Familial Syndrome Combining Deaf-Mutism, Stippled Epiphyses, Goiter and Abnormally High PBI: Possible Target Organ Refractoriness to Thyroid Hormone[1,2]

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ABSTRACT. The occurrence of a bizarre familial syndrome combining deaf-mutism, stippled epiphyses, goiter and abnormally high PBI in 2 of 6 children of a consanguineous marriage is described. Mean PBI levels were 14 and 21 μg/100 ml; BEI 9 and 15 μg/100 ml; T_4-by-column 11 and 14 μg/100 ml; 24-hr ^{131}I uptake 49 and 70%; 24-hr $PB^{131}I$ conversion ratios 40 and 41%; thyro-binding index 0.81 and 0.93; TBG 17 and 20 μg/100 ml; antithyroglobulin titer less than 1:16. Potassium perchlorate discharge test was normal. Iodine metabolism studied in one subject revealed thyroid iodine clearance of 24 ml/min and renal clearance of 26 ml/min. Urinary iodide excretion was 294 μg/day, and $PB^{131}I$ was over 70% as T_4. The T_4 was identified on paper chromatography in 3 solvent systems. The free thyroxine level was 4.9 mμg/100 ml. An infant of 8 weeks had a mean PBI of 19.3 μg/100 ml, TBG of 15.8 μg/100 ml, and presumably also has the syndrome. Another sib had a mean PBI of 11 μg/100 ml. Two sibs and the parents are normal. A hypothesis is advanced suggesting the possibility of inhibition of thyroid hormone transport into tissue, or end-organ resistance to the hormone in view of the eumetabolic state of the subjects in the presence of high circulating levels of blood thyroxine and normal thyroxine binding capacity. (*J Clin Endocr* **27**: 279, 1967)

GOITER and hypothyroidism are often associated and are responsible for the recognition of five known inborn errors of thyroid metabolism (1). Each of these heritable thyroid anomalies presumably is caused by the inheritance of a recessive genetic factor interfering with a specific step in the thyroid hormone biosynthesis.

Deaf-mutism is also commonly associated with hypothyroidism. In fact, perceptive deafness is a constant finding in Pendred's syndrome. The presence of goiter in this syndrome is known to be caused by an inborn failure of the thyroid to organify iodide (2).

High PBI values in the presence of normal thyroid function have been recognized in families with abnormalities in the thyroxine binding globulin, a character transmitted as a simple mendelian dominant (3).

A single case of severe hypermetabolism of nonthyroid origin has been also described and was attributed to a defect in

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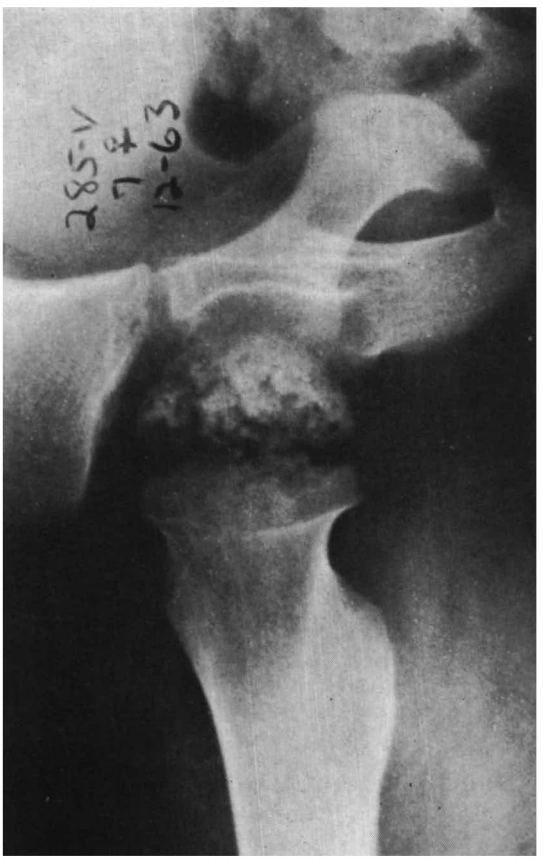


FIG. 1. Roentgenogram of the proximal end of the right femur of v.G. Mottled areas of increased density are present throughout the ossification centers of the head of the femur. The appearance is that of an epiphysis formed from multiple minute centers which have coalesced to a degree. The gross outline of the epiphysis is normal.

the mitochondrial enzyme organization, resulting in a severely lowered capacity for respiratory control (4).

This communication presents observations on a sibship with heritable thyroid, osseous and auditory abnormalities and which is euthyroid in spite of abnormally elevated PBI levels. Evidence suggests that the underlying problem is that of peripheral resistance to thyroid hormone action.

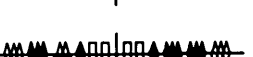
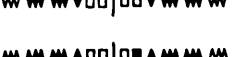
Case Presentation

Our attention was first attracted to the G. family when v.G., a 6-yr-old girl deaf from birth, was brought to another hospital for the care of minor injuries sustained in a car accident. Radiological skeletal survey disclosed stippling of the major secondary ossification centers, and the epiphyses appeared to have developed from multiple centers (Fig. 1). Epiphysial dysgenesis due to hypothyroidism was considered, even though clinically she did not appear cretinoid, and the thyroid gland was not found abnormal on palpation. She did not present symptoms or signs of hyper- or hypothyroidism. The PBI was recorded as 19.8 μg/100 ml and the BEI on another occasion 12.8 μg/100 ml. The serum cholesterol, calcium, phosphorus and alkaline phosphatase were within normal limits. The VDRL (Venereal Disease Research Laboratory) was nonreactive. Further inquiry in the family history revealed that an older brother (m.G.) was also deaf from birth. A radiological survey of the brother revealed similar stippling of the major secondary ossification centers. The PBI and BEI were 14.6 and 9.2 μg/100 ml, respectively. Contact with the family was lost until $2\frac{1}{2}$ yr later, when an effort was made to locate them for investigative purposes.

The subjects studied comprise the parents and 5 children. Preliminary studies on a newborn infant are included. Only members of one generation are affected; and there is no familial history of goiter, deafness, or other congenital abnormality in other generations on either the paternal or maternal sides. The affected generation is a product of a consanguineous union in which the father is also a second cousin to his children. Three other half-siblings, from a previous marriage of the mother, are normal (Fig. 2). All the children of the affected generation were born in southern California, where goiter is nonendemic. With the exception of the last child, who was prematurely born by cesarean section, they were products of full-term, uncomplicated pregnancies and deliveries, and appeared at birth normal in every respect. Their birth weights varied from $8\frac{1}{2}$ to 5 pounds (Table 1). Both parents are third generation Americans of Mexican extraction. The mother (J.G.) was born in Tempe and the father (G.G.) in Glendale, Arizona.

Only 2 of the children (m.G. and v.G.) present the complete syndrome of deaf-mutism, stippled epiphyses, goiter and abnormally high PBI. Past history and physical examination of the parents and 2 of the nonaffected siblings (e.G. and t.G.) are noncontributory so that detailed descriptions of these subjects will be omitted. During the time the study was done, the mother was in her last trimester of the pregnancy which later terminated in the induced premature birth of ma.G.

TABLE 1. Growth and development

SUBJECT	CHRONOLOGIC AGE (yrs)	TEETH	HEIGHT (inches)	WEIGHT (pounds)	BIRTH WEIGHT (lbs)	FIRST TOOTH (mos)	SAT UP (mos)	STOOD UP (mos)	WALKED (mos)	TALKED (mos)	STIPPLED EPIPHYSES	BONE AGE (according to ossification centers) PRIMARY	BONE AGE (according to ossification centers) SECONDARY
mG	12½		56½	80	6¼	8-9	12	14	20	mute	+	11yrs	9yrs 6mos
eG	10½		56	82½	8½	6	6	10	14	18	o	11yrs	11yrs
tG	9½		51¾	72½	7	6	6	10	12	18	o	9yrs	9yrs
vG	8½		45½	42	5	6	6	15	24	mute	+	6yrs 10mos	3yrs 6mos
lG	3½		35	28½	6½	4	6	9	12	18	o	22mos	22mos
maG	8wks		18½	7½	4½	o	o	o	o	o	-	normal newborn	

□- INCISOR, PERMANENT
■- INCISOR, DECIDUOUS
Δ - CANINE
M - PRE-MOLAR
MM - MOLAR

m.G. is a 12½-yr-old boy, 6¼ pounds at birth. His early development was somewhat delayed (Table 1), and deafness was noted during early infancy. Past medical history included measles, chickenpox, and tonsillectomy-adenoidectomy at the age of 6. His school record from Hyde Park School for deaf children classified him well above the average in general performance, intelligence and learning abilities. He was a well-developed boy with normal body proportions and normally erupted teeth for his age (Table 1). He was deaf-mute, able to enunciate only a few words, but alert and able to comprehend communication by gestures. He exhibited bird-like facies, pigeon breast and winged scapulae (Fig. 3). The thyroid gland was diffusely enlarged on palpation, estimated to be about 4 times the size of a normal gland. There was no thrill or bruit. Otoscopic examination was within normal limits. Except for the brisk Achilles tendon reflexes, there were no other stigmata suggestive of thyroid dysfunction. There was a full range of motion at all joints with no evidence of deformity.

v.G. is an 8½-yr-old girl, 5 pounds at birth. Deafness was observed during early infancy. Her early development was the slowest when compared to her siblings (Table 1), and her stature somewhat smaller. Except for being prone to many minor household accidents during early childhood, her record of previous illnesses is noncontributory. Although inferior to that of her brother (m.G.), her record from the school for deaf children ranged well within the average in general performance, intelligence and learning abilities.

She was a thin, small girl with normal body proportions, normally erupted teeth (Table 1), deaf-mute but alert, very active, and comprehending communication by gestures. She could not enunciate words but emitted squeaking sounds. The resemblance of her facial features to those of her brother was striking, for she exhibited the bird-like facies, pigeon breast and winged scapulae (Fig. 4). Her thyroid gland was also diffusely enlarged on palpation and estimated to be approximately 3 times the expected normal size. There was no bruit or thrill over the gland. The otoscopic examination was within normal limits. Again, brisk Achilles tendon reflexes, elevated pulse rate and probably slight hyperactivity were the sole physical findings compatible with possible hyperthyroidism. There was a full range of motion at all joints, with no evidence of deformity.

l.G. is a 3½-yr-old girl and was the youngest of

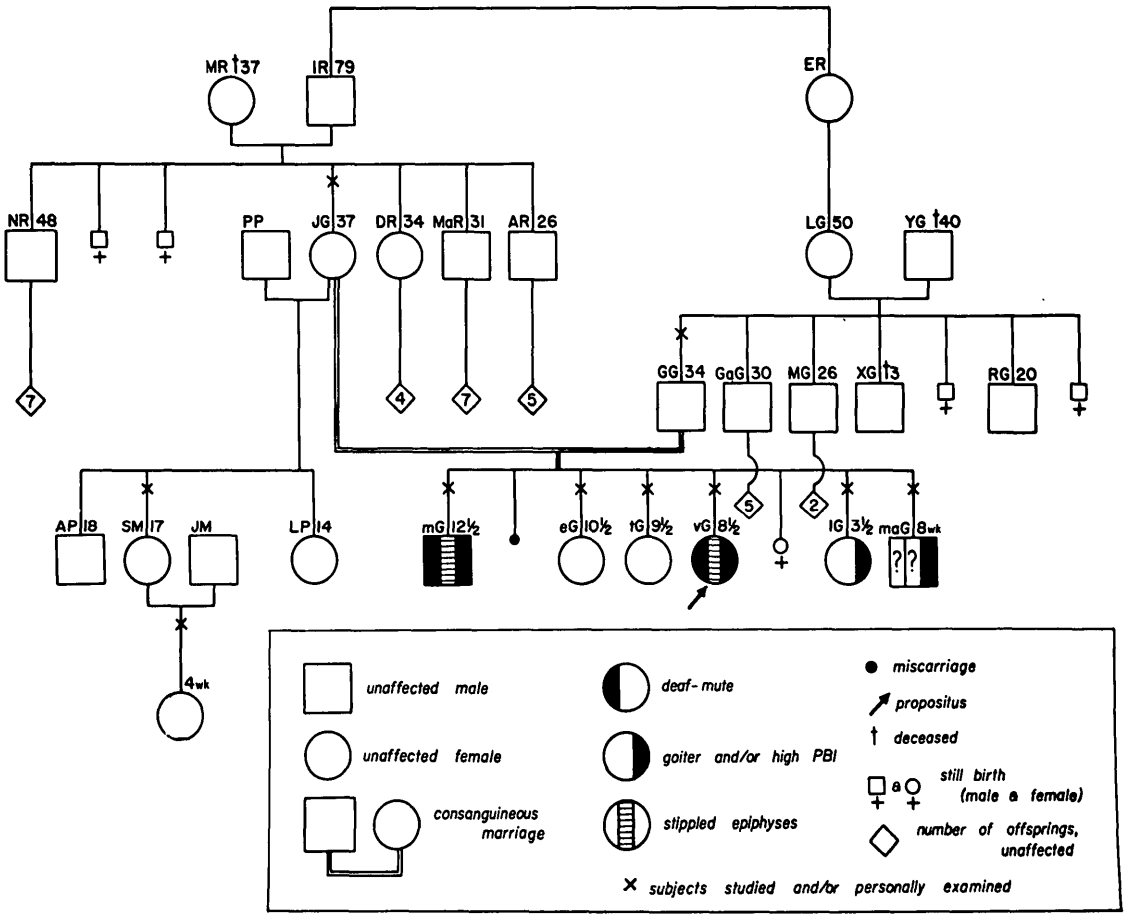


FIG. 2. Pedigree of family G. Initials and age are given above each symbol.

the siblings at the time of the study. Although her birth weight was 6½ pounds, her early development was very rapid, so that by the age of 1½ she could talk and make 3-word sentences. Her past medical history is noncontributory. She was a well-developed and proportioned child, speaking English and Spanish fluently. The teeth were normal. Her facial features had no resemblance to those of v.G. or m.G. and exhibited the normal broad nose, large eyes, high and broad cheek bones and round facies which characterize the parents and the 2 other normal siblings (t.G. and e.G. [Fig. 5]). Her thyroid was only slightly enlarged, smooth, and without audible bruit. Except for a rapid pulse rate accompanying a slight degree of apprehension, her physical examination was within normal limits.

ma.G. was born at the Los Angeles County General Hospital after the completion of the major part of this study. During the third trimester of pregnancy, the mother developed pre-eclampsia; and induction of labor was attempted in the 38th week of gestation by artificial rupturing of membranes. Labor was terminated by cesarean section. At birth this premature baby weighed 4 pounds 8 ounces and measured 17½ inches in length. He was kept in the hospital's nursery for 10 days and was discharged apparently in good health.

About 6 weeks after discharge, the infant was readmitted because of labored breathing accompanied by stridor. On this admission he weighed 7 pounds 4 ounces, his breathing was stridorous, associated with sternal retraction and tachycardia varying in rate between 220 and 140 beats/min. The infant was active, could raise his head from a ventral decubitus position, and turn it from side to side. The stridor varied in severity during the day. The thyroid was nonpalpable, and his temperature was normal.

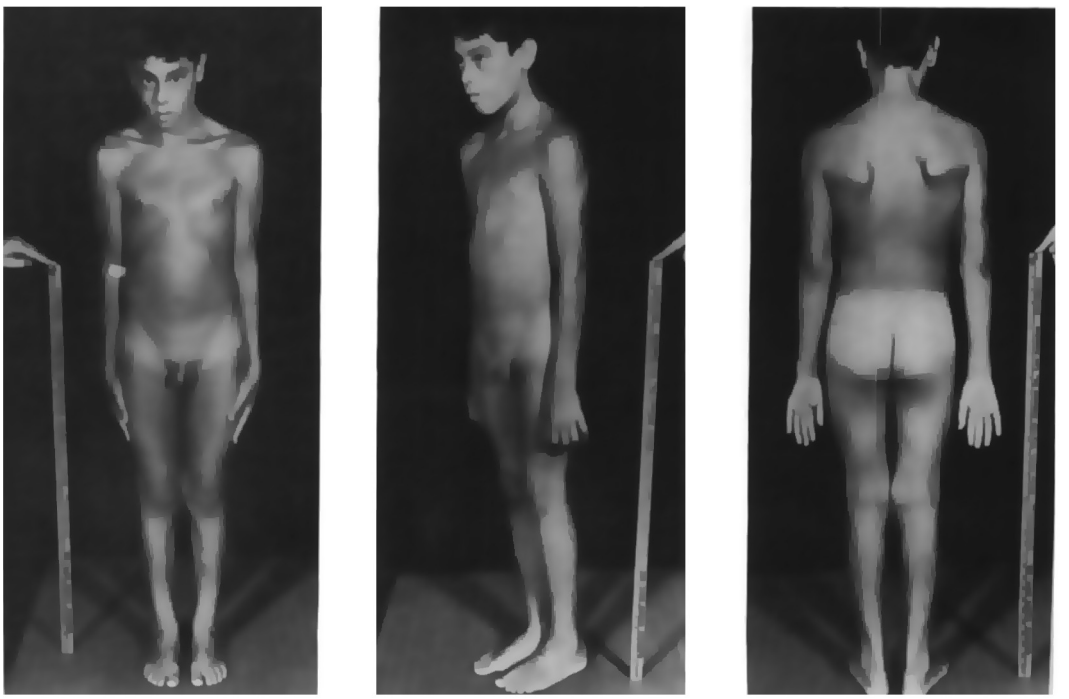


FIG. 3. m.G., 12½-yr-old boy, illustrating the body features described in the text, including bird-like facies, pigeon breast and winged scapulae.

Laboratory data obtained during this admission are listed in Table 2. Additional studies included a WBC of 12,000/mm³ with normal differential. Blood sugar, BUN, potassium, sodium and carbon dioxide were within normal limits. The chest x-ray was normal. Lumbar puncture, upper gastro-intestinal series and EEG yielded no positive results. Thyroid scan revealed a gland normal in size, location and uniformity of radioiodine distribution.

On direct laryngoscopy the vocal cords were not visualized, and it was the impression of the consulting otorhinolaryngologist that the infant suffered from laryngomalacia. During the course of 22 days of hospitalization, he continued to gain weight and behaved normally except for a few short periods of intermittent stridor accompanied by tachycardia. He was discharged on no thyroid medication. During this hospitalization, the authors had the opportunity to see and examine this infant for the first time, and the lack of clinical evidence of hypo- or hyperthyroidism was confirmed.

Materials and Methods

Data for the completion of the growth and development curves (Fig. 6) and Table 1 were obtained from school records and hospital charts. The growth curves were compared to standard curves based on Bayley's measurements of 300 healthy California children (5). The adult height was predicted using Bayley and Pinneau's Height Prediction Tables (6) based on the system relating the child's skeletal age to the proportion of his adult stature achieved. The bone x-rays were read by Richard R. Schreiber, M.D., of the Los Angeles Orthopedic Hospital, and the skeletal age was computed using the 1950 Greulich-Pyle standards (7).

The PBI was determined by the Barker dry ash method (8) and the BEI by a method combining Barker's dry ashing technique with Man's butanol extraction method (9) as described by Klein and Chernaik (10). The serum thyroxine level was determined by Bio-Science Laboratories, California, using the "T_4-by-column" method of Pileggi *et al.* (11).

The resin uptake of ^{131}I-triiodothyronine was determined by the method described by Scholer (12) using resin prelabeled by ^{131}I-L-triiodothyronine and expressed as thyro-binding index of the plasma.

The 24-hr plasma PB^{131}I conversion ratio was determined concomitantly with the 24-hr ^{131}I uptake using 3 ml of plasma aliquots trans-

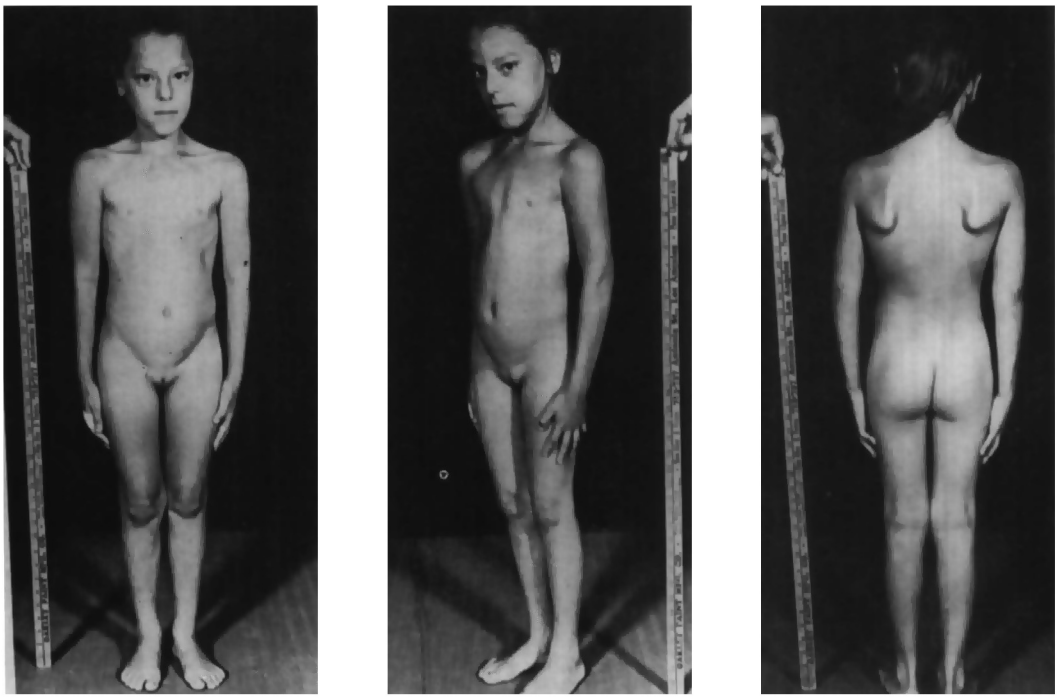


FIG. 4. v.G., 8½-yr-old girl, illustrating the body features described in the text, including slightly retarded growth, bird-like facies, pigeon breast and winged scapulae. Note striking resemblance to brother (m.G.).

ported through an ion exchange resin (Amberlite IRA 400) column by gravity to remove the inorganic ^{131}I. The $PB^{131}I$ ratio is expressed in percentage of the proportion of ^{131}I present in the plasma in organic combination as compared to the total ^{131}I present in the plasma.

The capacity to organify inorganic iodine in the thyroid gland was evaluated in one of the subjects (v.G.) by determination of the ^{131}I uptake prior to and 1 hr after the administration of 2 g of potassium perchlorate. The perchlorate was given 2 hr after administration of the tracer dose of ^{131}I.

Quantitative data of the metabolism of iodine and the secretion of thyroid hormone were obtained from one sibling (m.G.). For the iodine kinetic study 200 μc of $Na^{125}I$ and 2 μc of $Na^{131}I$ were given intravenously on August 7, 1965. Serial determinations were made of the thyroid isotope uptake (^{131}I), serum and urine isotope content (^{125}I), and serum and urine stable iodine content over a period of 9 days. The determinations were made and the rate constants, clearances and pool sizes were calculated as described previously (13). During this period the patient remained at home and consumed the regular family diet. Single dimensional chromatographs were run on all serum and urine samples collected. The labeled components present in the thyroxine zone of the above-mentioned chromatographs in the butanol-acetic acid, butanol-ethanol-ammonia or collidine-water systems were eluted in ethanol-ammonia and re-run in alternate systems.

The amount of thyroxine-binding globulin (TBG), measured in terms of its thyroxine-binding capacity, was determined by Bio-Science Laboratories in Los Angeles using an adaptation of the standard Durrum type cell for reverse-flow paper electrophoresis (14). The antithyroglobulin titers were determined by the same laboratory using tanned sensitized sheep erythrocytes (15).

It was not possible to obtain BMRs on the children, due to their apprehension and our inability to communicate directions.

Results and Interpretation

On clinical grounds all affected siblings appeared to be in a euthyroid state. Review of past medical records since birth are devoid of any clear-cut evidence suggesting clinical hyper- or hypothyroidism.

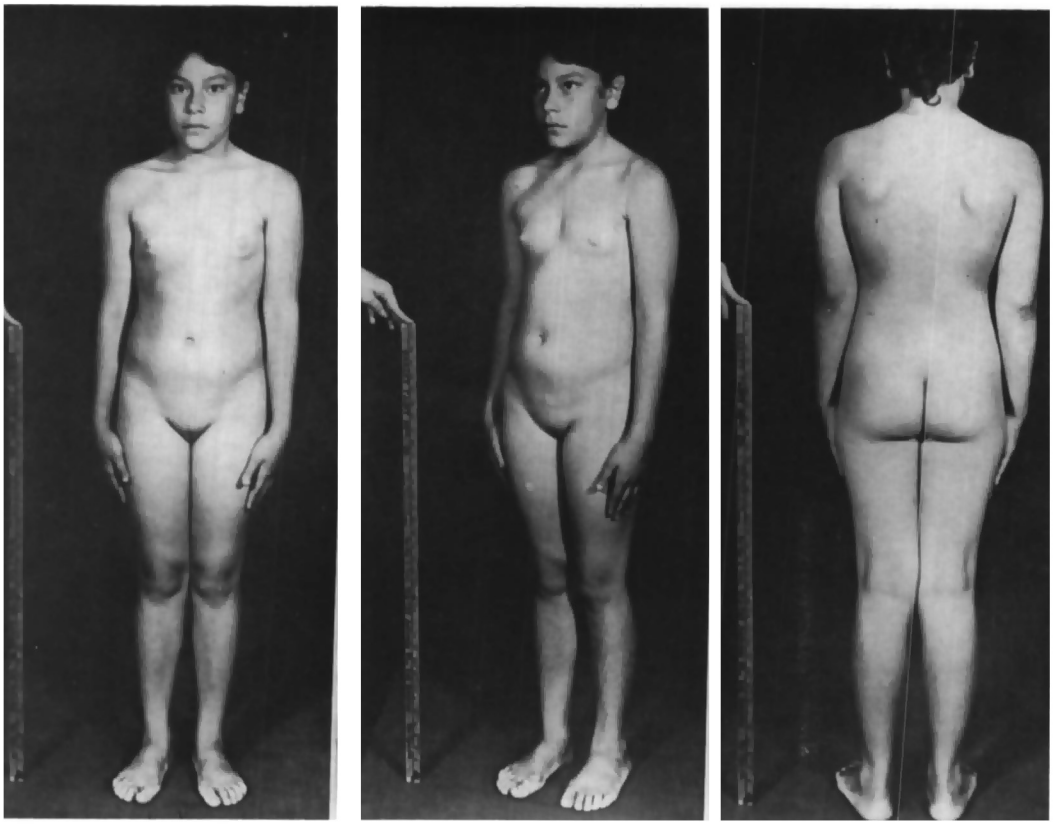


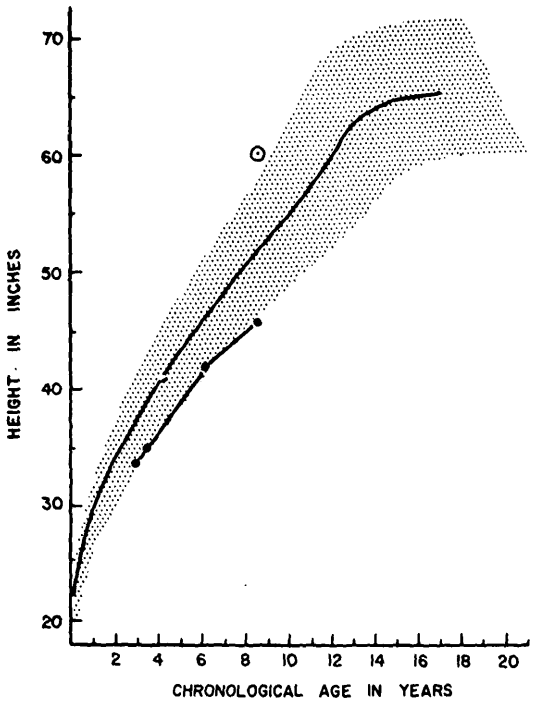
FIG. 5. e.G., 10½-yr-old girl, illustrating the normal body and facial features which also characterize her parents and normal siblings.

A. The possibility of hypothyroidism was raised on the following grounds:

1. *Retarded growth of m.G. and v.G.* Their growth curves (Fig. 6) are, however, uniform and follow the same channel throughout the years, suggesting that no drastic changes in their thyroid status has occurred. The slight disparity in the direction of the weight curve as compared to the height curve of m.G. reflects the normal tendency of children to put on extra weight during the prepubertal period of life (5). On the other hand, the predicted adult heights of 60 inches for v.G. and 68 inches for m.G. are well within the normal limits when compared to the mean parental stature of 65 inches. The apparent retarded growth is of even less significance when taking into consideration the well-known limitations in the use of North American standards for body size and physical development when applied to populations of foreign origin (16).

2. *Discrepancy between the chronological and skeletal ages with delay in bone maturation of m.G., v.G. and l.G.* This retarded bone development is associated in m.G. and v.G. with the x-ray appearance of stippled epiphyses (Fig. 1, 7). Curiously enough, in none of the subjects studied is there delay in dental development (Table 1), whereas retarded bone development secondary to hypothyroidism is, as a rule, associated with delayed dentition.

Abnormalities of epiphysial ossification are known to occur in hypothyroidism and were first recorded by Läwen (17) in 1909. Stippling of the epiphyses can also occur in achondroplasia, aseptic necrosis of the epiphyses, Legg-Calvé-Perthes' disease, syphilis, osteochondrodystrophies (such as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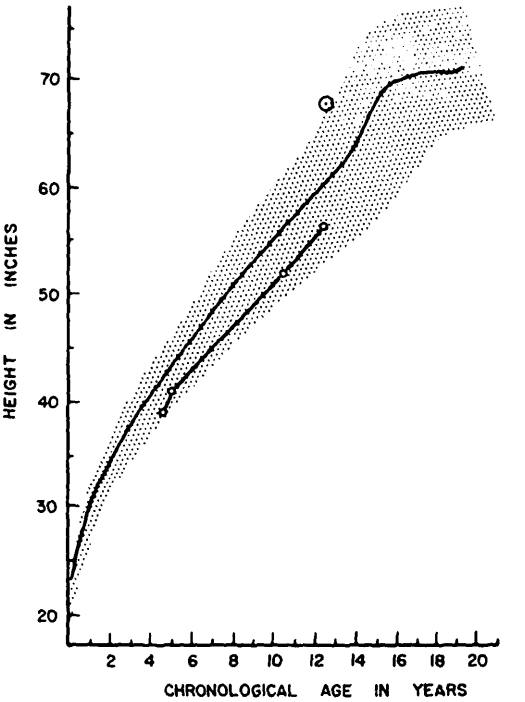
CHRONOLOGICAL AGE IN YEARS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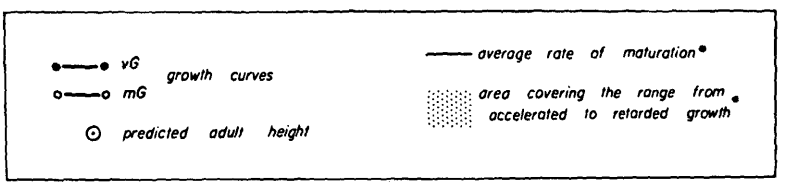
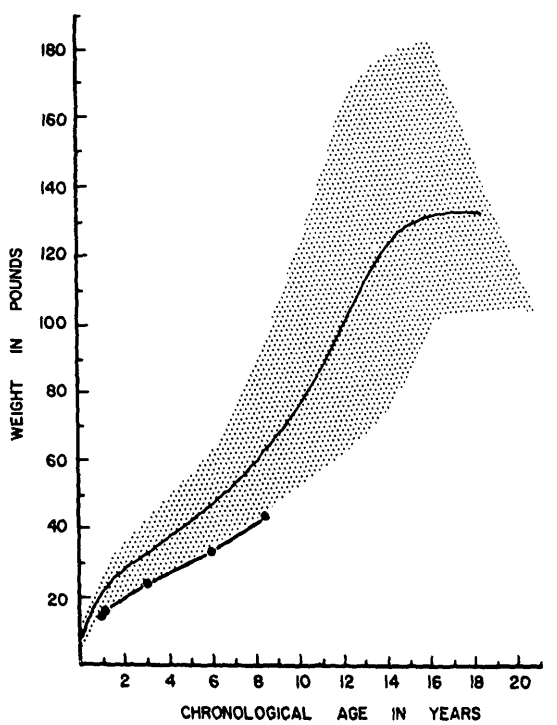

vG
mG
growth curves
predicted adult height
average rate of maturation*
area covering the range from accelerated to retarded growth


WEIGHT IN POUNDS
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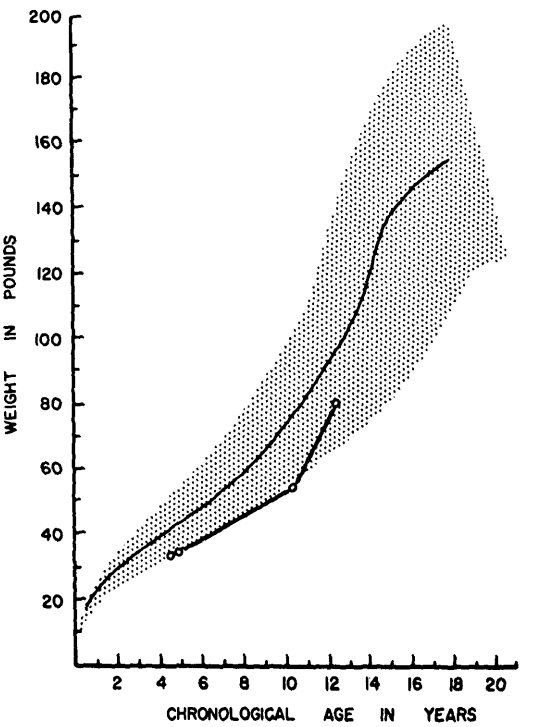
CHRONOLOGICAL AGE IN YEARS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CHRONOLOGICAL AGE IN YEARS

TABLE 2. Laboratory data

Test	Normal ranges	J.G. Mother	G.G. Father	m.G.	e.G.	t.G.	v.G.	l.G.	ma.G.*
Calcium, mEq/liter	4.5–5.5	4.5	—	5.1	5.0	5.3	5.2	5.0	5.2
Phosphorus, mEq/liter									
Adults	2.5–5.5	3.3	—	5.0	5.0	4.9	5.2	5.2	6.0
Children	4–7								
Alkaline phosphatase, Bessy-Lowry units									
Adults	<2.5	2.7	—	6.7	4.1	5.4	5.1	4.5	8.0
Children	<7								
Cholesterol, mg/100 ml	130–250	298	242	232	197	212	146	212	—
PBI, μg/100 ml									
Mean	4–8	7.4	5.7	14.0	7.2	8.1	20.8	11.0	19.3
Range		(8.1–6.6)	—	(15.0–11.7)	(8.0–6.5)	(8.6–7.6)	(30.0–12.7)	(12.0–9.9)	(25–15.0)
BEI, μg/100 ml	3.2–6.4	—	—	9.2	5.3	5.8	14.8	8.0	—
T_4-by-column, μg/100 ml	3–7	5.9	6.9	11.2	5.3	6.9	14.0	7.8	15.8
^{131}I uptake, %									
6 hr		12	—	28	17	14	62	27	—
24 hr	20–50	14	22	49	15	22	70	24	51‡
24-hr conversion ratio, % plasma PB^{131}I	13–40	59.5	—	41.1	21.9	29.8	39.8†	34.8†	—
T_3 uptake (thyro-binding index)	0.86–1.20	1.22	1.01	0.81	0.88	0.94	0.93	1.01	11.4§
TBG, μg/100 ml as T_4	12–20	30.8	10.1	16.9	14.8	16.7	20.0	20.2	15.4
Antithyroglobulin titer	less than 1:32	—	—	<1:16	—	—	<1:16	—	<1:16

* All laboratory data on ma.G. were obtained through the courtesy of the Los Angeles General County Hospital.
† The amount of plasma obtained for these determinations was smaller than the standard used in our laboratory.
‡ This value does not take into account a possible loss of ^{131}I from regurgitation 1 hr after ingestion of the tracer dose.
§ Different method was used for this determination (Bio-Science, Los Angeles), with a normal range of 10.3–14.3%.

Hurler's and Morquio's disease), dysplasia epiphysialis multiplex, and as a separate entity first described by Conradi (18) in 1914 under the name "chondrodystrophia foetalis hypoplastica." Although many authors claim that the diagnosis of "congenital stippled epiphyses disease" can be easily made on radiological grounds alone (19), Reilly and Smyth (20) questioned the existence of this as a separate entity, suggesting that an earlier worker (21) failed to recognize the thyroid disturbance associated with the bone abnormality. By treatment with thyroid hormone they succeeded in accelerating ossification, with subsequent disappearance of the stippling. Wilkins (22) states that he has never seen unquestioned epiphysial dysgenesis in any condition except hypothyroidism. Nevertheless, case reports describing this bone abnormality as a congenital disease not associated with endocrine disturbance continue to appear (23–29).

In favor of considering stippled epiphyses as a separate disease entity, genetically transmitted as a mendelian recessive, is the common association of bilateral congenital cataracts in half the cases (28), contractures with deformity of the involved joints, congenital heart diseases, and gross morphological anomalies of the extremities. Also, in the congenital stippled epiphyses syndrome, deposition of discrete, punctate calcific densities in the region of the developing epiphyses is premature and present before the normal time of appearance of the ossification centers (29). This finding contrasts with the usual picture of delayed bony development and ossification of hypothyroidism. No abnormalities of thyroid or of calcium and phosphorus metabolism have been described to date in this

FIG. 6. Growth curves of height by age (top) and weight by age (bottom) for v.G. (left) and m.G. (right). The normal range is according to Bayley's measurements (5).

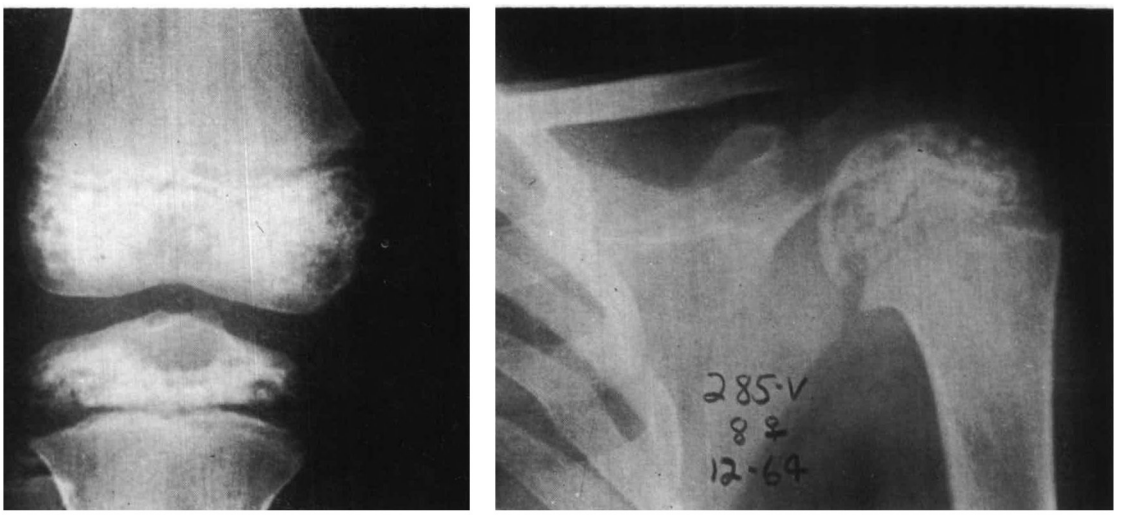

FIG. 7. Roentgenogram of the right knee and left humerus of v.G., disclosing stippled epiphyses except for bone immediately beneath the articular cartilage.

syndrome. Death in infancy is frequent in the severe form of this bone disorder, and in the few reported follow ups of mildly affected children the stippling has regressed by the fourth year of life. Shortening and/or other gross deformities of the limbs are common in the cases which survived infancy. In a detailed analysis of the congenital stippled epiphyses syndrome, Silverman (30) suggested that this is only a more severe neonatal form of dysplasia epiphysialis multiplex. In the present cases it cannot as yet be determined whether the osseous anomalies are due to mild (and possibly earlier) hypothyroidism or to a separate process.

3. *Congenital deafness.* Deafness was observed early in infancy and is undoubtedly the primary cause for the mutism of m.G. and v.G. since no evidence of mental retardation was found on psychological evaluation. The deafness, as in cases of Pendred's syndrome (see below), is bilateral and symmetrical, of perceptive type, and more marked in the higher frequency tones (Fig. 8).

Congenital deaf-mutism is known to constitute a part of at least 27 known syndromes (31). In Pendred's syndrome it exists as perceptive deafness associated with goiter, with or without hypothyroidism, and is inherited as a simple recessive

TABLE 3. Iodide kinetic study data

Determination	m.G.	Average of 4 control subjects
Iodide space (liters)	20	22.9
Iodide space (% body weight)	55	38.6
Thyroid clearance (ml/min)	24	10.2
Renal clearance (ml/min)	26	26.4
Plasma iodide disappearance rate (fraction/hr)	0.216	0.124
Theoretical maximum thyroid uptake (%)	50	29
Protein-bound iodine (μg/100 ml)	14.5	6.2
Plasma iodide (μg/100 ml)	0.78	0.35
Urinary iodine excretion (μg/24 hr)	294	128
Thyroid iodine release rate constant (fraction/day)	0.0045	0.009
Thyroid organic iodine content (μg)	80,000	10,690
Thyroid iodine secretion (μg/day)	368	130
Absolute iodine uptake (μg/day)		
From uptake data	294	54
From clearance data	275	71
From plasma iodide disappearance data	403	52

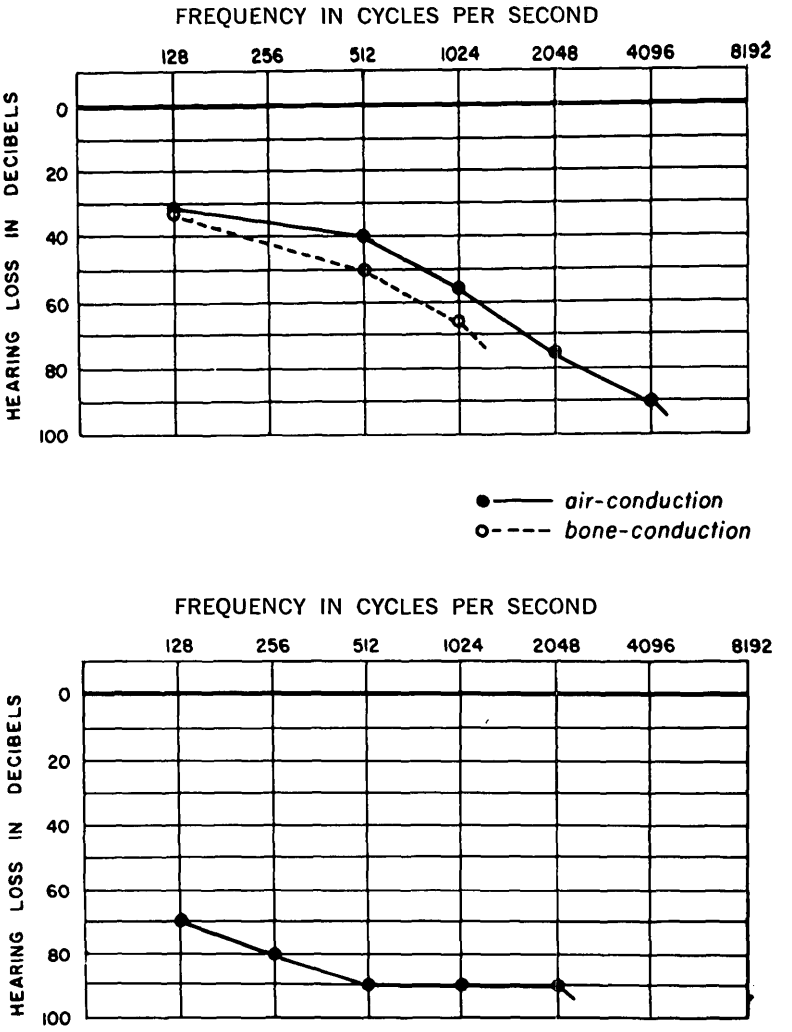

FIG. 8. Left ear pure tone audiograms of m.G. (top) and v.G. (bottom). Similar audiograms were recorded from the right ear, both demonstrating inner ear deafness, most prominent in the high frequency tones. In the case of v.G. no vestiges of bone conduction could be demonstrated.

trait (32). Although the subjects described were deaf from birth, with the goiters dating from middle childhood, deafness secondary to damage to the acoustic nerve from hypothyroidism *in utero* is not excluded (33). Another entirely speculative hypothesis advanced is the impairment of auditory function by toxic substances produced through an aberrant metabolic pathway (34).

A feature in many recently reported cases of Pendred's syndrome (32, 35–37) is early discharge of the tracer dose of radioiodine upon administration of perchlorate of thiocyanate. Thus, the goiter probably results from inability to organify trapped iodine at a normal rate. In 1964, Hollander (38) reported a case of congenital deafness and goiter, demonstrating a possible partial defect in the condensation of iodotyrosines.

The relation of the deafness to the abovementioned two metabolic defects has not yet been clarified, and no chromosomal abnormalities have been established (2). Deafness in congenital and endemic cretinism is typically associated with mental retardation.

All other laboratory findings were incompatible with the diagnosis of hypothyroidism. The normal elevation of the alkaline phosphatase levels for this age

group further substantiates the unlikelihood of a hypothyroid state (39).

B. The possibility of hyperthyroidism was entertained on the basis of the following clinical and laboratory findings:

1. *Rapid heart rate of v.G. and l.G.* (112 and 120 beats/min, respectively). This finding was not shared by m.G., whose heart rate was 72 beats/min and who certainly in all other respects is as severely affected as his sister, v.G. The interest of v.G. in her surroundings during her visits at the hospital and her associated physical overactivity are common occurrences in deaf-mute children and probably account for the mildly elevated heart rate. The rapid heart rate of baby ma.G. was due to respiratory distress, and subsequent normal heart rates during sleep are well documented.

2. *The half relaxation time of the Achilles tendon reflexes for m.G. and v.G.* were 215 and 240 msec, respectively. Considering 260 to 380 msec as the normal range, the above values fall within the hyperthyroid bracket. Unfortunately, this measurement is of no value in the diagnosis of hyperthyroidism and is of only limited assistance in the diagnosis of hypothyroidism (40).

3. *The mean PBI levels of m.G., v.G., and ma.G.* (14.0, 20.8 and 19.3 μg/100 ml, respectively) are unquestionably in the hyperthyroid range. l.G. also presents a high PBI level (Table 2). Those results have been confirmed on repeated determinations, and similar values were obtained from different laboratories. A single determination (Bio-Science Laboratories, California) of the free thyroxine level of m.G. was 4.9 mμg/100 ml (normal is 1.6–2.4 mμg/100 ml). High PBI levels have been documented in m.G. and v.G. for $2\frac{1}{2}$ years prior to conducting the present study. It is our belief that high PBI levels were present since birth. This is suggested since ma.G. had PBIs of greater than 25 and 18 μg/100 ml at the sixth week postpartum. The PBI of the mother during the last trimester of her gestation was 8.1 μg/100 ml, with no evidence of an exogenous source of contamination with organic iodine.

The BEI and T_4-by-column values merely follow and confirm the PBI values (Table 2). The gap between the PBI and BEI determinations in the same subject is somewhat larger than the normally expected 20%. This could be only partially explained by the presence of small amounts of circulating iodotyrosines as demonstrated by radiochromatographic studies.

High PBI levels without hyperthyroidism are known to occur as a consequence of an increase in the binding capacity for thyroxine of the thyroxine-binding globulins during pregnancy (41), as a result of estrogen therapy (42), in some women with metastatic breast cancer (43), and, more rarely, as familial idiopathic elevation of TBG (44) genetically transmitted as a simple mendelian dominant (3). A case of a mildly hypothyroid, goitrous girl with abnormally high PBI levels was reported by Werner *et al.* (45). The elevated PBI was due to the presence of large amounts of circulating iodotyrosines. On the basis of paper chromatography studies of the thyroid tissue digest, it was suggested that this abnormality was caused by a metabolic defect consisting of failure to couple iodotyrosines. Elevated PBI in eumetabolic individuals can also occur in the presence of abnormal iodinated serum proteins (46, 47). None of these explanations is appropriate in our cases.

4. *The 24-hour uptake of ^{131}I by the thyroid gland* falls within the hyperthyroid range in the case of v.G. (70%) and is borderline for m.G. and ma.G. (49 and 51%, respectively). There is no doubt that this finding is a reflection of a rapid iodine turnover within the gland. Scans of the neck in all subjects studied showed somewhat irregular distribution of radioiodine throughout symmetrical thyroid glands. The considerably larger size of the glands of m.G. and v.G. only confirms the initial clinical impression.

5. *The 24-hour plasma $PB^{131}I$ conversion ratio* of the mother (J. G.) was in the hyperthyroid range. That of v.G. was 39.8% and m.G. 41.1 and 43% on two separate determinations. Unfortunately, the amount of plasma used for the determination of the conversion ratio of v.G. and l.G. was insufficient, and the estimated results (Table 2) are of questionable accuracy. The high $PB^{131}I$ conversion ratio of the mother is unexplained but may be related to the accelerated rate of production of thyroid hormone by the fetus *in utero*. Indeed, shortly after birth the infant ma. G. demonstrated evidence of rapid iodine turnover.

6. *The thryo-binding index* is analogous to the T_3 uptake test. The index expresses in arbitrary units the thyroxine-binding power of plasma. The value of the standard pooled plasma is unity. The index is depressed in hyperthyroidism and raised in hypothyroidism. The results of this test fall within normal limits in all subjects except m.G., whose thyro-binding index is 0.81, slightly in the hyperthyroid range. That of the mother (J. G.), 1.22, reflects the elevated thyroxine-binding globulin level associated with her pregnancy.

C. *Other clinical studies.* The cholesterol levels of all subjects studied were normal. Electrocardiograms and chest and skull x-rays were all within normal limits except for the epiphysial dysgenesis apparent on the chest x-rays as described above. The serum protein electrophoretic pattern was normal in all subjects except the mother (J. G.), revealing a slight decrease in albumin (3.2 g/100 ml) and an increase in beta-globulin (1.4 g/100 ml).

The antithyroglobulin titer was determined in three subjects: m.G., v.G. and ma.G. All determinations were negative at 1:16 dilution with a normal of less than 1:32.

TBG was measured in all subjects (Table 2) and proved to be normal except for the pregnant mother (30.8 μg/100 ml as T_4). Such high TBG levels are a normal

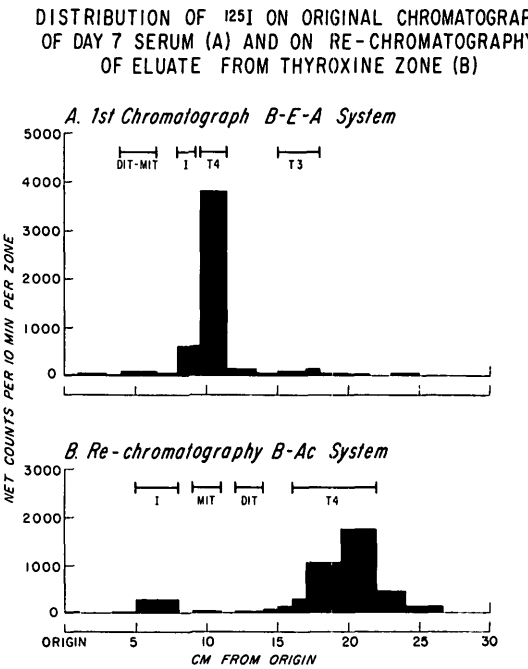

FIG. 9. Chromatography and re-chromatography of serum extract of endogenously ^{125}I-labeled compounds in m.G. B-E-A: butanol-ethanol-ammonia system; B-Ac: butanol-acetic acid system.

occurrence in pregnancy. Repeat TBG determination after delivery was 20.0 μg/100 ml as T_4.

In one of the affected subjects (v.G.) the ability of the thyroid gland to organify iodide was determined by repeating the ^{131}I uptake prior to and following the administration of potassium perchlorate. The thyroid gland failed to release the ^{131}I.

Chromosomal analyses on the blood of subject v.G. and the father (G. G.) were performed at the Children's Hospital of Los Angeles. It revealed a normal number of 46 chromosomes with a normal distribution within the groups A to G and no evidence of a consistent structural abnormality.

D. *Iodide kinetic study.* In order to obtain quantitative data on the metabolism of iodine and the secretion of thyroid hormone, an iodide kinetic study was performed on one of the affected subjects

(m.G.). The data of this study are given in Table 3. The distribution space of iodide was increased, thyroid iodide clearance from plasma was elevated, and renal clearance was normal. Serum isotope disappearance rate was augmented, and the thyroid uptake fraction was elevated. The protein-bound iodine again proved to be in the "thyrotoxic" range, and serum inorganic iodine was unusually high. The latter observation is presumably related to a high iodine intake if the observed urinary isotope excretion reflects the steady state iodine balance. The release rate of thyroid iodine was not accelerated, but, because of the enormous pool size, thyroid iodine release was well above the average of control subjects. Absolute iodine uptake, calculated by three methods, was high. Thyroidal release of nonhormonal iodine was indicated by the shape of the urinary isotope excretion curve and the 5-fold excess of observed urinary isotopic iodine excretion over the predicted value in the final day of the study (13).

Serum PB^{131}I at 48 hours (0.026% d/l) was normal, but conversion ratio (43%) is above the normal range. During days 3 to 9 from 10 to 20% of serum isotope was butanol insoluble. This is a normal value. During the study period there was a progressive increment in the proportion of plasma isotope migrating on chromotographs in the iodothyronine zones, and by day 7 thyroxine constituted 75% or more of plasma isotope. The thyroxine-triiodothyronine ratio was approximately 14:1.

In six studies utilizing two or three chromatographic systems in sequence, the major labeled component always moved in the thyroxine zone (Fig. 9). A small and variable portion of plasma isotope (0–9%) moved in the iodotyrosine zones.

Urinary isotope behaved on chromatography as iodide during the first 48 hours, but subsequently 3 to 7% of the isotope appeared in the MIT and DIT zones, and from 3 to 14% was present in the iodothyronine zones.

Discussion

Five types of defects in thyroid metabolism associated with goiter are widely accepted: inability of the thyroid to "trap" or accumulate iodide, inability of the thyroid to organify iodide, impaired dehalogenation of iodotyrosines, presence of abnormal iodoproteins, and inability to couple iodotyrosines. The demonstration of an adequate ^{131}I uptake, and the lack of discharge of the trapped iodide upon administration of perchlorate rules out the first two. The lack of rapid and spontaneous release of radioactivity from the thyroid gland after having reached a peak uptake, the absence of circulating abnormal iodoamino acids or iodoproteins, and the rather large amount of circulating thyroxine rule out the latter three types of thyroid dyshormonogeneses.

It should also be noted that most patients with inborn error of thyroid metabolism are either hypothyroid or, due to the presence of only partial defect, have achieved a eumetabolic state through a rapid turnover: a compensatory process mediated presumably through the thyro-pituitary axis. The occurrence of high PBI levels is due to the presence of precipitable iodine other than thyroxine and triiodothyronine. In the present study the kinetic data indicate that at least one of the subjects (m. G.) ingested a diet containing adequate iodine; that the thyroid accumulation of iodine was several times the normal level; that the thyroid concentrated and bound iodine adequately and, in fact, appeared to have established a remarkably high organic iodine store; that the gland secreted iodine at an excessive rate; and finally that the main secretory product was thyroxine, which was present in the circulation in abnormally high concentration. The fact remains that in the presence of high levels of circulating thyroxine our subjects at no time showed signs of hyperthyroidism. In fact, hypothyroidism was suggested on the basis of the x-ray findings

of the bones. The latter abnormalities could, however, be of genetic origin unrelated to the thyroid activity.

It may be considered that the children (m.G., v.G., ma.G.) have an unusual variant of thyrotoxicosis associated with deafmutism and abnormal bones from some other cause. This hypothesis requires that hypermetabolism has been present since birth in three of six siblings, and is associated with retarded bone age, steady growth, and normal alkaline phosphatase. If hyperthyroidism is present, it apparently exists without the typical cutaneous, neural and cardiac manifestations of the disease. It has been impossible to exclude this explanation, but our opinion is that the children are not hypermetabolic and are in some way resistant to their circulating thyroid hormone.

Three mechanisms were initially postulated to explain the resistance of peripheral tissues to the circulating thyroxine. First, the presence of an insufficient amount of free thyroxine due either to the presence of abnormally high levels of TBG or to the binding of thyroxine to another protein. However, TBG levels were found to be normal, and the possibility of abnormal sites for thyroxine binding is unlikely in the presence of a normal thyro-binding index.

Second, a stereochemical abnormality of the thyroxine molecule, otherwise undetected by the laboratory methods used but sufficient to render the circulating hormone relatively ineffective. Although possible on chemical grounds, such a theory is biologically remote.

Finally, inability of the hormone to pass from blood to cells or target organ refractoriness to thyroid hormone appears the most reasonable interpretation.

The relation of the deafness, facial, body and osseous abnormalities to the thyroid is unclear. Evidence so far considered does not exclude either a pleiotropic effect of the same abnormal gene, an associated heritable anomaly, or earlier hypothyroidism. The reason for the development of goiter is also unclear, except that the postulated end-organ refractoriness could be shared by the thyro-pituitary axis as well.

Further investigation including the performance of a long-term thyroxine suppression test and the clinical observation on the effect of administration of high doses of exogenous thyroxine are planned and might throw further light on the metabolic defect of this intriguing family.

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