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A Study of Thyroid Hormone in Children and Adolescents in a Series of MZ and DZ Twins and Their Siblings

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Stabenau and Pollin (1968) observed, in a study of 23 pairs of adult MZ twins, that a significant correlation existed between birth-weight (a measure of fetal maturity) and adult protein-bound iodine (PBI) ($r = +0.58$, $P < 0.001$). In a subsample of 12 individuals, the correlation between birthweight and thyroxine-binding globulin (TBG) was $+0.94$ ($P < 0.001$). These data suggested that differences in protein hormonal binding may be established as a result of intrauterine factors, the effect of which may persist into adulthood. The study of neonates has demonstrated that measures of PBI and butanol-extractable iodine (BEI) are higher at birth than in later adulthood, and that rapid changes in individual values occur during the early neonatal period. Marks and Man (1965), Perry et al (1965) and Man (1966) have demonstrated that BEI and PBI values are higher for infants who are heavier in weight at birth and lower for infants of low birthweight. The weight of a fetus at birth has been used as one single estimate of fetal maturity when measures such as fetal length and gestational age are unavailable.

A sample of children and adolescent MZ and DZ twins and singletons was studied to test the hypothesis that measures of thyroid hormone activity are related to maturity at birth. In addition, estimates of the relative genetic control for thyroid hormone levels were made.

The sample consisted of 31 pairs of MZ, 13 pairs of same-sexed and 7 of opposite-sexed DZ twins, and 46 siblings, aged 3-19 years. All subjects were studied at the Clinical Center, NIH, where physical examination for thyroid abnormality, measurement of standing height and body weight were conducted, and an analysis of a blood sample for protein bound iodine, thyroid-binding globulin, thyroxine by column (T_4) and free thyroxine (FT_4) was performed. Maternal history for gestational age, birthweight and birth length (documented by hospital records) was also obtained for the majority of subjects. All biochemical determinations were performed on randomly coded samples of sera by the Bio-Science Laboratories. Duplicate and retest analyses were performed where sufficient amounts of sera were available. Split sample duplicate reliabilities were: PBI, $r = 0.89$;

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T_4, r = 0.83; FT_4, r = 0.89 and 0.93; and TBG, r = 0.73 and 0.84. PBI expressed as μg/100 ml serum was determined by a modification of the alkaline ash method (Barker et al, 1951). TBG, a measure of the total thyroxine binding of serum, was determined by the reverse flow paper electrophoretic separation method and was reported as μg/100 ml thyroxine (Elzinga et al, 1961). T_4, a measure of thyroxine, reported as μg/100 ml serum was determined by a column chromatographic method (Pileggi et al, 1961). "Free" thyroxine (FT_4) was reported as mμg/100 ml serum and was established by a radioactive tagging and dialysis method (Lee et al, 1964). Zygosity was established by serological comparison of blood groups between members in each twin pair.

Tab. I demonstrates the correlation between the four thyroid hormone variables. A high degree of correlation exists between FT_4 and T_4 (0.68) and T_4 and PBI (0.65). A moderate relation for FT_4 and PBI is noted (0.43), and, as might be ex-

Tab. I. Correlation matrix for thyroid variables *

	PBI	T_4	FT_4	TBG
PBI (N = 153)	1.00			
T_4 (N = 147)	0.65	1.00		
FT_4 (N = 148)	0.43	0.68	1.00	
TBG (N = 136)	0.31	0.37	0.27	1.00

$r = 0.25$; $P < 0.01$; $N = 100$.

* Mean of duplicate and retest values for each subject was used.

pected, only a low level of correlation was found for TBG and T_4 (0.37), PBI (0.31), and FT_4 (0.27).

Birthweight was more highly correlated with length at birth (0.76) than with gestational age (0.57). Length at birth and gestational age were less significantly related (r = 0.50).

No significant relationship was found between birthweight and any of the four thyroid variables (Tab. II). However, for this sample of children (aged 3-19 years) T_4, FT_4, and TBG were each significantly negatively correlated with current age, current weight, and current height (r = —0.24 to —0.37). PBI had a similar but not significant negative correlation with age, weight, and height. Since age, height, and weight are intercorrelated, attempts were made to parcel out the most significant variable. Partial correlation coefficients suggested that the decreasing values of the three thyroid hormone measures (T_4, FT_4, and TBG) were most significantly related to the increasing body weight of the child. Thus, as the children became older, taller, and heavier, the values for each of these thyroid hormones decreased over time.

Tab. II. Correlation matrix for biologic and thyroid variables *

	Weight**	Age**	Height**	Birth weight
T_4	—0.31	—0.27	—0.30	—0.13
FT_4	—0.31	—0.24	—0.27	—0.14
TBG	—0.37	—0.30	—0.35	—0.02
PBI	—0.10	—0.02	—0 08	—0.01

$r = 0.25$; $P < 0.01$; $N = 100$.

* Mean of duplicate and retest values for each subject was used.

** At time of study.

Estimates of the degree of genetic control for these thyroid variables were made by employing the coefficient h^2 proposed by Holzinger (1929). The equation is

$$h^2 = \frac{\sigma^2 \text{ DZ} - \sigma^2 \text{ MZ}}{\sigma^2 \text{ DZ}}$$

Weight and especially height in children are considered to have a strong genetic component. Tab. III indicates that, as expected, the within-pair variance for height and weight is significantly smaller for MZ than for DZ twin pairs. These variances subsequently yield a high heritability coefficient (h^2) of 0.90 for height and 0.92 for weight, indicating the genetic effect in these variables.

For the thyroid hormone variables, h^2 was moderately high for PBI (0.60). For FT_4 (0.44) and T_4 (0.40) the heritability index indicated a lesser degree of genetic influence. TBG, the binding protein, appears to be little influenced by genetic factors as measured by this method ($h^2 = 0.06$).

Neonatal study of PBI and BEI indicate that infants who weigh more at birth have a significantly higher BEI or PBI value than infants who weigh less at birth (Marks and Man, 1965; Perry et al, 1965; Man, 1966). The values of PBI and BEI rapidly decrease with increasing age. Oddie and Fisher (1967), in a review of published data on 279 male and female euthyroid subjects between 0.1 and 20 years of age, found a decrease in PBI and BEI from high values in the neonatal period to minimum values in adolescence. The lowest values for females occurred at 13.7 years and at 15.0 years for males. The values then rose to approach asymptotically the more constant adult level by the third decade of life. The finding of a significant negative correlation for age, height, and weight of the child with each of the thyroid variables, T_4, FT_4, and TBG, are supportive of the changing pattern of thyroid hormone during the growth period as observed by Oddie and Fisher. The lack of correlation between any of the thyroid variables during the growth period and weight

Tab. III. Estimate of genetic component and thyroid variables

	Zygosity	N. of pairs	Mean	Within-pair variance (σ)	h^2
Height (cm)	MZ	29	121.4	1.3	0.90
	DZ	20	129.8	12.0	
Weight (kg)	MZ	29	25.1	1.1	0.92
	DZ	20	30.6	13.7	
PBI (μg%)	MZ	29	5.4	0.11	0.60
	DZ	20	5.7	0.29	
Free * T_4	MZ	26	1.57	0.03	0.44
	DZ	18	1.64	0.05	
T_4 (μg%)	MZ	26	4.93	0.15	0.40
	DZ	19	5.19	0.25	
TBG**	MZ	23	17.7	4.4	0.06
	DZ	16	17.0	4.2	

* mμg of thyroxine. ** μg/100 ml thyroxine.

at birth is understandable in light of the variability of hormone level. From the limited data of the NIMH Adult Twin Study, it appears that when the period of maximal growth has passed (i.e., into the 2nd and 3rd decade) a relation between weight at birth and PBI level becomes demonstrable (Stabenau and Pollin, 1968).

The hypothesis has been proposed that thyroid hormone, as measured by PBI or BEI, is in part determined by factors related to intrauterine growth and development and involves nongenetic factors affecting the levels of bound hormone (Stabenau and Pollin, 1968). The data from this sample suggest that there may be an interacting, moderately potent genetic component for PBI, a less considerable but important effect on FT4 and T4, and little genetic effect on the value of the binding protein of thyroid hormone (TBG).

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