

# THYROID TODAY

Editor: J. H. Oppenheimer, M.D.

Volume 4, Number 1

January/February, 1981

## HYPERTHYROIDISM CAUSED BY TROPHOBLASTIC TUMORS



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Trophoblastic hyperthyroidism is the condition of clinical hyperthyroidism in patients with trophoblastic tumors, either benign hydatidiform moles (Figure 1) or malignant choriocarcinoma or one of its variants. Hydatidiform mole occurs in about one per 2000 pregnancies in the United States and is 10 times more frequent in Asian countries. Choriocarcinoma occurs in only one per 60,000 pregnancies; about 40% of cases follow hydatidiform moles. In men, choriocarcinoma or its variants comprises about 3% of malignant testicular tumors. The precise prevalence of hyperthyroidism in patients with these uncommon disorders is unknown. Although increased thyroid function is probably common, hyperthyroidism which is severe and easily recognized probably occurs in only a small minority of patients and is most likely seen in women with large trophoblastic tumors and very high levels of human chorionic gonadotropin (HCG).

In 1955, Tisné and his colleagues in South America found that thyroid uptakes of radioiodine were very high in three women with hydatidiform mole, and that one of these women had clinical hyperthyroidism which disappeared within a few days after delivery of the mole.<sup>1</sup> Dowling and associates reported laboratory evidence of increased thyroid function in three women with moles, but these women were not clinically hyperthyroid.<sup>2</sup> Galton et al found that 20 women with mole had increased thyroid function with high thyroid uptake, increased serum T4 levels and free T4 levels, and increased thyroidal iodine turnover.<sup>3</sup> The abnormalities of iodine metabolism disappeared rapidly

after removal of the molar pregnancy. In 1971, Hershman and Higgins reported two cases of severe hyperthyroidism associated with hydatidiform mole,<sup>4</sup> and four years later Higgins and his associates described the spectrum of clinical hyperthyroidism in women with mole.<sup>5</sup>

Odell and his colleagues at the National Cancer Institute found increased thyroid function without convincing clinical evidence of hyperthyroidism in 7 of 93 patients with choriocarcinoma in 1963.<sup>6</sup> Two years earlier, Myers had reported a woman with choriocarcinoma and clinical hyperthyroidism which subsided with chemotherapy.<sup>7</sup> In 1976, Morley et al reported three women with choriocarcinoma who had clinical and biochemical evidence of hyperthyroidism.<sup>8</sup>

Two men with hyperthyroidism and metastatic malignant testicular trophoblastic tumors, and one man with colonic choriocarcinoma, have been reported in detail.<sup>9-11</sup> In 1974, I saw a 27-year-old man with metastatic testicular choriocarcinoma who had a normal-sized thyroid gland, gynecomastia, increased thyroid function and a markedly elevated urine HCG (8000 U/ml). I have recently learned about two other men with this disorder.

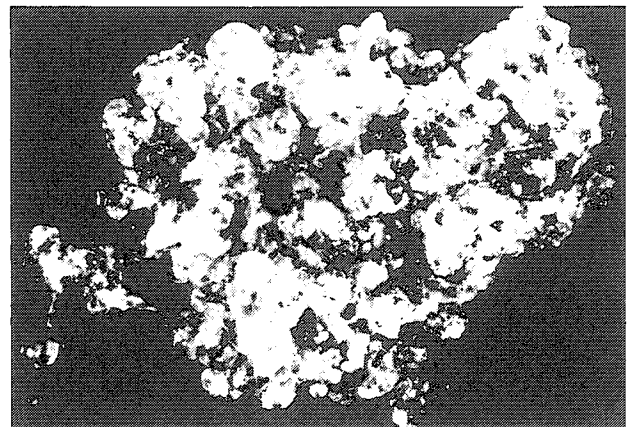


Figure 1  
Hydatidiform mole of a patient with hyperthyroidism showing the typical "bunch of grapes" appearance. (New Engl J Med 284:573, 1971.)

Thus, it appears that patients with benign and malignant trophoblastic tumors show a spectrum of thyroid function ranging from normal to biochemical hyperthyroidism to severe clinical thyrotoxicosis. I shall review the clinical features and pathogenesis of this syndrome, and treatment modalities.

### Clinical Features

Of 20 patients with hydatidiform mole studied by Higgins and Hershman in Toronto, 12 were euthyroid, 6 were severely hyperthyroid, and 2 were mildly hyperthyroid.<sup>12</sup> The six patients with severe hyperthyroidism had many symptoms and signs of their disease, and all six had palpable goiters. Two women developed rapid supraventricular tachycardia and pulmonary edema. Four had increased sweating and heat intolerance, two had weight loss, two had hyperdefecation, four of the six had muscle weakness, and five had a fine tremor. Because most patients with endocrine disorders have only a few of the classic symptoms, it is not surprising that patients with milder hyperthyroidism had only minimal symptoms and signs of the disorder.

In a recent study of 15 patients by investigators in Japan where mole is more common than in North America, none of the patients had goiter or clinical features of hyperthyroidism, although most had increased circulating thyroid hormones.<sup>13</sup> The lack of clinical features of hyperthyroidism in patients with clearly elevated free thyroid hormone levels has not been explained. Perhaps the relatively short duration of increased thyroid secretion may not be sufficient for the development of typical symptoms and signs in some women. In addition, the diagnosis of hyperthyroidism may not be suspected because the clinical findings are confused with those of toxemia which is common in patients with hydatidiform mole.

In patients with choriocarcinoma, there is also a spectrum of thyroid function which varies from normal to increased to severely hyperthyroid. Here again, thyrotoxicosis could be confused with a catabolic state due to metastatic choriocarcinoma.<sup>8</sup> Gynecomastia is a common presenting complaint in men with choriocarcinoma, but since gynecomastia occurs in about one-fifth of hyperthyroid men, this finding is not a specific indication of trophoblastic disease as the cause of the hyperthyroidism.

Absence of exophthalmos is helpful to differentiate these patients from those with coexistent Graves' disease. A woman reported by Smiley and Clements in 1940 had malignant trophoblastic disease, hyperthyroidism, a large goiter, and exophthalmos; her exophthalmos might have been attributable to brain metastases rather than Graves' disease.<sup>14</sup>

### Thyroid Function Tests

In patients with trophoblastic tumors, thyroid hormone levels vary from normal to greatly increased.<sup>5</sup> The increase in thyroid hormone binding globulin (TBG) in molar pregnancies is more variable than in normal pregnancies.<sup>3</sup> Free

T4 and free T3 concentrations are often greatly increased.<sup>3,15</sup> In some patients the ratio of serum T3 to serum T4 is less than that found in typical Graves' hyperthyroidism. This could be attributed to reduced peripheral conversion of T4 to T3 due to systemic illness, now a widely recognized phenomenon in diverse stressful illnesses.

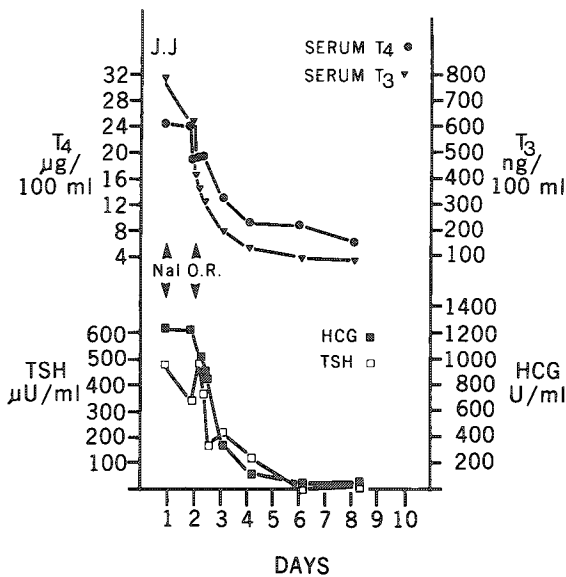
In most reports serum thyroid stimulating hormone (TSH) levels measured by radioimmunoassay are low or normal. The "normal" TSH levels in hyperthyroid patients are probably a consequence of the weak cross-reaction of HCG in the TSH radioimmunoassay. In patients with elevated serum thyroid hormone levels, the TSH response to thyrotropin-releasing hormone (TRH) is suppressed.<sup>15</sup> Thus, there is evidence of excess circulating thyroid hormone at the level of the pituitary.

Figure 2 shows thyroid function tests in a woman with hydatidiform mole. She was a 40-year-old primigravida with a six-week history of tremulousness, tachycardia, muscle weakness, nausea, vomiting, and weight loss of 5 kg. Her last menstrual period had occurred four months before hospital admission. Her heart rate was 104, BP 150/80. She had a stare and lid lag (von Graefe's sign) but no exophthalmos. Her thyroid gland was slightly enlarged, and her uterus was enlarged to the size of a six-month gestation. Her skin was warm and moist. She had a fine, finger tremor and weakness of the shoulder girdle muscles. She was thought to be moderately hyperthyroid based on clinical judgment. Ultra-sound abdominal scan showed the snowflake pattern of hydatidiform mole. Thyroid uptake of <sup>99m</sup>Tc pertechnetate was 24% at 20 minutes and the scan showed a diffusely active gland.

To reduce thyroid hormone levels quickly, she was treated with 1 gm sodium iodide intravenously; she was also given propranolol preoperatively. A 1035 gm hydatidiform mole was evacuated by hysterectomy, and the patient made an uneventful recovery. Postoperatively, there was a marked fall in her greatly elevated levels of serum T4 and T3. Her preoperative serum HCG was 1200 U/ml, a value more than ten-fold greater than the usual peak of HCG concentration of normal pregnancy. Her serum thyroid-stimulating activity measured by bioassay (molar TSH) was nearly 500  $\mu$ U/ml; normal TSH bioassay values are undetectable (less than 20  $\mu$ U/ml). Note that the HCG level and the molar TSH level declined in parallel postoperatively (Figure 2).

In collaboration with Dr. P. K. O'Brien of Toronto, I studied an unusual patient with choriocarcinoma and hyperthyroidism. This 29-year-old woman had a hydatidiform mole treated in 1968 with repeated uterine curettage until the titer of HCG became undetectable. In March, 1971, she was found to have metastatic tumor in her lungs and an HCG level of 360 U/ml. After thirteen courses of methotrexate, her HCG level became undetectable, but it rose again two months later to 460 U/ml, and chemotherapy was ineffective. In August, she developed persistent tachycardia and slight enlargement of the thyroid. Her serum T4 was 25  $\mu$ g/dl, free T4 index was greatly increased, and the 24 hour

thyroid uptake of radioiodine was 45%. Her serum HCG was over 1000 U/ml. Serum TSH by bioassay was 1760  $\mu$ U/ml, but only 12  $\mu$ U/ml in the human TSH radioimmunoassay. Despite treatment with potassium iodide, propylthiouracil, and additional antineoplastic chemotherapy, she had rapidly progressive metastatic spread of the tumor and died 5.5 months after admission to the hospital. At autopsy, she had extensive metastatic choriocarcinoma in her lungs, liver and spleen, and a small nodule of choriocarcinoma in the left lobe of the thyroid (Figure 3). It is tempting to speculate that the thyroid metastasis provided a direct source of a thyroid stimulator in addition to the stimulator in the blood.



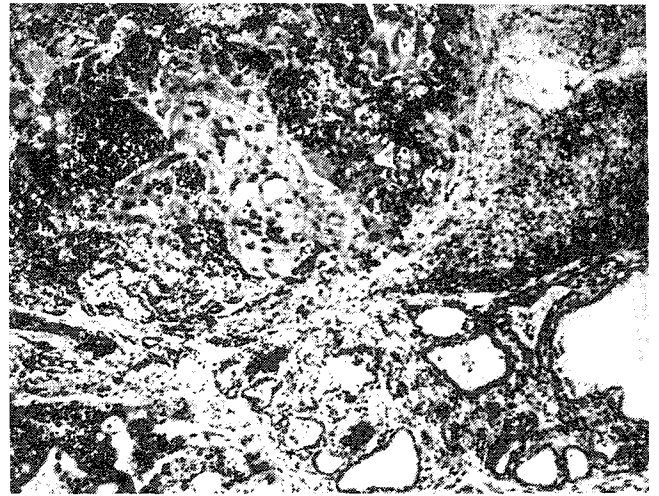
**Figure 2**  
Serum T<sub>4</sub>, T<sub>3</sub>, and HCG concentrations measured by radioimmunoassays, and molar TSH measured by bioassay, in a 40-year-old woman with hydatidiform mole and hyperthyroidism. She was treated with NaI intravenously and had the mole removed by hysterectomy. (*Ann Intern Med* 83:703, 1975.)

In our experience, serum HCG levels usually exceed 300 U/ml in patients with trophoblastic tumors associated with hyperthyroidism.<sup>5</sup> The relation of HCG to the pathogenesis of the hyperthyroidism is discussed below.

### Pathogenesis

Removal of the trophoblastic tumor causes rapid resolution of the thyroid hyperfunction, suggesting that the tumor produces a thyroid stimulator. Bioassays of the serum of these patients and of extracts of the tumors show considerable thyroid-stimulating activity.<sup>3,16,17</sup> This thyrotropin extracted from the moles is called molar thyrotropin,<sup>16</sup> and there is a direct correlation between serum levels of the molar thyrotropin and serum T<sub>3</sub>.<sup>5</sup>

It is now appropriate to consider four potential thyroid stimulators to explain this condition. First, pituitary TSH, reviewed in an earlier issue of *Thyroid Today* (see I. A.



**Figure 3**  
Photomicrograph of thyroid of 29-year-old woman containing a metastatic nodule of choriocarcinoma. This shows the choriocarcinoma cells in the upper portion and the adjacent thyroid follicles. (Slides provided through the courtesy of Dr. P. K. O'Brien, Sunnybrook Hospital, Toronto, Canada.)

Kourides, Vol. 3, No. 2, April/May 1980), was shown to be different from molar thyrotropin. The material extracted from the moles is a larger molecule and has a longer duration of action in bioassay.<sup>16</sup> In addition, pituitary TSH levels measured by radioimmunoassay are not elevated, but are instead low or normal. Also, TSH levels do not increase after administration of TRH, indicating that pituitary TSH is suppressed by the increased circulating thyroid hormone.

Second, the thyroid stimulator in these patients differs from that of Graves' hyperthyroidism which is an IgG immunoglobulin; purification of molar thyrotropin separated it from IgG.<sup>16</sup> In addition, the thyroid stimulator in Graves' patients has a longer duration of action than molar thyrotropin in bioassays, and the disappearance of the molar thyroid stimulator from serum is much faster than the half-time in serum of IgG.

A thyroid stimulator was extracted from normal placentas in two unrelated laboratories and called "chorionic thyrotropin," (hCT).<sup>18,19</sup> This was the third candidate for the molar thyrotropin. HCT was similar to pituitary TSH in its molecular size and cross-reacted with antibodies to bovine or porcine pituitary TSH.<sup>18,19</sup> The content of hCT in different placentas varied considerably,<sup>20</sup> and the quantities of chorionic thyrotropin recovered from batches of normal placentas have been very small, despite the application of many extraction methods and a more sensitive radioimmunoassay.<sup>21</sup> This suggests that the small amount of "chorionic thyrotropin" found in normal placentas is an artifact of immunoassay and that the large amount recovered in the earlier work may be attributable to inadvertent contamination with bovine pituitary thyrotropin, despite precautions to prevent that possibility. A biologic thyroid-stimulating substance can be readily extracted from normal placentas, but it is not "hCT"; instead it is probably "molar"

thyrotropin. We have never found significant levels of hCT in the serum of normal pregnant women.<sup>19,21</sup> The small amounts measurable in the radioimmunoassay of about one-third of pregnant women could represent nonspecific serum cross-reaction.<sup>21</sup>

Purification of molar thyrotropin by gel filtration, affinity chromatography, isoelectric focusing, and gel electrophoresis yielded a material which was enriched with human chorionic gonadotropin. In fact, the thyrotropic activity could not be separated from HCG.<sup>17</sup> Others have obtained similar data in the study of a woman with choriocarcinoma and hyperthyroidism.<sup>22</sup> Our group and that of Nisula<sup>23</sup> have shown that highly purified HCG has intrinsic thyroid-stimulating activity and that this activity is similar in its biologic characteristics (duration of action) to molar thyrotropin. Thus, the fourth and favored explanation: HCG is the molar thyrotropin.

#### HCG as a Thyroid Stimulator

There is still some controversy about HCG as a thyroid stimulator. Our group and others have shown that HCG displaces TSH from the thyroid receptor for TSH, which is evidence for a specific interaction.<sup>24,25</sup> Other investigators have found that crude commercial HCG which is made from the urine of pregnant women had greater TSH-displacing activity than highly purified HCG.<sup>26</sup> Unfortunately, this receptor system is relatively insensitive to TSH and subject to nonspecific influences of proteins and salts. Nevertheless, in the TSH receptor assay an extract of choriocarcinoma urine was active in proportion to its content of HCG, and the TSH-competing activity could not be separated from HCG.<sup>27</sup>

HCG increases the adenylate cyclase activity in human thyroid membranes and increases cyclic AMP generation.<sup>25,28</sup> Although the maximum stimulation of adenylate cyclase by HCG is far less than the maximum stimulation by TSH, the relative effect of HCG in this system is similar to that in the mouse thyroid bioassay, i.e., HCG had about 1/1000 the potency of a partially purified TSH molecule (~30% pure TSH)<sup>28</sup>; 1.0 U HCG was equivalent to 0.27  $\mu$ U hTSH, a value in close agreement with our recent bioassay data in which 1.0 U HCG was equivalent to 0.21  $\mu$ U bovine TSH.<sup>21</sup>

What is the role of HCG as a thyroid stimulator in normal pregnancy? Peak HCG levels of about 50 U/ml occur at 9-10 weeks of pregnancy and persist at values exceeding 20 U/ml until 18 weeks. At the time of the peak HCG levels, there is a reduction of serum TSH levels compared with the rest of pregnancy, even though serum TSH remains measurable. Between 9 and 16 weeks of pregnancy serum TSH measured by bioassay is modestly elevated compared to the rest of pregnancy, a rise which corresponds to the time of peak HCG levels.<sup>21</sup> Free thyroid hormone levels are slightly higher during this period of pregnancy, particularly when compared with normal non-pregnant controls. The data indicate that HCG exerts a

modest thyroid-stimulating effect during normal pregnancy, possibly increasing thyroid hormone secretion, and thus mildly suppressing TSH secretion. However, these changes take place within the boundaries of the normal physiologic range because the normal pregnant woman is clearly *not* hyperthyroid.

The molecular basis for the thyroid-stimulating effect of HCG is of some interest. Human luteinizing hormone also increases adenylate cyclase in human thyroid membranes and is about 80 times more potent than HCG.<sup>28</sup> The pituitary glycoproteins, LH, FSH, and TSH, share a common alpha subunit with HCG. The beta subunits differ but have considerable homologous amino acid sequences. The beta subunits of LH and HCG are very similar, but HCG has an extra 30 amino acids at the C-terminal end and has other carbohydrate side chains. Although HCG is a very weak thyrotropin, it is capable of activating the thyroid when the concentration of HCG is sufficiently high. Figure 4 illustrates the interaction of HCG with the TSH receptor on the thyroid cell plasma membrane, an example of "specificity spillover" of receptor-ligand interaction. The binding of HCG to the TSH receptor activates the thyroid in patients with trophoblastic tumors secreting large amounts of HCG. In our experience, HCG concentrations must exceed 300 U/ml to cause hyperthyroidism. It is likely that the duration of the high HCG level is also important for the pathogenesis of clinical hyperthyroidism in patients with trophoblastic tumors.

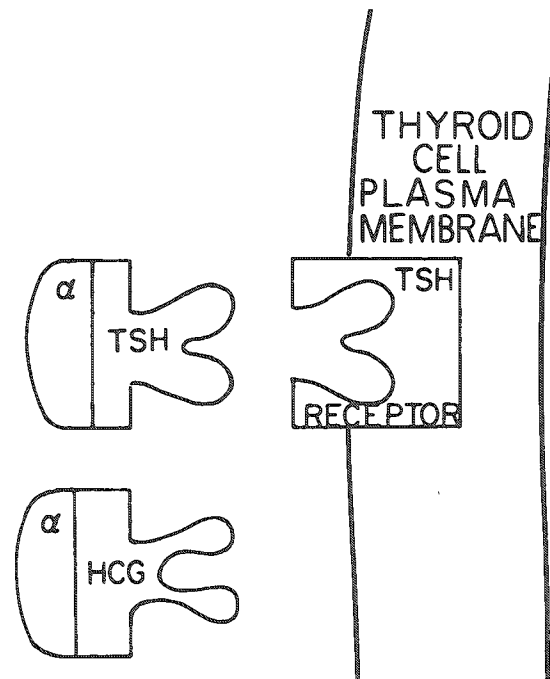


Figure 4  
Interaction of TSH and HCG with the TSH receptor on the thyroid cell plasma membrane. The alpha subunits of both molecules are identical. Although the beta subunit of HCG does not fit the receptor as well as TSH, very high concentrations of HCG can trigger a TSH effect. This explains the thyrotropic effect of HCG secreted by trophoblastic tumors.

## Therapy

After the diagnosis of hyperthyroidism is established in the patient with a trophoblastic tumor, therapy will vary with individual circumstances. Administration of intravenous sodium iodide has effectively reduced serum T4 and T3 levels of women with molar thyrotoxicosis.<sup>5</sup> Propranolol is useful to slow the tachycardia of these patients. Surgical removal of the hydatidiform mole is the definitive treatment of the hyperthyroidism and should be carried out as soon as possible. In patients with choriocarcinoma, symptomatic hyperthyroidism may be treated with antithyroid drugs (propylthiouracil or methimazole), stable iodine, and propranolol. Effective chemotherapy of the tumor will reduce serum HCG levels and thus serve as the definitive treatment of the hyperthyroidism.

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