSH levels in maternal and cord blood at delivery.



The relationship between the mother and the fetus in iodine deficiency is illustrated in Figure 9. Since there is a physiologic increase in the maternal thyroxine binding capacity of the serum proteins, and also an impaired thyroid hormone secretion because of iodine deficiency, there is relative unsaturation of thyroxine binding globulin, leading to a low concentration of free thyroxine. On the fetal side in contrast, the free thyroxine level is significantly higher. If we assume that the gradient concentration of free thyroxine may play an

important role in determining the direction of its flux across the placenta, it follows that the fetuses of iodine-deficient mothers are constantly in danger of having inadequate levels of thyroid hormone for normal development. The possibility that a compensatory increase in fetal secretion of  $T_3$  might occur does not seem likely, but needs further assessment.

Some supportive evidence that iodine-deficiency is a real danger for the fetus comes from follow-up studies which we have published (22). These show that children born to iodine-

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FIGURE 7. Relationship between maternal and fetal serum thyroxine levels (left) and between maternal and fetal serum thyrotropin levels (right).

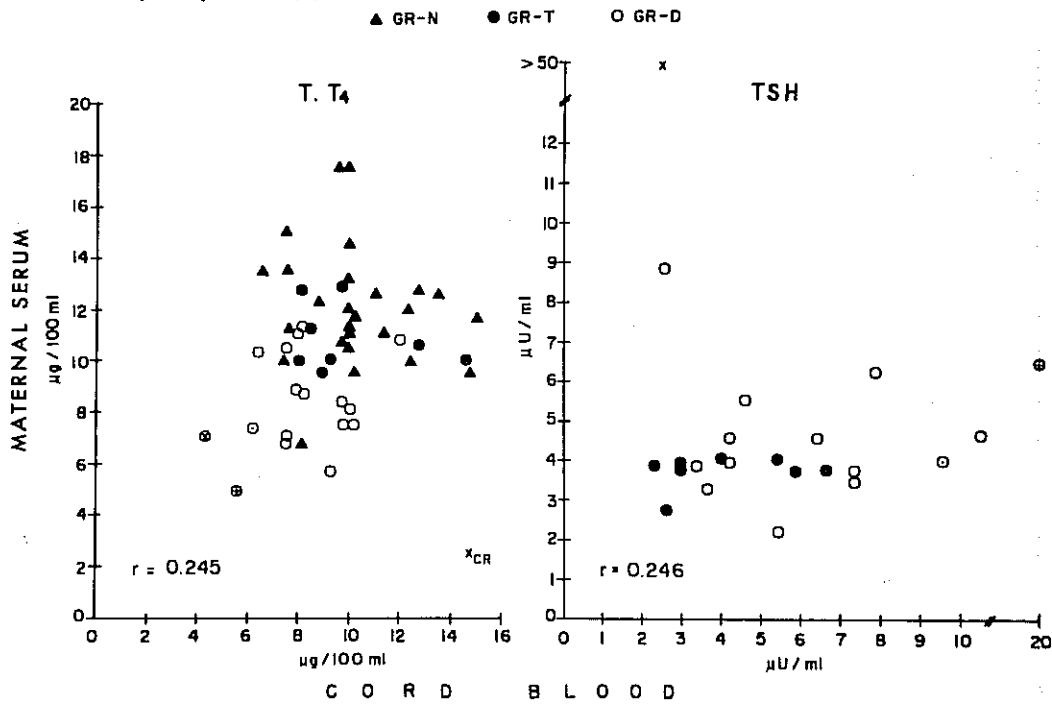


FIGURE 8. Relationship between serum T<sub>4</sub> and TSH in maternal blood (left) and in cord blood (right).

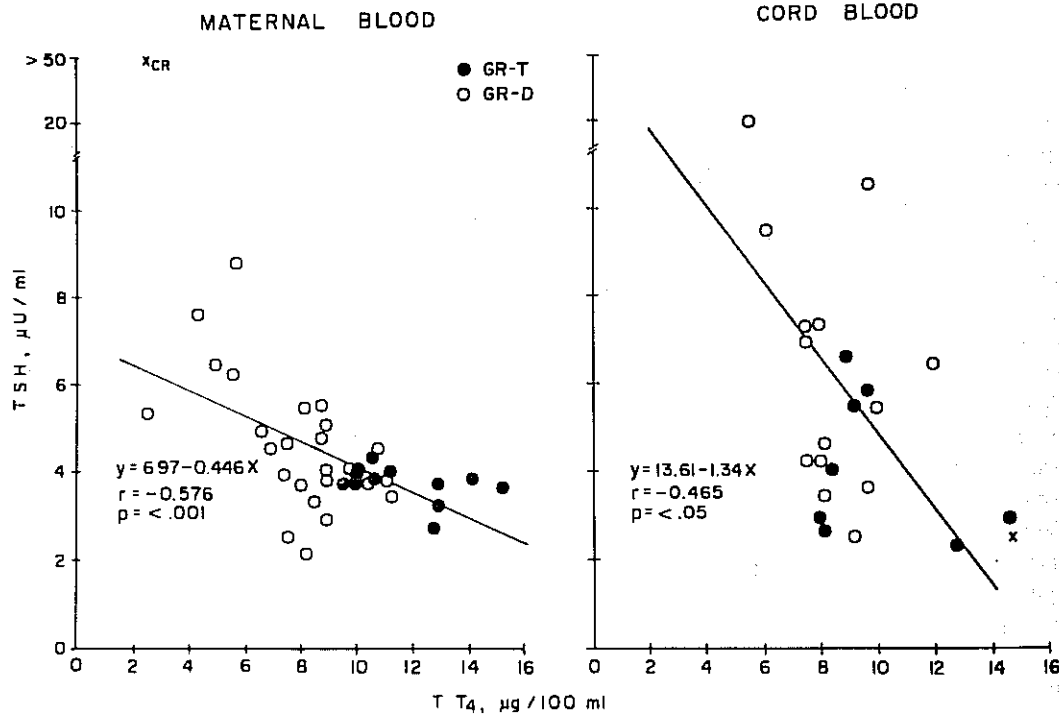
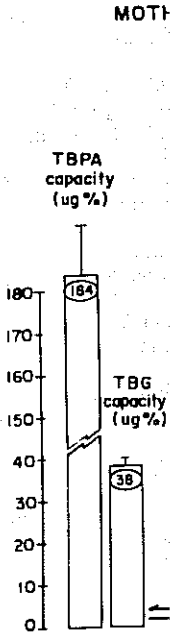


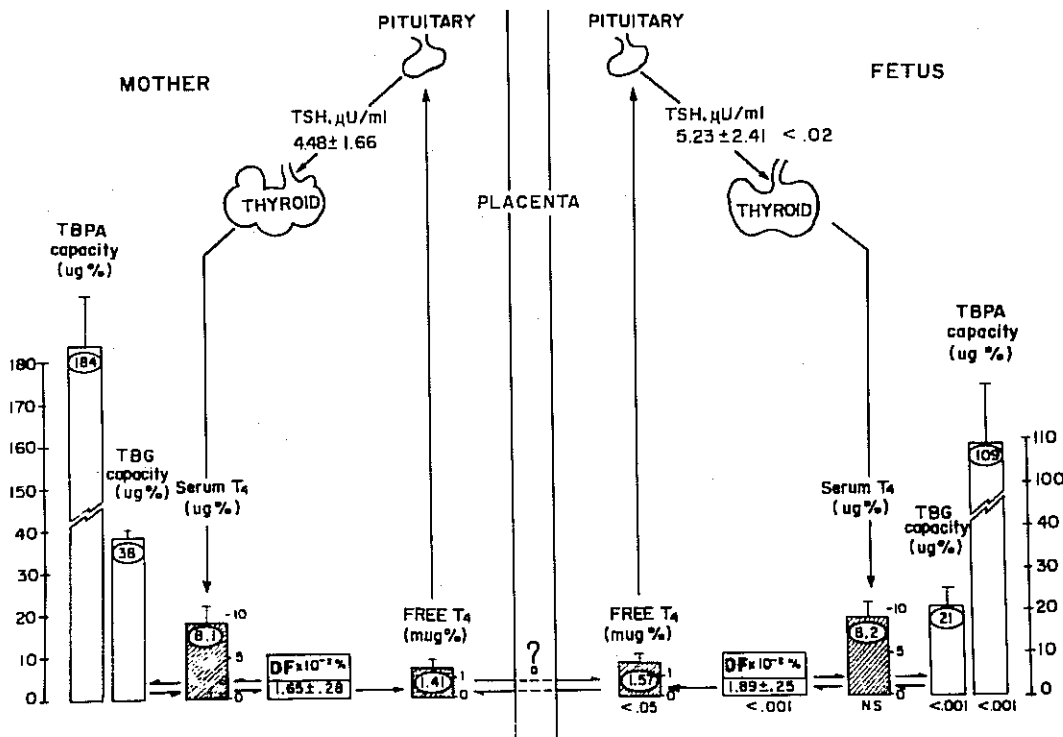
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FIGURE 9. Relationship between fetal (at term) and maternal thyroid function in chronic iodine deficiency.



deficient mothers tend to have IQ's lower than those recorded among children of iodine-treated mothers.

SUMMARY

The studies reported here have shown that iodine deficiency in pregnant women is associated with low values for maternal serum thyroxine and serum triiodothyronine. These decreases can be correlated with the severity of iodine deficiency. They were accompanied by an increased secretion of TSH. Maternal iodine deficiency produced a decrease in fetal serum thyroxine, but it was of smaller magnitude than that in the mothers. We attribute this difference to placental mechanisms developed to protect the fetus, similar to those for other nutrients.

In iodine deficiency, fetal serum has higher TSH levels and lower thyroxine binding globulin capacity than maternal serum, suggest-

ing a relative increase in fetal free thyroxine. These changes may lead to a gradient of free thyroxine from fetus to mother. Persistence of this gradient could produce a fetal loss of thyroid hormone, with deleterious effects on maturation of the central nervous system. The fetal hypothalamic-pituitary-thyroid axis in iodine deficiency appears normal and independent of the mother. However, several individual cases with very low fetal thyroid hormone levels corresponded to low maternal values, suggesting that severe iodine deficiency might affect both mother and fetus equally.

The prophylactic administration of iodine to women of childbearing age resulted in normal synthesis of thyroid hormones in both mother and fetus. The latter effect may be partly responsible for the higher scores on intelligence testing of children of iodine-treated mothers when compared with those of untreated controls.

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## DISCUSSION

Delange: You suggested that the low value for cord  $T_3$  that you found might be because  $T_3$  crossed the placenta with difficulty. I

believe that Lieblich and Utiger indicated that normally  $T_3$  was very low in the cord blood and that it crossed the placenta with ease.

Pretell: At with iodine de lower than th tion. Neverth  $T_3$  gradient f found in oth caused in par placenta. Als may be faster not be secret these are po and Utiger. O cord blood s group and ty three iodine- the normal iodine-treated of the metho

Ibbertson: and have con at birth and birth. We r inadvertently 20th week promptly pu day. On that 500 and 1,0 ever, at birth 100 ml, the was very low was not cro firmed this given  $T_3$  dt overtreated you can dep during pregn

Scriba: sequence of the first hou then, perhap glycerate-ar ship to the

**Pretell:** About half of our pregnant women with iodine deficiency had  $T_3$  levels which were lower than those for a normal pregnant population. Nevertheless, there was still a significant  $T_3$  gradient from mother to fetus, as has been found in other areas. This gradient may be caused in part by the poor passage across the placenta. Also, the turnover of  $T_3$  in the fetus may be faster. In addition, the fetal gland may not be secreting high amounts of  $T_3$ . All of these are possibilities considered by Lieblich and Utiger. Our results here are limited to three cord blood samples from the iodine-deficient group and two from the treated group. The three iodine-deficient values tend to be above the normal published values, while the two iodine-treated values were below the sensitivity of the method.

**Ibbertson:** We have measured cord blood and have confirmed the fact that  $T_3$  is very low at birth and rises within about 15 minutes after birth. We recently had a patient who had inadvertently received radioiodine during the 20th week of pregnancy and therefore was promptly put on 120 micrograms of  $T_3$  per day. On that dose her serum  $T_3$  was between 500 and 1,000 nanograms per 100 ml. However, at birth the cord  $T_3$  was 30 nanograms per 100 ml, the serum TSH was about 300, and  $T_4$  was very low. This clearly indicated that the  $T_3$  was not crossing the placenta. We have confirmed this result in a second patient who was given  $T_3$  during pregnancy because she was overtreated with carbimazol. So I don't think you can depend on  $T_3$  crossing the placenta during pregnancy.

**Scriba:** In normal newborns there is a sequence of events: first, a rapid rise of TSH in the first hours of life; second, a rise in  $T_4$ ; and then, perhaps related, a rise of 2, 3-diphosphoglycerate—and this in turn may have a relationship to the affinity of hemoglobin for oxygen

in the newborn. Do you have any information on how this sequence of events runs in newborns in iodine-deficient areas?

**Pretell:** We found that iodine-deficient infants, as well as those treated with iodine, did increase their  $T_4$  values during the first several days. Their TSH values were down to normal several days later, which is to be expected, since the rise in TSH is limited to the first 24-48 hours after birth. Nevertheless, we found two iodine-deficient children and one iodine-treated child in whom the  $T_4$  values did not increase, and they coincidentally maintained a very high TSH value even three or four days after birth.

**DeGroot:** I thought there were good data indicating that if you gave enough  $T_3$  or  $T_4$ , it got across the placenta. Could you clarify this for me?

**Pretell:** The literature has demonstrated that there is some transfer of  $T_4$  and  $T_3$  across the placenta from the maternal to the fetal side in humans. But to be significant this transfer seems to require very high levels on the maternal side. I wonder whether under physiologic conditions there are really any significant fluxes to the fetus or not. As already stated, the fetal  $T_3$  level is significantly lower than normal ones, being about 30 micrograms per 100 ml, compared with normal values in the nonpregnant population of from 70 to 150 nanograms per 100 ml.

**Ibbertson:** I think this point about  $T_3$  passage across the placenta is very important, because it relates directly to the treatment of a thyrotoxic mother with an antithyroid drug plus thyroid hormone. The evidence so far suggests that transfer is very limited, and it seems unrealistic to rely on  $T_3$  that is given to the mother to reach the fetus. I think this whole area should be reviewed in light of the recent ability to measure  $T_3$  and TSH.

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