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Hyperthyroidism in young female twins

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The first report of hyperthyroidism in twins was in 1851 (8) but it was a number of years before additional reports appeared in the literature. Neff (5) in 1932 cited the simultaneous development of hyperthyroidism in twin girls at the age of 8 years. In Neff's twins, physical development was normal at the time hyperthyroidism was diagnosed. Fife (2) described the development of diffuse toxic goiter in 22-year-old twin males. Further reference to thyrotoxicosis in twins has occurred in several genetic studies but clinical details have usually been meager or absent.

Although the effect of thyrotoxicosis on growth is generally thought to be one of acceleration Bloom (1) described retardation of stature occurring in a series of cases. In 1941, Hertz and Mainini (3) stated that in juvenile thyrotoxic patients, overgrowth occurs with such regularity that it can be considered one of the cardinal symptomatic manifestations of the disease. Records of growth were kept in 44 of the 62 cases reported by Reilly (6); 36 of his patients were taller than normal for chronologic age and showed marked acceleration of epiphyseal age. Reilly noted that increased growth was often apparent before the patient was clinically thyrotoxic. Talbot and Sobel (9) on the other hand, concluded that there is no consistent tendency to accelerated or delayed skeletal maturation in hyperthyroid children. Probably the differences of opinion arise from failure to distinguish between growth and maturation, or to appreciate the influence of duration of the disease as well as the age of onset. In this regard, McClintock, Frawley, and Holden (4) in 1956 found that accelerated growth and development occur only if the hyperthyroidism has existed for sufficient time (probably at least six months) and that those children who grow more rapidly during the period of hyperthyroidism do not as a group attain ultimate heights that are greater or less than the average. Wilkins (10) also found that, even though growth and osseous development are accelerated in hyperthyroidism, these are detected only when the hyperthyroid state has existed for a sufficient period of time.

The present report concerns the findings before and after treatment of hyperthyroidism in young twin sisters. These twins are very similar in appearance but definite evidence of their being genetically identical is lacking. It is of particular

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interest that hyperthyroidism was diagnosed at 2 1/2 years of age in one twin and at 7 1/2 years of age in the other. Thus, one twin was " normal " when the other became thyrotoxic. Furthermore, following therapy, the first twin to become thyrotoxic was euthyroid for over four years before thyrotoxicosis developed in the second.

Case reports

TWIN No. 1

At age 1 year, this patient was two pounds heavier and one inch taller than her sister, although birth weights had differed by only one ounce. Increased growth (Fig. 1) and nervousness occurred during the second year of life. The mother noted that the child's eyes became more prominent during the five months preceding her first hospital admission at age 2 years and 5 months. At that time, June 24, 1947, she was extremely irritable and hyperactive. There was definite exophthalmos as well as both coarse and fine tremors of the hands. She was considerably taller and heavier than her twin sister. The patient weighed 14.9 kg. The thyroid was diffusely enlarged. The pulse rate was 200 per minute. Roentgenographic studies of the wrists were reported as showing bone maturation of a 5 1/2-year-old child. Comparative roentgenograms of her twin's wrists revealed maturation consistent with the chronologic age.

Propylthiouracil therapy was initiated and on the seventh day a morbilliform rash appeared over the entire body and the temperature was elevated to 38.8° C. The propylthiouracil was then discontinued, with prompt disappearance of the rash and decrease of temperature. Between July 8, 1947 and July 16, 1947, the patient received roentgenotherapy consisting of approximately 1,200 r (air) to the thyroid region.

Transient improvement followed the radiation therapy, but symptoms soon recurred and were present for several weeks preceding the child's first examination at the University of California Hospitals in October 1949. At this admission, age 2 3/4 years, examination showed a pulse rate of 152 per minute, and a respiratory rate of 26 per minute. Her height was 100.2 cm. and weight 16.3 kg. She had a fine tremor of the hands with warm, moist skin. There was a marked stare with widening of the palpebral fissures and exophthalmos. The thyroid gland was enlarged symmetrically, firm, and without palpable nodules. Cardiac enlargement was present with the point of maximum intensity located between the midclavicular line and the anterior axillary line in the fifth intercostal space. A high-pitched systolic murmur was heard at the cardiac apex and in the left third interspace.

Laboratory studies showed a cholesterol of 80 mg. per 100 ml. and protein bound iodine (PBI) of 10.4 $\mu g.$ per cent. The thyroidal uptake of radioiodine was 60 per cent at three hours. (The upper limits of normal in this laboratory are 24, 30, and 45 per cent at three, five, and twenty-four hours, respectively). Roentgenographic studies were consistent with an epiphyseal age of 7 years (Fig. 2).

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Fig. 1. Photograph at age 15 months. Twin No. 1, left, already shows increased weight and stature, approximately one year before thyrotoxicosis was first diagnosed

The child was given an oral dose of 2.0 millicuries of radioactive iodine (I-131) on November 10, 1947. By December 15, 1957, there was considerable clinical improvement. She was less nervous and had a better appetite than prior to therapy. The tremor had disappeared. The pulse rate was 132 per minute and the blood pressure 164/90. The skin was pliable and warm. She was still exophthalmic without lid-lag. The thyroid gland was enlarged and firm with a thrill but no definite bruit.

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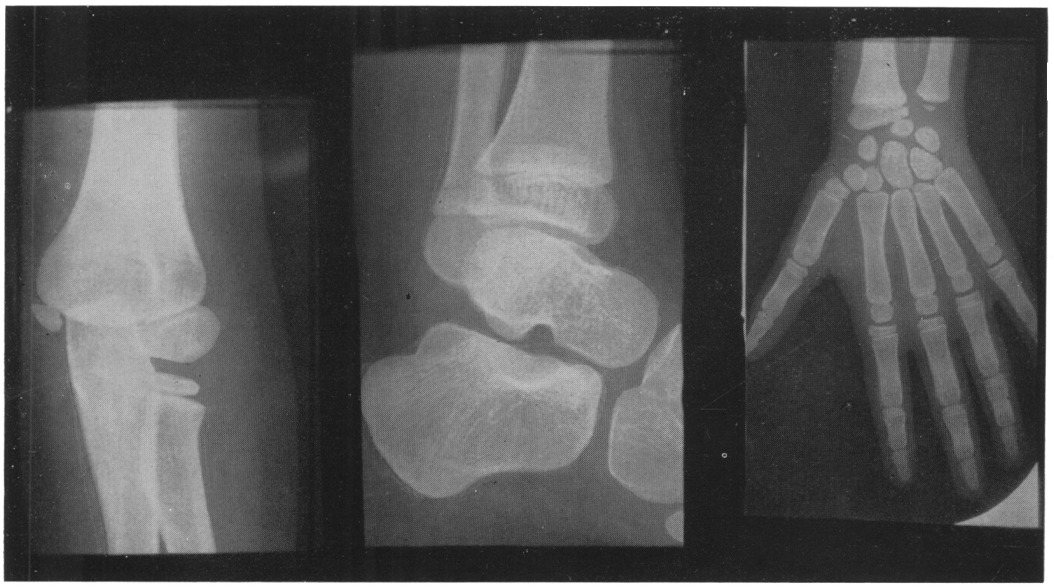

Fig. 2. Roentgenograms of Twin No. 1 at age of 2 3/4 years. Marked advancement in maturation consistent with that of 7 years

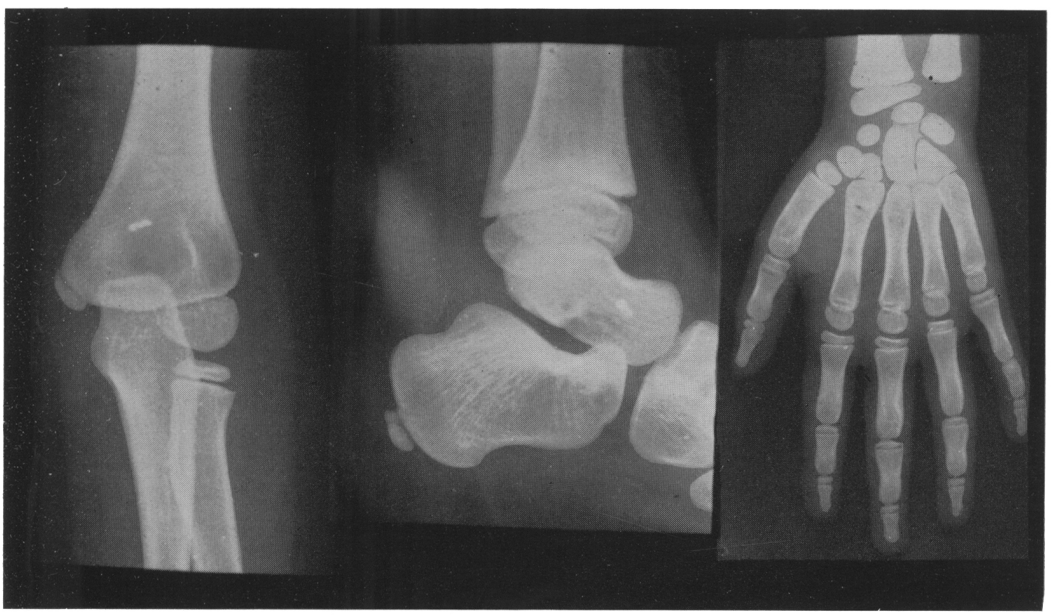

Fig. 3. Roentgenograms of Twin No. 1 at 4 1/2 years. Slight increased maturation in comparison with that at age 2 3/4 years (Fig. 2)

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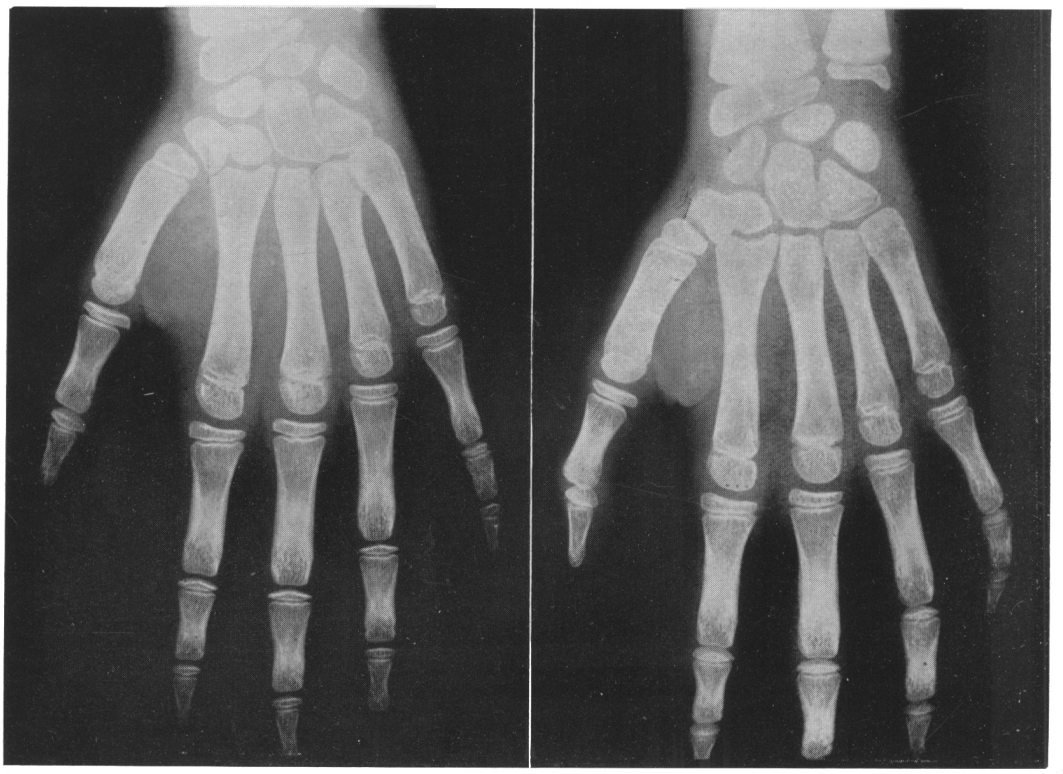

Fig. 4. Comparative roentgenographic studies of the hands and wrists of both twins at age of 7 1/2 years. Maturation nearly equal and consistent with chronologic age. Twin No. 1, left; Twin No. 2, right

Reflexes were physiological. The PBI was 10.2 *μg.* per cent, and the cholesterol was 171 mg. per cent. No further therapy was given.

Two months after the radioiodine therapy, the child was thought to be normal by the mother. She was only slightly irritable and was sleeping well, without medication. There were two or three bowel movements per day. Her appetite was slightly greater than the twin's. The pulse rate was 120 per minute with a blood pressure of 120/72. The height was 103 cm. and weight 17.9 kg. The skin was warm and moist. The eyes were unchanged. The thyroid gland was still slightly enlarged. Laboratory tests showed a PBI of 5.9 *μg.* per cent and a cholesterol of 233 mg. per 100 ml. It was the consensus of medical examiners that she was now euthyroid.

Roentgenographic studies for bone age taken at the age of 4 1/2 years (Fig. 3) showed little change in maturation compared to studies at 2 3/4 years of age. By age 7 years, bone maturation was consistent with the chronologic age (Fig. 4) and growth and development were nearly equal to twin sister (Fig. 5). Both growth

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and maturation have been normal and have corresponded with chronologic age since that time.

Beginning two months after I-131 treatment, this patient has been clinically euthyroid. PBI determinations have been in the midnormal range throughout the

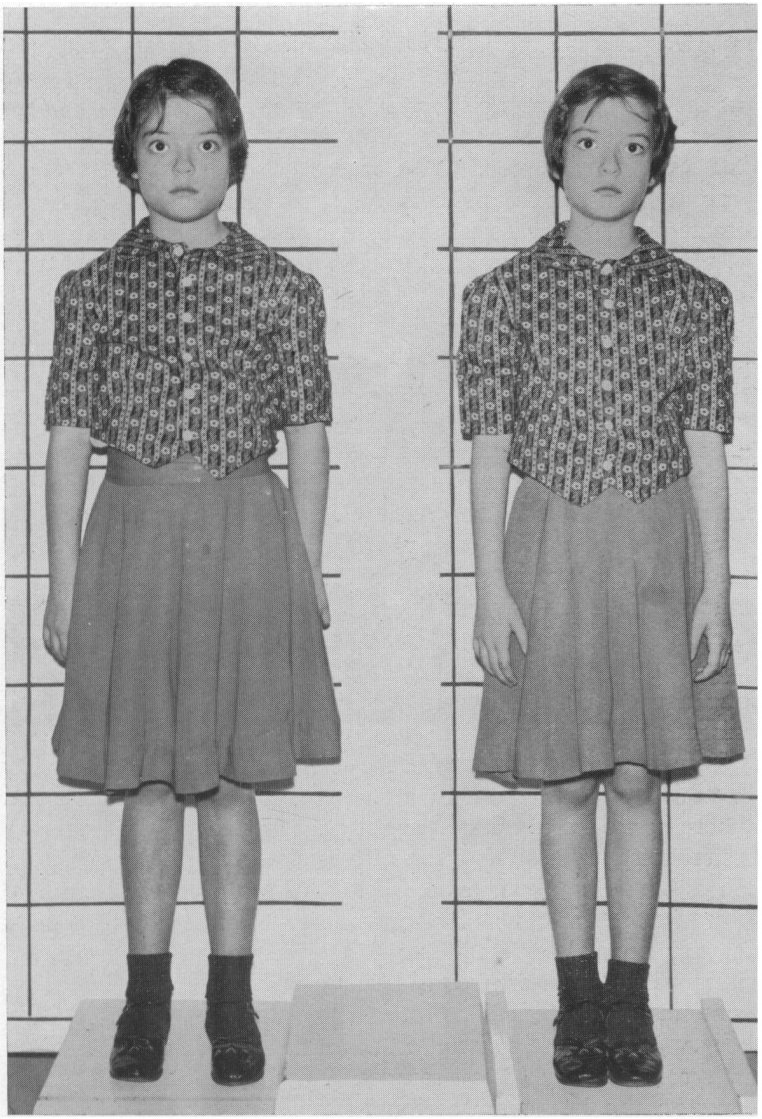

Fig. 5. Photograph of twins at age 7 1/2 years. Twin No. 1, left, was euthyroid at this time and Twin N. 2, right, was thyrotoxic

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post-treatment period. The thyroid gland has become and remained normal in size and consistency, and without nodularity, since the age of 7 years. The last examination was in August 1959.

TWIN N. 2

The second twin was observed periodically in conjunction with the twin reported above.

In 1949, at the age of 4 years 7 months, she was described by the mother as having in the preceding six to eight months a gradual increase in appetite, nervousness, irritability, and neck prominence. There were no other symptoms. The pulse rate was 126 per minute and the thyroid was questionably enlarged. There was no other sign of thyrotoxicosis. Laboratory studies revealed a cholesterol of 170 mg. and a PBI of 7.3 $\mu g.$ per cent. The thyroidal uptake of radioiodine was 13 per cent at three hours and 24 per cent at five hours. Roentgenographic studies for bone age (Fig. 6) revealed a level of approximately 6 years or slightly in advance of her chronologic age of 4 1/2 years. This twin was observed again two months later at which time she was entirely asymptomatic and apparently euthyroid. The thyroid gland was no longer considered enlarged.

When next studied, three years later at the age of 7 1/2 years, the child was the same height as her sister (127 cm.) but weighed 3.2 kg. less (24.1 kg.) (Fig. 5). Her pulse rate was 124 per minute. The patient's mother had noted definitely increasing nervousness and perspiration for the previous two to three months. The thyroid gland was enlarged approximately 50 per cent over the normal size for this age. There was a fine tremor with warm dry skin. The PBI was 9.9 $\mu g.$ per cent. The thyroid uptake of radioiodine was elevated with three, five, and twenty-four hour values of 32, 45, and 74 per cent, respectively. Roentgenograms of the wrists (Fig. 4) showed a bone age comparable with her chronologic age.

A diagnosis of toxic diffuse goiter was made; the history suggested that toxicity was only of about three months' duration. A therapeutic dose of 2.5 millicuries of I-131 was administered orally on July 1, 1952. By September 15, 1952 she was euthyroid. There had been a 3.6 kg. weight gain in the previous month. The thyroid gland was unchanged in size. The pulse rate was 78 per minute. The PBI was 3.7 $\mu g.$ per cent, with a basal metabolic rate (BMR) of minus 23 per cent. In December 1952, she showed no symptoms of abnormal thyroid activity. The thyroid gland was approximately normal in size. The BMR was minus 2 per cent. Slight exophthalmos was recorded. She was considered euthyroid.

This patient has been studied at intervals to August 1959 and development and maturation (Fig. 7) have been normal on all occasions. No further signs or symptoms of abnormal thyroid activity have occurred. The thyroid gland was normal in size and consistency on the last examination in 1959.

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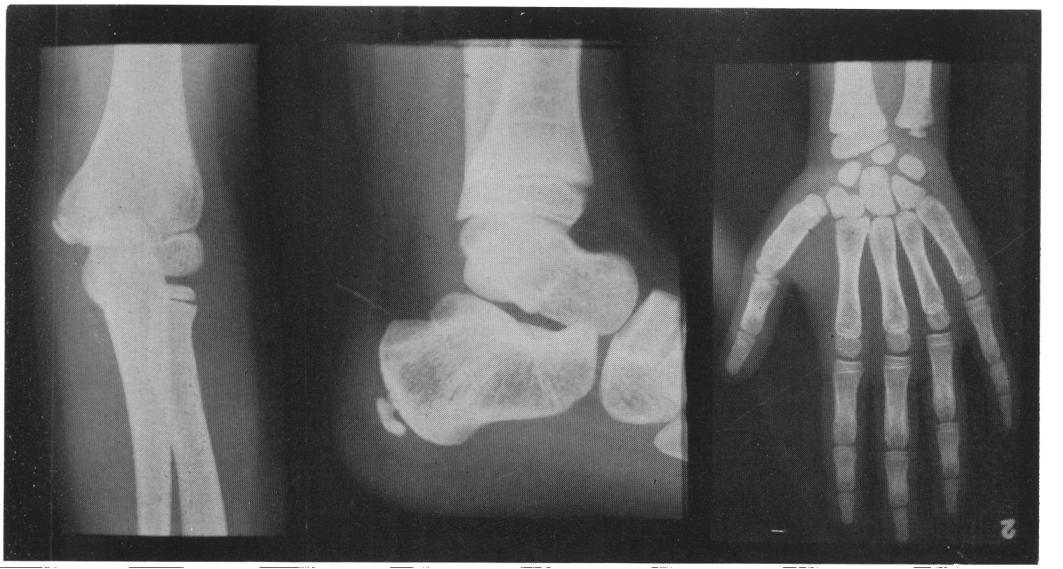

Fig. 6. Roentgenograms of Twin No. 2 at 4 1/2 years shows bone age slightly advanced for this chronologic level

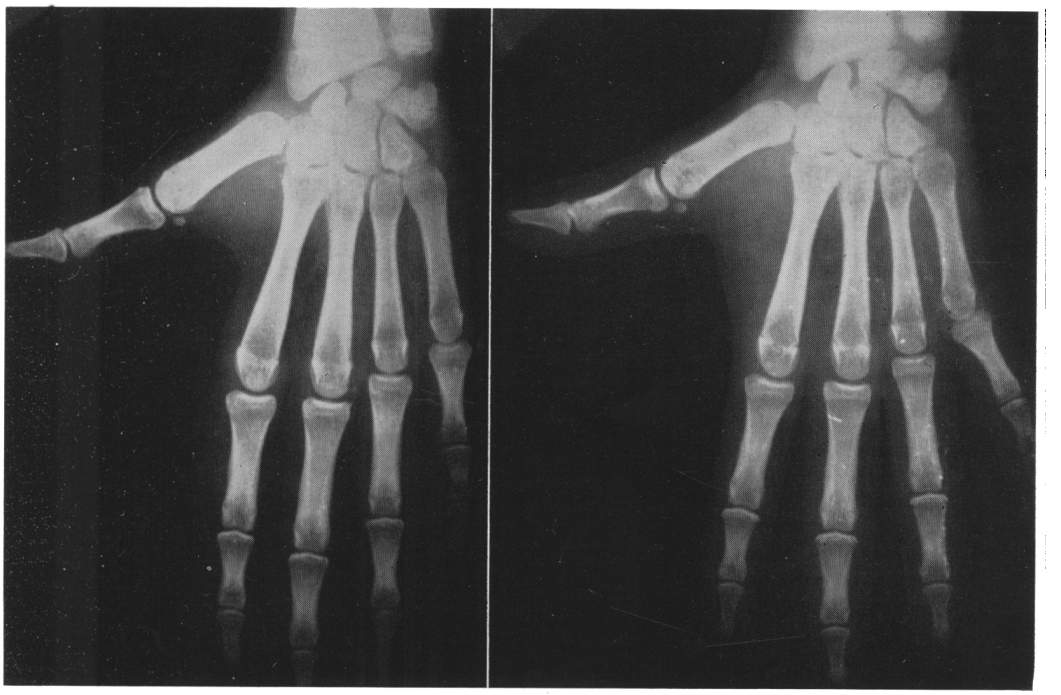

Fig. 7. Comparative roentgenograms of hands and wrists of the twins at age 12 1/2 years. Twin No. 1, left; Twin No. 2, right. Maturation level consistent with chronologic age

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Discussion

These twin sisters have provided an interesting study of the effects of thyrotoxicosis in children. The appearance of thyrotoxicity at an early age in the first twin provided an opportunity to study the effects of thyrotoxicosis, with the second twin as a " normal " control. In the first twin, the disease was undetected and uncontrolled for a relatively long time, and both maturation and growth were markedly advanced at the time of diagnosis. After therapy, bone maturation remained nearly static for five years by which time it had become consistent with the chronologic age of 7 1/2 years. Height and weight increased progressively but at a slower rate than in her twin sister, up to the age of approximately 4 1/2 years. After this age, the development in both girls was nearly equal. The lack of accelerated growth and maturation associated with thyrotoxicosis in the second twin seems most probably related to the shorter time interval between the initial signs and symptoms of thyrotoxicosis and the definitive therapy. However, the age at which thyrotoxicity developed may have played a part.

The clinical picture at the age of 15 years is that of normal development and maturation. The height, weight, physique, and activities are approximately the same in both twins. At re-evaluation in August 1959, there were no demonstrable adverse effects from the earlier thyrotoxicosis.

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RIASSUNTO

Quest'articolo discute gli effetti della tirotossicosi in bambini e descrive i cambiamenti verificatisi in due gemelle che svilupparono la tirotossicosi a età diverse. La prima fu trattata all'età di due anni e nove mesi ed aveva dimostrato uno sviluppo anormale prima del trattamento. Nella seconda, la funzione della tiroide e lo sviluppo furono normali fino all'apparizione della tirotossicosi all'età di sette anni e mezzo. Dopo il controllo della tirotossicosi nella prima gemella, lo sviluppo e la maturazione delle ossa diminuirono sensibilmente fino all'età di cinque anni, al qual tempo le due gemelle erano quasi eguali. La tirotossicosi fu trattata prontamente nella seconda gemella, la quale non presentò un aumento di sviluppo coll'aumento della funzione della tiroide. Entrambe erano normali per quanto riguarda la funzione della tiroide ed erano egualmente sviluppate quando furono esaminate all'età di quattordici anni e mezzo.

RÉSUMÉ

Cet article traite des effets de la thyrotoxicose chez les enfants et décrit les changements se produisant chez des jumelles qui développèrent la thyrotoxicose à d'âges différents. La première de ces jumelles fut traitée à l'âge de deux ans et neuf mois, et montre des altérations de maturité et de développement antérieures au traitement. Chez la seconde jumelle la fonction thyroïdienne, aussi bien que le développement et la maturation étaient normaux jusqu'à l'apparition de la thyrotoxicose à l'âge de 7 ans et demi. Après le contrôle de la thyrotoxicose chez la première jumelle, son développement et la maturation des os diminuèrent d'une façon remarquable jusque près de cinq ans, âge auquel les deux jumelles étaient presque égales. La thyrotoxicose fut rapidement contrôlée chez la seconde jumelle qui ne présente pas d'augmentation de développement avec l'hyperfonction de la thyroïde. Les jumelles étaient normales en ce qui concerne la fonction de la thyroïde et également développées lorsqu'elles furent examinées à l'âge de 14 ans et demi.

ZUSAMMENFASSUNG

Kindliche Thyreotoxikose und die Beobachtungen an einem Paar weiblicher Zwillinge werden diskutiert. Einer der Zwillinge zeigte abnorme Reifungs- und Wachstumsbeschleunigung, als sie im Alter von 2, 3/4 Jahren behandelt wurde. Schilddrüsenfunktion, Wachstum, und Reifung des zweiten Zwillings waren bis zur Zeit der klinischen Manifestation der Thyreotoxikose im Alter von 7, 1/2 Jahren normal. Knochenreifung und Wachstum des ersten Zwillings waren nach der Behandlung deutlich verlangsam und im Alter von 5 Jahren waren die Zwillinge in dieser Hinsicht fast gleich. Als die Thyreotoxicose sich manifestierte, wurde sofort die zweite Zwillingsschwester behandelt, die keine Wachstumsbeschleunigung zeigte. Im Alter von 14, 1/2 Jahren war die Schilddrüsenfunktion beider Zwillinge normal und sie zeigten keine Unterschiede in Grösse und allgemeiner Entwicklung.

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