Pickford(2) reported that doses of oxytocin comparable to those used in the present study markedly enhance Diodrast clearance, approximately doubling it in some instances, we were unable to detect significant changes in either Diodrast or para-amino hippurate clearances after injection of oxytocin into our dogs. Ali(3) also reported increased glomerular filtration rate after oxytocin. We could not detect any consistent changes in exogenous creatinine clearances in our dogs after natriuretic doses of oxytocin. An undetectable increase in glomerular filtration rate could, however, account for the observed small increase in sodium excretion. Enhancement of either glomerular filtration or renal plasma flow comparable in magnitude to that reported by Brooks and Pickford(2) and Ali (3) should, nonetheless, have been clearly evident if they occurred in our clearance experiments. They did not. The significance of this discrepancy is not evident at this time. Our results are, however, more consistent with those of Heidenreich *et al.*(5) who observed that oxytocin had minimal effects on renal hemodynamics in normal dogs.

Natriuretic responses of dogs to vasopressin and oxytocin are relatively small and of uncertain physiological significance. Similar responses have not been demonstrated in man. These phenomena appear, however, of sufficient interest to merit further investigation. Many aspects of the humoral regulation of renal sodium excretion remain quite mysterious. Study of those factors that can be related to this important renal function can only serve to reduce the area of mystery.

Summary. Low doses of arginine vasopressin cause natriuresis in conscious dogs only if administered during water diuresis. If vasopressin is infused there is an initial natriuresis which rapidly subsides, although antidiuresis persists for the duration of the infusion. Oxytocin, in low doses, produces natriuresis only at low urine flows produced by withholding water or by infusing vasopressin. Antidiuresis appears to be a prerequisite for the natriuretic response to oxytocin.

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Placental Transfer of L-Thyroxine and Tri-iodo-L-thyronine in Rats During Late Pregnancy.* (27622)

SARIT K. ROY† AND YUTAKA KOBAYASHI (Introduced by Ralph I. Dorfman)
Worcester Foundation for Experimental Biology, Shrewsbury, Mass.

The fetal requirement of thyroid hormones can be met in two ways: either by the fetal thyroid gland or by placental transfer of hormones from the mother. Clinical observations have demonstrated the likelihood of placental transfer of thyroid hormones(1) and in a manner similar to rabbits(2). In rabbits, Hall and Myant(3) and Myant(4) report that thyroid hormones are transferred and that tri-iodothyronine passes more readily than thyroxine in all stages of pregnancy. In guinea pigs, Peterson and Young(5) present evidence for transfer of thyroxine whereas Hirvonen and Lybeck(6) present evidence to the contrary.

This problem has not been studied in detail in the rat. Knobil and Josimovich(7) gave indirect evidence of greater placental permeability to thyroxine than tri-iodothyronine based on the greater suppressive action of

* Post-doctoral Fellow in Reproductive Physiology Training Program, 1961-62. Present address: Central Drug Research Inst., Lucknow, India.

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thyroxine on fetal goiter. Nataf *et al.*(8) described tri-iodothyronine radioactivity in fetal plasma to be nearly half that of the mother within one hour and near equilibration within 2 hours.

This paper reports a study in the rat during late pregnancy in which the distribution of radiothyroxine and radiotri-iodothyronine between fetal and maternal serum was determined.

Methods. Mature female Sprague-Dawley rats weighing 215-200 g were mated during estrus and day one of pregnancy designated by observance of a vaginal plug. Implantation was checked by observing erythrocytes in the vaginal smear on day 12.

Each rat was injected with 100 μc of I^{131}-labelled L-tri-iodothyronine either on the 20th or 21st day of pregnancy. Similarly, 100 μc of I^{131}-labelled L-thyroxine was injected into each rat in 2 other groups. All rats received a constant total dose of 3 μg of hormone as well as a constant amount of radioactivity.

Rats were autopsied exactly 24 hours after injection and maternal blood was drawn by heart puncture. The uteri were cut open and fetal blood was similarly collected and pooled from all fetuses. Radioactivity of the samples of maternal and fetal serum (1 ml) was counted in a Nuclear Chicago well-type scintillation counter, Model DS 5. Twenty mg of chorionallantoic placental tissue which included both maternal and fetal portions were assayed for radioactive content. An indication of the relative ability of placental tissue to concentrate or bind radioactivity was obtained empirically by a placental concentration factor which is defined as:

$$\frac{\text{Counts per minute per 20 mg placental tissue}}{\text{Counts per minute per ml maternal serum}} \times 100.$$

Results. No attempt was made to account for all of the radioactivity injected into each animal. Only a sample of maternal and fetal serum, and a weighed portion of placental tissue were assayed for total radioactive content. Radioactivity recovered per ml of maternal serum after T_4 injection was always approximately 5 times the T_3 values indicating a more rapid clearance of T_3. The average value for T_4 was 128,200 cpm/ml maternal serum, and that for T_3 was 23,300 cpm/ml maternal serum.

With radioactive tri-iodothyronine administration on day 20 of pregnancy, fetal serum concentration of the hormone was twice that of the mother indicating an active transfer toward the fetal side (F:M concentration ratio of 2.18) and a marked change in this ratio to near unity was observed on day 21 (Table I). With thyroxine, on day 20 of pregnancy, the average F:M ratio indicated the fetal serum concentration of the hormone was only one-half that of the mother indicating a transfer of T_4 from the mother to the fetus, but no concentration of T_4 by the fetus. The average F:M ratio for T_4 was the same for both day 20 and 21 of pregnancy.

The placental concentration factor was

TABLE I. Fetal to Maternal Serum Concentration Ratio and Placental Concentration Factor of Tri-iodothyronine and Thyroxine in Rats during Late Pregnancy.

		20 days of pregnancy		21 days of pregnancy	
Substance	Dose, μc	F:M conc. ratio	Placental conc. factor	F:M conc. ratio	Placental conc. factor
Tri-iodo-L-thyronine	100	2.18 $\pm$ .747 GROUP A (5)*	60.0	.82 $\pm$ .173 GROUP B (8)	86.0
L-thyroxine	100	.48 $\pm$ .099 GROUP C (7)	4.0	.56 $\pm$ .102 GROUP D (7)	6.0

Analysis of F:M concentration ratio:

Group A *vs* B $p < .01$ (significant)
" C *vs* D $p > .05$ (non-significant)
" A *vs* C $p < .01$ (significant)
" B *vs* D $p > .05$ (non-significant)

* No. of rats.

considerably higher in the T_3 group than in the T_4 group. The placental transfer factor did not change statistically within each group between day 20 and 21 of pregnancy.

Discussion. In these experiments, it has been assumed that the measured radioactivity was due primarily to that present in the hormone(4,9), and that there was no significant conversion of T_3 to T_4, or the reverse. The results of these experiments confirmed the observation that T_3 has a shorter biological half-life than T_4(10). This was indicated by the smaller number of counts per ml of maternal serum collected 24 hours post-injection of T_3 since 100 μc of each hormone of identical specific activity was used in each case.

The data presented show that both T_3 and T_4 are transferred from the mother to fetal blood. An interesting result was the difference in the F:M concentration ratio of T_3 observed between the 20th and 21st day of pregnancy. The 20th day ratio indicates the concentration of T_3 by the fetal blood, whereas on the 21st day, there is equilibration between the blood of the mother and fetus. No such change in F:M ratio was observed for T_4 between the 20th and 21st day. This rather marked change in the F:M ratio of T_3 between the 20th and 21st day may indicate an association of T_3 with the onset of parturition. This speculation, however, must await the determination of F:M ratios of T_3 from, say the 18th to the 21st day of pregnancy.

The placental concentration factor was devised to give some basis for comparing the relative amount of hormone present in the placental tissue with that in the maternal serum. The actual amount of hormone bound per unit weight of tissue could not be accurately determined because of the variation in size and vascularization among placenta samples, resulting in an uncontrolled variation in the blood volume in these placenta. The data clearly indicate that, based on the concentration factor, the placental tissue concentrates T_3 approximately 15-fold more than T_4 from maternal serum. It appears likely that the concentration factor for T_3 represents actual binding of this hormone by the placental tissue because the blood volume contained in 20 mg of tissue can not account for this amount of hormone. The same can be said for T_4. The data give evidence that the rat placenta concentrates both T_3 and T_4 from maternal blood. These data, therefore, support the observations of Nataf *et al.*(8). A possible explanation of the comparatively high placental concentration factor for T_3 as opposed to T_4 may be associated with the more rapid clearance of T_3 from the mother serum. If we assume that the placental tissue binds approximately equal amounts of T_3 and T_4, T_3 must necessarily give a higher placental concentration factor because of its more rapid clearance from maternal blood.

Summary. The placental transfer of L-thyroxine and tri-iodo-L-thyronine during late pregnancy in the rat was studied using radioactive hormones. It was found that both hormones cross the placental barrier into the fetus. The concentration of T_3 in fetal serum on day 20 of pregnancy was twice that of maternal serum, but was equivalent to maternal serum on day 21. The concentration of T_4 in fetal serum was one-half of that in maternal serum on day 20 and 21 of pregnancy. Both T_3 and T_4 were concentrated by the placenta. T_3 was concentrated 15-fold more by the placenta than was T_4 from an equivalent amount of hormone in maternal serum.

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