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Thyroid hormonal studies in normal and severely malnourished infants and small children

Thyroid hormone levels have been determined in nutritionally normal infants and in infants with marasmus or marasmic kwashiorkor. In the normal subject, serum thyroxine is higher during the first year of life than at birth or after one year. Free thyroxine is higher at 2 to 3 months of age than later. TBG falls slightly but not significantly with age. Elevated TSH of cord serum falls to normal adult levels by 2 to 3 months. Despite normal TBG, serum thyroxine may be decreased in marasmus and during recovery; free thyroxine may be high to low initially and normal or low during recovery; serum TSH is low or normal at both times. In kwashiorkor, low initial TBG accounts for low thyroxine, but free thyroxine is normal or elevated; TSH is normal. During recovery, TBG returns to normal but thyroxine only partially so, and free thyroxine falls as does TSH. TBPA does not change significantly with age or nutritional state.

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INFANTS and children who survive prolonged and severe undernutrition often respond poorly to adequate feeding. Body

Abbreviations used

T_4: thyroxine
TBG: thyroxine-binding globulin
TBPA: thyroxine-binding prealbumin binding capacity
FT_4: free thyroxine
TSH: thyroid-stimulating hormone

composition, before and after rehabilitation, reveals alterations in utilization of nutrients,[1] suggesting that adaptation for survival may have lasting effects. The manner in which the marasmic infant makes substrate available for the energy needs of the brain and other vital organs is of special interest. Studies carried out on starved adults identify some of the major adjustments that take place: increased gluconeogenesis, decreased protein synthesis, and increased fatty acid mobilization and utilization.[2]

As part of a study of hormonal adaptations, we have determined the circulating levels in serum of thyroxine (T_4), thyroxine-binding globulin (TBG), thyroxine-binding prealbumin binding capacity (TBPA), free thyroxine (FT_4), and thyroid-stimulating hormone (TSH) in infants and small children suffering from marasmus or marasmic kwashiorkor. These studies were carried out within 24 hours of admission and again after partial rehabilitation. Control subjects appropriately matched for age and size were studied in the same manner.

SUBJECTS

All subjects were studied at the British American Hospital in Lima.

As part of another study, 13 male siblings of malnourished infants were admitted for up to 24 months to a convalescent unit before 3 months of age, after weaning had doomed them to certain malnutrition with a potential mortality rate of 50 per cent. Their condition was still good to excellent; the few who had poor growth were rehabilitated before being studied. All were of similar ethnic origin, primarily Mestizo: under ideal circumstances the growth of such children[3] parallels the twenty-fifth percentile of the Boston standard.[4] When plotted against this, mean heights and weights of our control subjects were close to the twenty-fifth percentile. Their radiologic bone ages[5] were appropriate for age. Eight infants were studied twice, once between 2.1 and 4.8 months of age and again between 6.0 and 14.0 months of age. Five were studied once. Six additional control subjects, between 30 and 39 months of age, were studied on an ambulatory basis. In height, three were just below the tenth, two at the fiftieth, and one at the ninetieth percentile. In weight, five were at the fiftieth and one was at the ninetieth percentile. They had been followed since birth and had had consistent growth patterns.

Six infants with severe marasmus were studied, five on two occasions. They were admitted on the afternoon prior to the study; all had histories of early weaning, grossly inadequate artificial feeding, frequent small "hunger" stools, and no indication of recent dehydrating diarrhea or severe infection. Physical examination and radiologic, hematologic, and bacteriologic work-ups suggested that they were free of major infections. In one, Case 223, blood culture taken on admission subsequently grew out *E. coli;* he died of sepsis after a stormy course. The remaining five were restudied 24 to 76 days after admission, when steady weight gain had been established.

Table I summarizes their characteristics at the time of each study: age, height, "height age" (referred to the Boston fiftieth percentile), bone age,[5] weight, and serum total proteins and albumin. Also listed is calorie intake achieved by the time of the second study (protein provided 8 per cent of calories) and rate of weight gain between studies. At the time of admission mean serum total protein was 6.50 and mean serum albumin was 3.56 Gm. per 100 ml., mean hematocrit was 34.5 per cent (range 32 to 40), and mean hemoglobin was 10.3 Gm./100 ml. (range 8.9 to 12.0). Serum sodium and potassium concentrations were between 130 and 142 (mean 137) and between 4.0 and 6.15 (mean 4.73) mEq. per liter, respectively. Serum bicarbonate was above 16 mEq. per liter in all cases.

All five survivors gained weight satisfactorily, but only the two with the greatest initial deficits in height had grown significantly when studied 76 and 66 days, respectively, after admission. At the time of the second study mean serum albumin was slightly over 4 Gm. per 100 ml., mean hematocrit and hemoglobin had not changed

Table I. Anthropometric and laboratory findings of marasmic male infants at the time of the first (A) and second (B) studies; calorie intake reached and rate of weight gain between studies are also given

Case No.	Hospital day	Age (mo.)	Height (cm.)	Height age (mo.)	Bone age (mo.)	Body weight (Kg.)	Serum protein total albumin (Gm./100 ml.)		Kcal./Kg./day	Weight gain (Gm./day)
221A	2	6.7	63	4.1	< 3	4.15	6.81	3.29	—	—
221B	24	7.4	63	4.1	—	4.69	7.70	3.99	150	25
223A	2	6.2	64	4.7	6	4.70	6.90	3.73	—	—
225A	2	7.2	56	1.4	< 3	3.30	5.69	3.16	—	—
225B	76	9.7	61	3.3	—	4.53	6.76	4.32	150	17
237A	2	9.9	66	5.9	3	5.96	6.63	3.67	—	—
237B	50	11.5	67	6.2	—	7.30	7.05	4.23	125	28
265A	2	10.9	61	3.3	3-6	4.30	6.73	3.99	—	—
265B	28	11.7	61	3.3	—	5.39	6.08	3.70	175	42
283A	2	5.4	56	1.4	3	3.40	6.24	3.54	—	—
283B	66	7.5	59	2.4	—	4.56	6.30	3.89	150	18

significantly, mean serum sodium (141.6) was moderately higher, and mean serum potassium (4.65) had not changed appreciably.

Seven children with marasmic kwashiorkor were studied within 24 hours of admission and after 24 to 43 days, when diuresis was complete, serum albumin had exceeded 3.0 Gm. per 100 ml., and they were gaining weight steadily. One, Case 258, had more than the usual superficial skin infection which characterizes severe kwashiorkor. Preliminary evaluation suggested no systemic involvement but blood culture, drawn on admission, grew out hemolytic *S. aureus*. He responded well and was restudied on the forty-second day. An eighth child, Case 228, was not studied on admission, but only on the forty-first hospital day. He had no significant deficit in height or weight and could more properly be classified as having "pure" kwashiorkor.

Pertinent findings are summarized in Table II. In addition to those in Table I, this includes an estimate of the edema present on admission (0 to 4+), skin and hair changes (severity estimated 0 to 4+), liver size in centimeters below the right costal margin, hospital day on which diuresis first became evident, the day on which the lowest body weight was reached, the amount of weight lost, and the rate of weight gain between this point and the second study. Protein provided 8 per cent of dietary calories during rehabilitation.

At the time of the first study, mean serum total protein was 3.86 and mean serum albumin 1.46 Gm. per 100 ml., mean hematocrit 27.9 per cent (range 19 to 36), mean hemoglobin 8.3 Gm. per 100 ml. (range 5.4 to 10.7), mean serum sodium 137.4 mEq. per liter (range 134 to 142), and mean serum potassium 3.90 mEq. per liter (range 2.85 to 4.85). Serum bicarbonate was above 20 mEq. per liter in all cases and blood pH, determined in four children only, was between 7.40 and 7.43. At the time of the second study total protein and albumin, hematocrit, hemoglobin, and serum potassium (mean 5.05, range 4.55 to 5.9) were much improved. All had received blood transfusions during the first few days of hospitalization. Mean serum sodium was 139.7 mEq. per liter.

METHODS

Control subjects were fasted for eight hours before blood for thyroid determinations was drawn.

The marasmic infants were given an oral dextrose-electrolyte mixture at a rate of 150 ml. per kilogram per 24 hours until midnight and then fasted until blood was drawn in the morning. Initial management was with

Table II. Anthropometric, clinical, and laboratory findings of male children with marasmic changes also listed

Case No.	Hospital day	Age (mo.)	Height (cm.)	Height age (mo.)	Bone age (mo.)	Body weight (Kg.)	Edema (0-4+)
254A	2	26.2	79.2	15.8	12	10.93	3+
254B	24	26.9	79.2	15.8	—	9.58	0
255A	2	23.8	78.5	15.1	21	8.64	2+
255B	31	24.8	78.5	15.1	—	8.35	0
257A	2	39.0	84.5	20.8	27	11.60	3+
257B	29	40.0	84.5	20.8	—	10.60	0
258A	2	22.5	75.0	12.0	12	9.22	3+
258B	42	23.8	76.1	12.9	—	9.54	0
262A	2	23.5	78.1	15.0	12-15	9.10	3+
262B	31	24.4	78.5	15.1	—	9.05	0
286A	2	35.5	85.0	21.0	15-21	13.00	4+
286B	27	36.3	85.0	21.0	—	11.47	0
296A	2	24.0	69.8	8.2	9	6.56	1+
296B	43	25.5	70.5	8.5	—	7.80	0
228A*	2	36.1	95.2	35.0	27	12.50	1+
228B	41	37.5	96.0	36.0	—	14.45	0

*No hormonal studies were carried out at this time.

progressively increasing amounts of the same modified cow's milk formula used for the control subjects (Similac with iron plus sugar and oil). They were fasted for eight hours before blood was drawn for the second study.

Patients with marasmic kwashiorkor, depending on the hour of admission, received one or two feedings, each providing 0.4 Gm. of protein (casein) and 15 Kcal. per kilogram, as well as the dextrose-electrolyte mixture. These were discontinued at midnight, and they remained fasting until blood was drawn eight hours later. Initial management was with a casein-sucrose-vegetable oil mixture, but once stabilized, they were changed to the modified cow's milk formula until the second study, when they were fasted for eight hours before blood was drawn.

Serum was separated from coagulated blood, frozen at −20° C., shipped in dry ice to Baltimore, and kept frozen until processed. Because samples were collected over more than two years, each set of determinations included samples from all three categories in a fairly even distribution.

The serum T_4, FT_4, TBG, TBPA, and TSH determinations were carried out as previously described.[6] The lower limit of sensitivity of the TSH assay is 1.25 μU per milliliter. Approximately 50 per cent of normal adults have TSH levels below this value.

RESULTS

Control group. In the control group, T_4 decreased from a mean of 15.6 ± 0.7 in the youngest (2.1 to 3.2 months of age) to 9.9 ± 0.5 μg per 100 ml. in those 30 to 39 months of age (Table III and Figs. 1A and 1B). According to the Student t test, differences between the two youngest groups and between them and the oldest were significant ($p < 0.05$). Although a downward trend in TBG was noted, there was no significant difference between the means. There was no significant change with age in TBPA. FT_4 values for the youngest group were significantly higher than those for the other control subjects. All TSH values were in the normal or low range. Our assay does not differentiate between all normal and low values, as 50 per cent of normal adults have values less than sensitivity.

Marasmic infants. The marasmic infants at admission had a mean T_4 of 9.5 μg per 100 ml., significantly lower than the mean of 12.3 ± 0.6 for control subjects of comparable age. Five of the six values at admission were more than two standard deviations

kwashiorkor at the time of first (A) and second (B) studies; calorie intake and body weight

Skin hair (0-4+)	Liver (cm.)	Serum protein total albumin (Gm./100 ml.)		Onset of diuresis (day)	Low weight (day)	Weight loss (Gm.)	Kcal./Kg./day	Weight gain (Gm./day)
2+	1	3.83	1.39	4	9	2,000	—	—
0	—	7.00	4.14	—	—	—	100	35
3+	4	3.64	1.03	6	10	640	—	—
0	—	6.53	3.06	—	—	—	100	17
2+	5	3.80	1.60	5	12	1,150	—	—
0	—	7.10	4.03	—	—	—	100	9
4+	7	4.14	1.44	9	15	910	—	—
0	—	7.85	4.02	—	—	—	100	45
2+	4	4.27	1.55	3	8	950	—	—
0	—	7.52	4.06	—	—	—	125	39
2+	2	3.71	1.55	3	11	2,070	—	—
0	—	6.80	3.68	—	—	—	125	31
2+	0	3.64	1.70	7	7	0	—	—
0	—	7.58	4.22	—	—	—	125	34
1+	0	4.19	1.63	10	16	620	—	—
0	—	7.65	4.41	—	—	—	100	103

below the control mean when plotted against chronologic age (Fig. 1A) or against height (Fig. 1B). TBG determinations at admission were not abnormal (Figs. 2A and 2B), and mean TBPA was not significantly different from that of the age or height control subjects. However, three of the six determinations were two standard deviations or more below the control mean (Figs. 3A and 3B). Although mean serum FT_4 was 3.22 ± 0.61 ng. per 100 ml., the scatter was remarkable (Figs. 4A and 4B): Two values were above and two below the normal range. Individual records did not reveal any clinical factors to account for this variability. All TSH values but one were below the sensitivity of the assay, as were those of two additional marasmic infants studied later and not included in this report.

Marasmic infants at recovery. These infants had no remarkable change in any parameter except FT_4, which fell in three of five paired values. Because Case 265 had low T_4 and FT_4 on both occasions, he was studied 12½ months later: He had gained 7.6 Kg. and grown 16 cm., and T_4 was now 10.4, TBG 28.9, TBPA 242.3, FT_4 2.44, and TSH < S.

Marasmic kwashiorkor infants. These infants had low T_4 and TBG levels and normal or high TBPA and FT_4 levels. Mean FT_4 was suggestively increased over control values: Four of seven were above the normal range for age or height (Figs. 4A and 4B). There was no evidence of TSH deficiency, as six of seven had values in the detectable range.

Marasmic kwashiorkor infants at recovery. These infants had a rise in T_4 and TBG levels, measured 22 to 41 days after admission. This time apparently is inadequate to correct totally the low T_4, although TBG values had returned essentially to normal. TBPA values in these infants compared to values in control subjects, remained elevated. FT_4 fell to a significantly low mean (1.64 ± 0.08 ng. per 100 ml.), compared to admission (3.35 ± 0.43 ng. per 100 ml.) or control (2.68 ± 0.13 ng. per 100 ml.) values. TSH fell in five of the six who had measurable levels at admission.

DISCUSSION

The most extensive report of normal serum thyroxine values at various ages is that of O'Halloran and Webster[7] on 341 infants of 0 days to 36 months. Mean cord T_4 was 11.3 μg per 100 ml.; at 1 to 2 weeks it was 13.2 μg per 100 ml. and fell slowly until 9 to 12 months. Increased T_4 values were ob-

Table III. Thyroid hormone levels in control subjects (mean ± S.E.M.) and in infants with marasmus and kwashiorkor, on admission (*A*) and after partial rehabilitation (*B*). For each particular determination (T_4, TBG, TBPA, or FT_4) means with the same superscript (reading downward only) are not significantly different ($p < 0.05$ by Student t test)

Control subjects age—mo.	*N*	*T_4 (μg/100 ml.)*		*TBG (μg/100 ml.)*		*TBPA (μg/100 ml.)*		*FT_4 (ng./100 ml.)*		*TSH (μU/ml.)*	
2.1- 3.2	6	15.6 ± 0.7^{a}		32.3 ± 2.0^{a}		213.9 ± 6.8^{a}		3.72 ± 0.15^{a}		All <S	
4.5-10.6	8	12.3 ± 0.6^{b}		30.0 ± 2.5^{ab}		236.0 ± 10.9^{acd}		2.72 ± 0.12^{b}		(7)<S; 2.6	
12.5-18.5	7	10.8 ± 0.5^{bc}		27.3 ± 1.6^{ab}		206.8 ± 13.2^{abc}		2.69 ± 0.16^{b}		(5)<S; 1.9, 3.3	
30-39	6	9.9 ± 0.5^{c}		26.6 ± 1.8^{ab}		180.9 ± 8.0^{b}		2.68 ± 0.13^{b}		(5)<S; 2.5	
	Case No. (age)	A	B	A	B	A	B	A	B	A	B
Marasmus	221 (6.7)	9.8	8.8	33.7	32.5	138.0	209.4	2.23	1.51	<S	<S
	223 (6.2)	10.0	—	25.7	—	166.8	—	3.60	—	3.0	—
	225 (7.2)	9.7	6.7	31.1	16.2	219.9	218.0	4.71	1.87	<S	<S
	237 (9.9)	12.8	11.8	18.4	28.6	147.0	160.6	5.20	2.99	<S	<S
	265 (10.9)	7.2	7.4	28.6	27.7	237.4	195.9	1.76	1.80	<S	<S
	283 (5.4)	7.4	10.3	29.6	30.6	219.8	254.3	1.84	2.31	<S	<S
	Mean	9.5^{cd}	9.0^{cd}	27.9^{ab}	27.1^{ab}	188.1^{ab}	207.6^{ab}	3.22^{ab}	2.10^{bc}		
	S.E.M.	0.8	0.9	2.2	2.9	17.4	15.2	0.61	0.26		
Marasmic kwashiorkor	254 (26.2)	6.2	8.7	11.2	22.3	226.4	303.3	3.79	1.57	<S	<S
	255 (23.8)	4.4	5.4	6.1	20.4	205.3	325.2	4.62	1.33	1.4	<S
	257 (39.0)	4.8	8.9	7.5	22.6	259.0	227.0	3.73	1.94	9.5	2.75
	258 (22.5)	6.1	8.1	12.5	24.1	233.0	227.5	4.58	1.82	5.0	<S
	262 (23.5)	3.6	7.3	12.2	25.0	413.0	365.2	1.98	1.59	3.5	3.5
	286 (35.5)	3.8	8.8	10.4	32.6	311.5	276.8	1.95	1.76	3.5	<S
	296 (24.0)	3.3	6.3	10.9	24.1	426.2	231.3	2.79	1.32	2.3	<S
	228 (36.1)	—	6.8	—	24.5	—	261.5	—	1.76	—	3.7
	Mean	4.6^{e}	7.5^{d}	10.1^{e}	24.5^{b}	296.3^{cd}	277.2^{d}	3.35^{ab}	1.64^{e}		
	S.E.M.	0.4	0.5	0.9	1.3	34.3	18.0	0.43	0.08		

S = Sensitivity of method for TSH.

served in the 12- to 36-month-old groups, although differences from the 9- to 12-month-old groups were probably not significant. They did not report standard deviations for each group, so statistical significance cannot be calculated.

Murray and associates[8] studied serum T_4 of children older than those reported by O'Halloran and Webster or by us. Their data suggest that infants at six months have higher values than after 12 months. The regression for our series indicates a constant fall until 12 months or longer. An apparent rise at 30 to 39 months may not be real, although O'Halloran and Webster also saw such a trend.

Actual TBG values have not been reported for infants and young children, although some T_3 resin uptake values are available. Murray and associates[8] reported a greater saturation capacity of TBG in children than in adults, and O'Halloran and Webster[7] tended to confirm this. Our data suggest a trend toward greater values in younger infants, although there is no significant difference between the four groups. Values in the younger group could account in part for increased T_4 levels.

The high FT_4 levels at 2.1 to 3.2 months are in accord with the free thyroxine index, an indirect and arbitrary measurement reflecting unbound or free T_4, reported by O'Halloran and Webster[7] as 9.3 ng. per 100 ml. in cord blood, 12.3 by 1 to 2 weeks, 10.9 at 2 to 4 weeks, 11.5 at 4 to 6 weeks, 10.2 at 2 to 3 months, and a plateau thereafter at 8.2 to 8.5 months. Apparently infants up to three months do have increased FT_4 values, of unknown etiology and significance, falling to a plateau before serum T_4 values decrease.

The physiologic role of TBPA remains un-

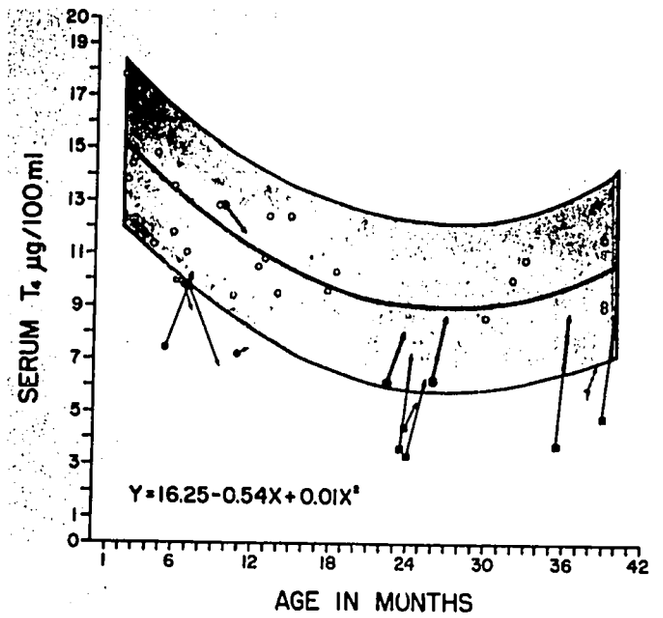

Fig. 1A. Serum thyroxine (T_4) as a function of age in normal control subjects (open circles): shaded area represents two standard deviations above and below the mean (solid line). Initial levels in marasmus represented by closed circles, partial recovery by tip of arrow. Initial levels for marasmic kwashiorkor represented by closed squares, partial recovery by tip of arrow. For one case there was no initial value. Note that values are for micrograms of thyroxine, *not* thyroxine iodine.

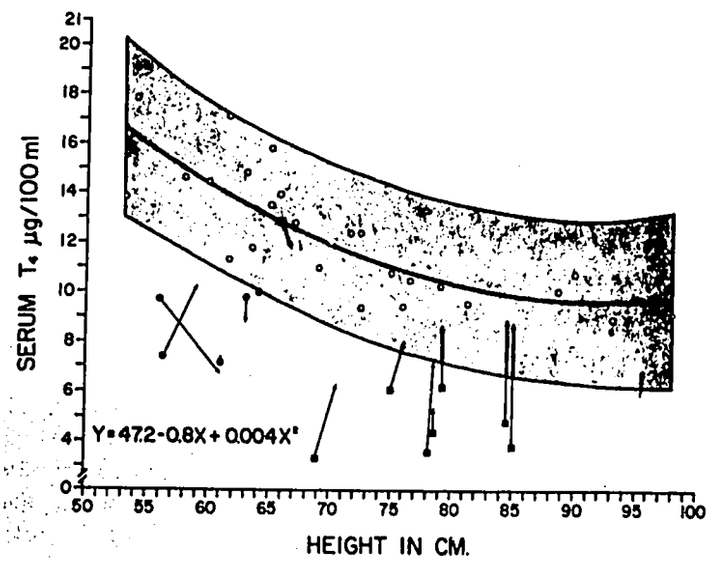

Fig. 1B. Serum thyroxine (T_4) as a function of height. For explanation of symbols, see Fig. 1A.

known; its concentration apparently is stable throughout infancy. Comments on TSH are not pertinent since there is no elevation in any control group, and normal cannot be differentiated from absent values with our assay. Values in cord blood[6] are higher (6.0 ± 2.0 µU per milliliter) than those in the youngest control subjects. FT_4 levels at birth were reported from our laboratory[6] to be 3.4 ± 0.7 ng. per 100 ml., similar to that in

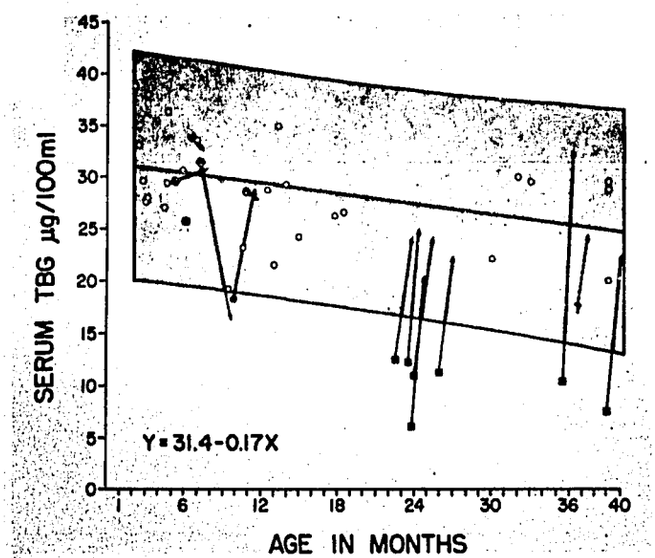

Fig. 2A. Serum thyroxine-binding globulin (TBG) as a function of age. For explanation of symbols, see Fig. 1A.

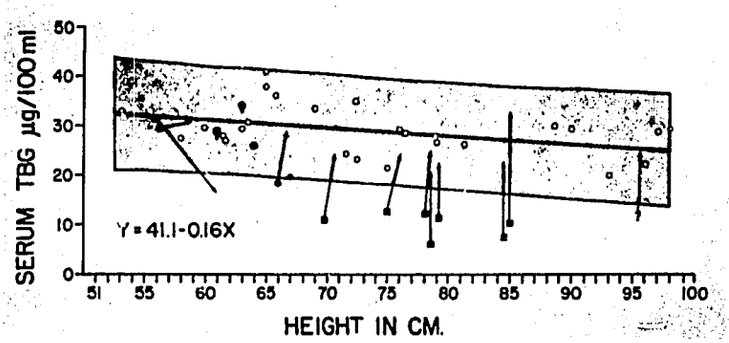

Fig. 2B. Serum thyroxine-binding globulin (TBG) as a function of height. For explanation of symbols, see Fig. 1A.

the present 2.1 to 3.2 month group. Since TSH levels have fallen by 2.1 to 3.2 months, although FT_4 remains constant, we conclude that the hypothalamic-pituitary-thyroid axis probably matures between 18 hours and 2 months.

Milner's[9] review found "general agreement from measurement of plasma hormone levels and metabolic rates that thyroidal function is depressed in malnutrition." Interpretation is made difficult by differences in methods, inappropriate "normal" subjects, and different units of reference for metabolic studies. Of some concern are variations in, or failure to identify, the timing of studies in relation to duration of treatment.

Most estimations of basal metabolic rate in untreated infants have found it normal, even if related to appropriate weight for age or height.[10-13] Some are normal for weight but low for surface area[14] or metabolic mass.[15] After treatment basal metabolic rate was still normal[11, 12] or normal in those growing well and low in those not responding, if related to predicted weight.[10] In those not responding administration of TSH increased oxygen consumption.[17]

Urinary I^{131} excretion has been reported

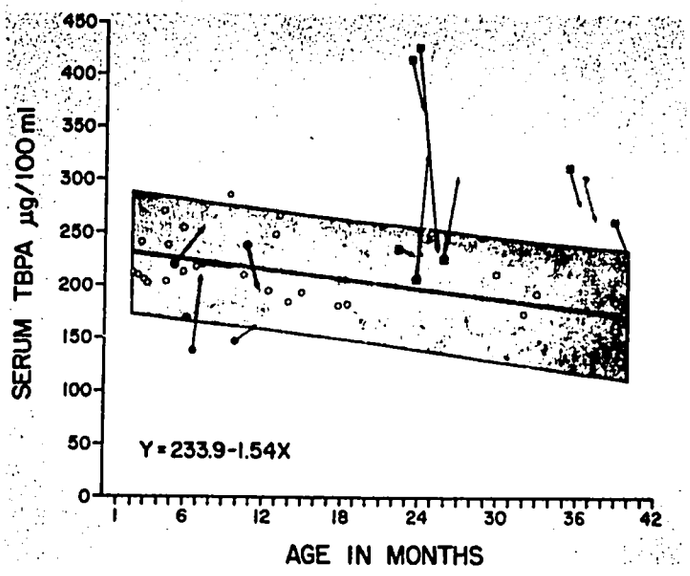

Fig. 3A. Serum thyroxine-binding prealbumin binding capacity (TBPA) as a function of age. For explanation of symbols, see Fig. 1A.

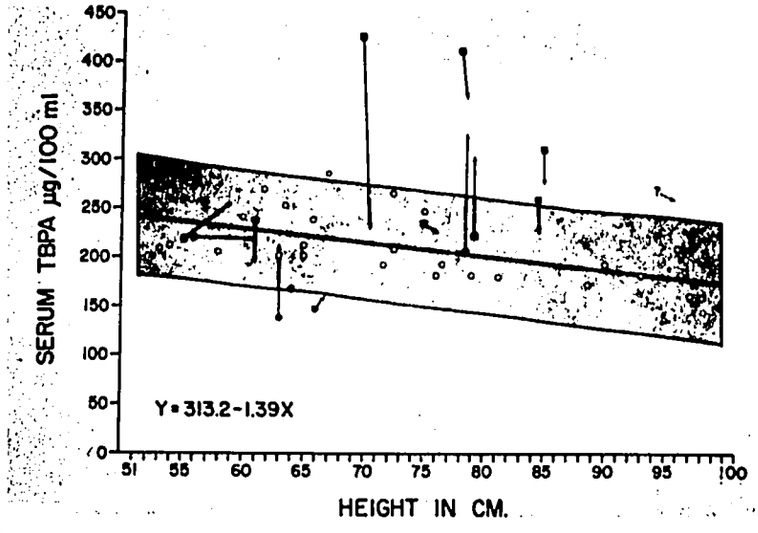

Fig. 3B. Serum thyroxine-binding prealbumin binding capacity (TBPA) as a function of height. For explanation of symbols, see Fig. 1A.

to be normal early, slightly increased during recovery from malnutrition.[18] Butanol-extractable iodine and I^{131} uptake were decreased in partially treated marasmus.[9, 17] Krieger and Good[19] found thyroxine iodine and I^{131} uptake low in malnourished infants but postulated that FT_4 might be normal. In one study of marasmic kwashiorkor, I^{131} uptake was low.[20] Glands of malnourished infants weight less than normal, but have no histologic abnormality.[21]

With the use of a bioassay, low serum and pituitary levels of TSH were found in patients with marasmus and kwashiorkor.[22]

In this study, T_4 was low in most patients with marasmus or kwashiorkor, particularly

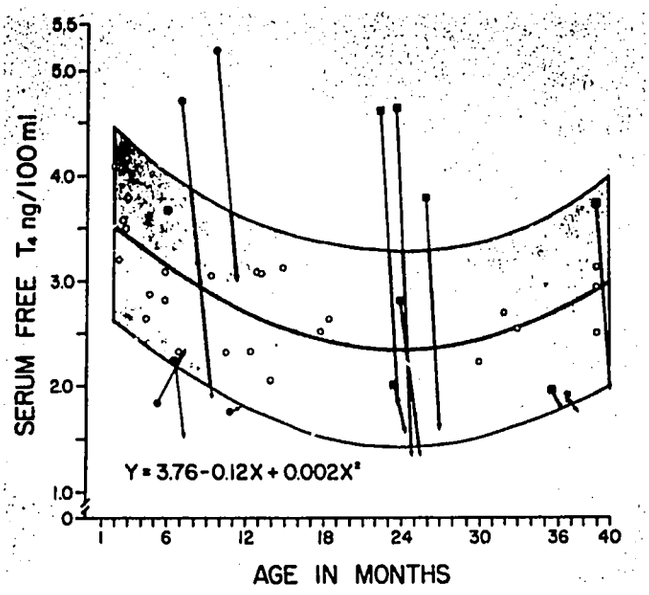

Fig. 4A. Serum free thyroxine (FT_4) as a function of age. For explanation of symbols, see Fig. 1A.

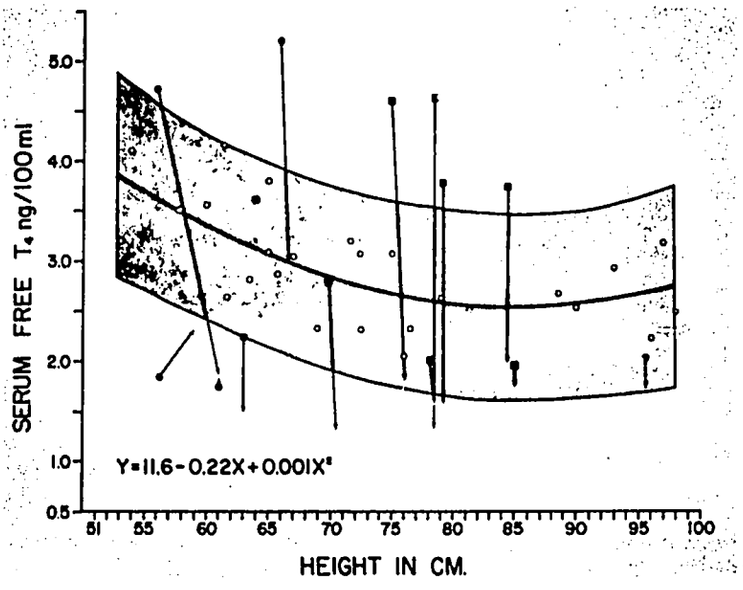

Fig. 4B. Serum free thyroxine (FT_4) as a function of height. For explanation of symbols, see Fig. 1A.

the latter, in which the finding could be attributed to decreased TBG. In marasmus TBG was not decreased enough to account for low T_4 values. FT_4 values suggest no deficiency of calorigenically active hormone in kwashiorkor, with increases frequently present. FT_4 data in marasmus are difficult to interpret: Even on the basis of age, two of six had low values and possibly were hypothyroid; there was an almost invariable reduction with recovery. In malnourished states an increase in FT_4 might occur be-

cause of relative peripheral resistance to FT_4, without symptoms of hyperthyroidism, or the thyroid might produce a disproportionate amount of T_4 relative to triiodothyronine (T_3); FT_4 would rise to compensate for the decreased secretion of T_3.

The failure of TBPA concentration to be affected is surprising; neither a normal intake of calories nor of protein may be essential for synthesis of this glycoprotein. There even is a suggestive increase in malnutrition.

TSH levels were normal or low in patients with marasmus, on admission and after treatment. In those with kwashiorkor they were normal on admission and low or normal during recovery. The findings are compatible with the response to TSH during recovery found in marasmic infants.[17] FT_4 was elevated in four of seven of our patients but, as in marasmus, when high on admission, fell to normal or low levels in a few weeks. TSH levels in kwashiorkor indicated no decrease in function of the hypothalamic-pituitary-thyroid axis.

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