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Thyroid function during exchange transfusion

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Milner, R. D. G., and Ratcliffe, J. G. (1975). *Archives of Disease in Childhood*, **50**, 40. **Thyroid function during exchange transfusion.** The changes in plasma thyroid hormone concentration were studied during exchange transfusion performed for haemolytic disease. 24 transfusions were performed using blood preserved with acid-citrate and dextrose and in 11 cases 10 or 50 μg glucagon was added to the donor blood. Plasma tri-iodothyronine (T_3), thyroxine (T_4), thyrotropin (TSH), thyroid hormone binding capacity, and free thyroxine index were measured in the donor blood and in the infant at the start and at intervals during the transfusion. Before transfusion the plasma TSH levels of the infants fell as postnatal age increased and plasma T_3 and T_4 were correlated with one another. In 20 transfusions the mean infant/donor ratio of TSH was approximately 10, of T_4 3, and of T_3 2. During these transfusions there was a progressive fall in the infant's plasma TSH, T_4, and T_3 concentration. In 3 transfusions in which the donor plasma TSH was greater than that of the infant, plasma TSH levels rose during the transfusion and in 2 cases this was associated with a late rise in plasma T_3 levels. The addition of glucagon to donor blood had no effect on thyroid hormone levels.

It is concluded that erythroblastotic infants have normal thyroid function and that they became biochemically hypothyroid during transfusion. Acute changes in plasma thyroid hormone and glucagon concentration do not induce TSH responses by the neonatal pituitary during the period of the exchange transfusion.

In the minutes after birth there is a dramatic rise in plasma thyrotropin (TSH) concentration which then falls slowly to regain values characteristic of the adult in the second half of the first week of life (Fisher and Odell, 1969; Czernichow *et al.*, 1971; Lemarchand-Béraud *et al.*, 1972). The serum thyroxine (T_4) and tri-iodothyronine (T_3) levels rise in response to the increase in TSH concentration to reach a maximum at the age of 24 hours (Erenberg *et al.*, 1974). The rise in T_4 and T_3 is in both the total and free concentration of the hormones, thus making the infant chemically thyrotoxic.

The control of pituitary-thyroid function at this stage of development is poorly understood, in part because of ethical difficulties in the direct study of the normal infant. In the present work we have taken advantage of the experimental situation occurring during exchange transfusion to study the changes in plasma TSH and in total T_4 and T_3 levels. Thyroid hormone binding capacity (THBC) and the free thyroxine index (FTI) were measured also because of possible differences in the thyroid hormone binding properties of donor and neonatal blood. The effect of glucagon added to the donor blood was investigated since glucagon is known to stimulate thyroid metabolism in animals (Burke, 1970) and the release of certain anterior pituitary hormones in man (Milner and Wright, 1967; Eddy, Jones, and Hirsch, 1970).

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Patients and methods

Twenty-four exchange transfusions were performed on 19 newborn infants suffering from haemolytic disease. In 5 infants haemolysis was due to ABO blood group incompatibility, in one the cause was unknown and the remainder were suffering from rhesus incompatibility. The average gestational age was 38 weeks (range 34 to 42 weeks) and each infant was of appropriate birthweight for gestational age. 10 were girls. The postnatal age at which transfusion was performed varied between 3 and 132 hours.

Exchange transfusions were performed via the umbilical vein using blood preserved with acid-citrate and dextrose (ACD) and in some transfusions 10 or 50 μg glucagon were added to the bottle of donor blood immediately before transfusion (Milner *et al.*, 1972; Milner, Chouksey, and Assan, 1973). The addition of glucagon raised the plasma glucagon concentration of the donor blood to pharmacological levels and resulted in a high plasma glucagon concentration in the infants at the end of transfusion. All transfusions were performed in a thermoneutral environment using blood warmed to body temperature.

Blood specimens were collected and stored as described previously (Milner *et al.*, 1972) until assayed for thyroid hormones. Plasma TSH was measured by radioimmunoassay using an antiporcine TSH antiserum and a double antibody separation method. TSH for iodination (DE32) was kindly supplied by Dr. A. S. Hartree and TSH for standardization (MRC 68/38) was provided by the Medical Research Council. The limit of detection of TSH was approximately 0·6 μU/ml and values less than this were assigned a value of 0·6 μU/ml for statistical calculations. The normal range of plasma TSH in euthyroid adults is $<$0·6–8·0 μU/ml with a mean value of 1·6 μU/ml. Plasma total T_4 and T_3 were measured by radioimmunoassay (Ratcliffe *et al.*, 1974) using 8-anilino-1-napthalene sulphonic acid to block binding of thyroid hormones to the plasma proteins. The interassay coefficients of variation throughout the standard curve were 4·7% for T_4 and 7·2% for T_3. The normal range for T_4 in euthyroid adults is 4·3–11·2 μg/100 ml, mean 7·7 μg/100 ml, and for T_3 0·6–1·8 ng/ml, mean 1·25 ng/ml. Thyroid hormone binding capacity (THBC) was measured by Thyopac 3 (Radiochemical Centre, Amersham) and the normal range for THBC in euthyroid adults is 90–120%. The free thyroxine index (FTI) was calculated from the total T_4 and THBC values and its normal range is 4·5–10·0.

Results

Pretransfusion hormone levels. Plasma TSH levels fell with increasing postnatal age ($P < 0·001$, Fig. 1) but there was no significant correlation between plasma T_3 or T_4 concentration and age. Pretransfusion plasma T_3 levels correlated significantly with TSH ($P < 0·01$) and T_4 ($P < 0·001$, Fig. 2), though the former relation depended for significance upon a single extreme value. The mean pretransfusion infant/donor ratio was 10 for TSH, 3 for T_4, and 2 for T_3. The infant pretransfusion T_4 concentration was always higher than that of the donor and in 18 cases the T_3 concentration was higher also. In 4 transfusions the donor TSH concentration was higher than 2 μU/ml and similar to or greater than that of the infant. These transfusions are reported individually, whereas those in which the donor TSH level was 1·6 μU or less and also lower than that of the infant are reported as a group.

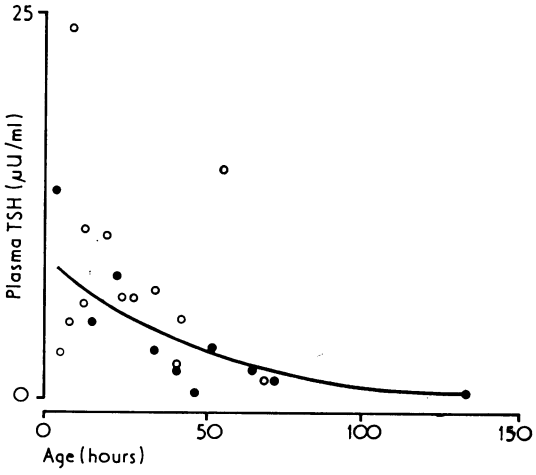

FIG. 1.—*Pretransfusion plasma TSH as a function of postnatal age. Infants who had exchange transfusion with glucagon-enriched blood ○, infants who received ACD blood ●. The solid line describes the curve, TSH = 2·26^{e} −0·02 hours for which the correlation coefficient is 0·685.*

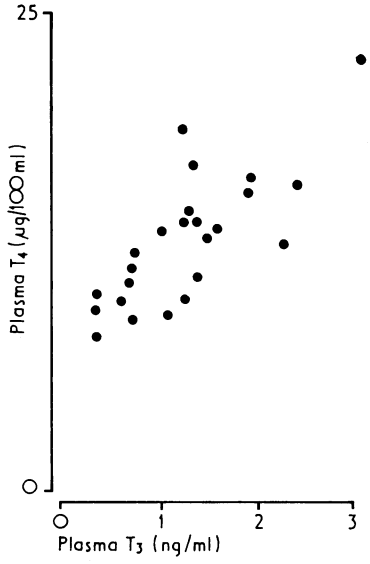

FIG. 2.—*Pretransfusion plasma T_4 as a function of T_3. Correlation coefficient = 0·70.*

Hormone changes during transfusion. In transfusions where the donor plasma TSH was less than that of the infant, being in most cases less than 0·6 μU/ml, the plasma TSH of the infant fell progressively during the course of the transfusion (Fig. 3, Table I). The infants receiving glucagon-

TABLE

Mean (±SE) thyroid hormone concentrations during exchange

	Donor	0 ml
ACD		
TSH (μU/ml)	0·70±0·10 (9)	4·34±1·06 (9)
T_3 (ng/ml)	0·72±0·07 (9)	1·09±0·21 (9)
T_4 (μg/100 ml)	4·63±0·31 (9)	12·96±1·12 (9)
THBC (%)	80·3±3·2 (9)	92·8 ±2·2 (9)
FTI	5·73±0·23 (9)	13·91±1·20 (9)
ACD+glucagon		
TSH (μU/ml)	0·69±0·09 (11)	9·00±1·85 (11)
T_3 (ng/ml)	0·61±0·04 (11)	1·42±0·24 (11)
T_4 (μg/100 ml)	4·15±0·26 (11)	12·76±0·86 (11)
THBC (%)	77·5 ±1·3 (11)	88·6 ±2·3 (11)
FTI	5·23±0·38 (11)	14·50±1·06 (11)
All transfusions		
TSH (μU/ml)	0·69±0·06 (20)	6·90±1·28 (20)
T_3 (ng/ml)	0·64±0·04 (20)	1·28±0·17 (20)
T_4 (μg/100 ml)	4·30±0·21 (20)	12·80±0·67 (20)
THBC (%)	78·8 ±1·5 (20)	90·5 ±1·6 (20)
FTI	5·46±0·23 (20)	14·23±0·79 (20)

Figures in parentheses indicate the number of observations.

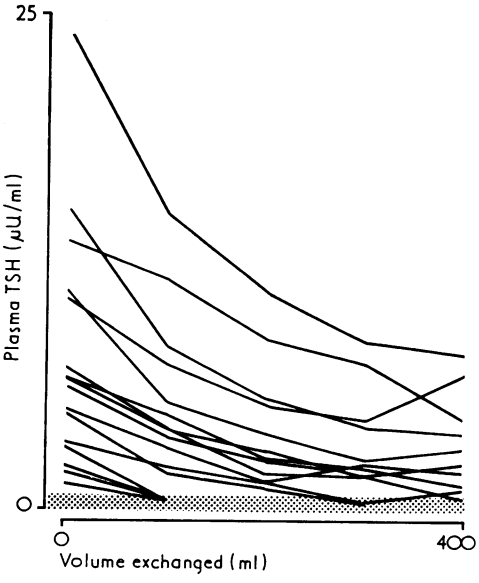

FIG. 3.—*Change in plasma TSH concentration during exchange transfusion in which donor plasma TSH concentration was 1·6 μU/ml or less. The hatched area indicates the limit of sensitivity of the assay.*

enriched blood had higher mean pretransfusion plasma TSH because they were transfused at an earlier postnatal age (Fig. 1). The use of glucagon-enriched blood had no significant effect on plasma TSH during transfusion and when the results of the two groups were combined the effect of exchange transfusion was to cause a fall in mean plasma TSH concentration to 36% of the initial value. In the 4 transfusions in which the donor plasma TSH was greater than 2 μU/ml the change in plasma TSH during transfusion also reflected the pretransfusion levels of TSH in the donor and infant's blood (Table II). All the results indicated that TSH secretion was not influenced acutely by sudden changes in plasma concentration of TSH or glucagon.

T_4 levels fell consistently and at the end of transfusion were 57% of the initial mean value (Table I). Corresponding but quantitatively smaller changes occurred in THBC so that there was a reduction in the FTI. T_3 levels fell less dramatically than T_4, the mean T_3 level at the end of transfusion being 81% of the initial value. In 6 infants the T_3 levels rose or remained unchanged during transfusion and the final concentrations were approximately those found in donor blood. In two patients, Cases 1 and 3, there was a progressive rise in plasma TSH, probably due to the higher TSH level in the donor blood, which was associated with an initial fall followed by a late rise in plasma T_3 concentration. Though an increase in T_3 concentration might have been due to increased T_3 secretion stimulated by TSH, this interpretation is weakened by the fact that no rise of T_3 concentration occurred in Case 4 in whom the largest increase of TSH concentration was observed.

Discussion

The present study shows that the thyroid status of newborn infants with haemolytic disease is similar to

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transfusion with ACD blood or ACD blood+glucagon

100 ml	200 ml	300 ml	400 ml
2·82±1·26 (9)	2·17±0·93 (9)	1·74±0·81 (9)	1·61±0·59 (7)
1·04±0·16 (9)	1·00±0·15 (9)	1·03±0·16 (9)	0·99±0·18 (7)
10·72±1·04 (9)	9·14±0·94 (9)	8·74±0·95 (9)	7·59±0·87 (7)
88·3 ±2·6 (9)	85·7 ±2·8 (9)	84·9 ±2·4 (9)	84·1 ±3·5 (7)
12·77±1·08 (9)	11·08±1·09 (9)	10·43±1·09 (9)	9·34±1·24 (7)
5·49±1·13 (11)	3·84±0·86 (11)	3·12±0·65 (11)	2·97±0·75 (11)
1·18±0·18 (11)	1·18±0·17 (11)	1·09±0·14 (11)	0·97±0·13 (11)
9·76±0·59 (11)	8·58±0·51 (11)	7·65±0·46 (11)	7·08±0·42 (11)
85·9 ±1·7 (11)	82·9 ±1·7 (11)	81·8 ±2·0 (11)	80·2 ±1·5 (10)
11·26±0·69 (11)	10·37±0·65 (11)	9·40±0·65 (11)	8·78±0·57 (10)
4·29±0·88 (20)	3·09±0·65 (20)	2·50±0·52 (20)	2·50±0·51 (18)
1·12±0·12 (20)	1·12±0·11 (20)	1·07±0·11 (20)	0·98±0·11 (18)
10·16±0·56 (20)	8·99±0·51 (20)	8·19±0·51 (20)	7·33±0·45 (18)
87·0 ±1·5 (20)	84·2 ±1·5 (20)	83·2 ±1·5 (20)	81·7 ±1·6 (17)
11·94±0·61 (20)	10·69±0·59 (20)	9·86±0·59 (20)	9·00±0·57 (17)

that of normal infants. The progressive fall of plasma TSH with postnatal age agrees with earlier reports (Fisher and Odell, 1969; Czernichow *et al.*, 1971). The mean plasma T_3 and T_4 levels before transfusion are similar to those reported for normal infants by some authors recently (Chan *et al.*, 1973; Abuid, Stinson, and Larsen, 1973), but are somewhat lower than the levels reported by Erenberg *et al.* (1974). The positive correlation between serum T_3 and T_4 before transfusion suggests that their plasma concentrations may be governed by a common factor such as TSH

TABLE II

Thyroid hormone concentrations during exchange transfusion of infants given donor blood with a high TSH concentration

	Donor	0 ml	100 ml	200 ml	300 ml	400 ml
Case 1						
TSH (μU/ml)	5·3	2·4	4·3	4·0	4·9	4·5
T_3 (ng/ml)	0·92	1·94	1·66	1·32	1·40	1·72
T_4 (μg/100 ml)	4·8	15·6	11·2	8·6	7·6	7·6
THBC (%)	87	88	85	85	80	85
FTI	5·5	17·7	13·2	10·1	9·5	8·9
Case 2						
TSH (μU/ml)	2·1	3·1	2·5	1·6	2·2	3·3
T_3 (ng/ml)	0·42	1·28	0·78	0·64	0·52	0·62
T_4 (μg/100 ml)	4·8	10·0	9·2	8·2	8·0	7·2
THBC (%)	74	112	99	94	91	87
FTI	6·5	8·9	9·3	8·7	8·8	8·3
Case 3						
TSH (μU/ml)	5·6	2·1	3·0	3·6	3·8	4·5
T_3 (ng/ml)	0·96	1·36	1·32	0·92	1·36	1·64
T_4 (μg/100 ml)	5·6	17·0	14·2	10·4	11·0	9·0
THBC (%)	95	101	97	99	92	—
FTI	5·9	16·8	14·6	10·5	12·0	—
Case 4						
TSH (μU/ml)	8·0	0·6	6·2	6·8	6·9	7·2
T_3 (ng/ml)	0·78	0·62	0·74	0·66	0·60	0·44
T_4 (μg/100 ml)	3·6	9·8	6·9	5·0	5·2	4·5
THBC (%)	84	77	89	86	83	77
FTI	4·3	12·7	7·7	5·6	6·3	5·8

secretion. The alternative explanation, that T_3 is correlated with T_4 because it may be derived from T_4 by deiodination seems unlikely as the fetus has a reduced ability to convert T_4 to T_3 in this way (Dussault *et al.*, 1972).

The main observation reported here is that exchange transfusion has a profound effect on circulating thyroid hormone levels and that by the end of the procedure the infants are biochemically hypothyroid. These data are in keeping with findings in dogs and rats (Suematsu *et al.*, 1970; Langer *et al.*, 1971, 1972) and extend the observations of Paletta, Rossipal, and Haidvogl (1969) who observed a fall in plasma protein-bound iodine levels during exchange transfusion of human infants. Since in the animal studies there was a rapid restoration of euthyroid status and Paletta *et al.* (1969) noted normal protein-bound iodine levels on the day after transfusion, it seems likely that the infants reported here would also become euthyroid in the post-transfusion period. It is noteworthy that the interaction of pituitary and thyroid hormones is based on a time-scale measured in hours rather than minutes.

The fall in T_3 levels was much less dramatic and less consistent than the fall in T_4. This may be due to the larger volume of distribution and/or the more rapid equilibration of T_3 than T_4 (Larsen, 1972), permitting re-entry of T_3 into the circulation as the transfusion proceeded. The marked fall of TSH levels during transfusions in which the donor blood had a lower TSH level than that of the infant suggested that the hypothalamus or pituitary of the newborn does not respond significantly to the fall in T_3 and T_4 levels during the period of the transfusion. The lack of TSH response might also be interpreted as being due to TSH secretion being maximal but this seems unlikely in view of the large rise in TSH concentration after birth. It was of interest that in 2 of the 3 cases in which the plasma TSH level increased, there was a small increment in T_3 levels in the latter part of the transfusion. However in the case in which the largest rise in TSH occurred (Case 4), there was no increase in T_3.

Although glucagon in pharmacological doses stimulates thyroid metabolism *in vitro* (Burke, 1970), it had no significant effect on plasma T_3, T_4, or TSH levels in the present situation despite raised plasma glucagon levels at the end of transfusion (Milner *et al.*, 1973). This suggests that the human neonatal thyroid gland and thyrotroph of the pituitary are insensitive to glucagon. As with TSH, the alternative explanation of maximal thyroid hormone secretion at the start of transfusion seems unlikely in view of the pronounced hormone release after birth.

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