Amiodarone-Induced Thyrotoxicosis

GILBERT H. DANIELS
Thyroid Unit and Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts 02114

Appropriate therapy for amiodarone-induced thyrotoxicosis (AIT) requires a diagnostic precision that may be difficult to achieve (1). Individual cases are rarely straight forward.

Case history

On June 14, 1999, a 71-yr-old man was hospitalized with a 1-week history of exertional shortness of breath, foot swelling, and feeling poorly.

In 1982, he was hospitalized with congestive heart failure and atrial fibrillation, attributed to myocarditis. In 1985, atrial fibrillation recurred and responded to chronic quinidine therapy. In early 1996, quinidine was stopped, followed by paroxysmal and then persistent atrial fibrillation with congestive heart failure (ejection fraction, 20–25%). Amiodarone was stopped, followed by amiodarone therapy. In early 1996, quinidine was stopped, followed by paroxysmal and then persistent atrial fibrillation with congestive heart failure (ejection fraction, 20 –25%). Amiodarone therapy was continued in 1997 but successfully restarted in March 1998 when atrial fibrillation recurred (TSH 2.3 μU/mL). Atrial fibrillation recurred and persisted, and amiodarone was discontinued in September 1998, 9 months before admission.

On admission (June 1999) he was in atrial fibrillation with a ventricular response of 180. His blood pressure was 90 systolic. He had mild proptosis (left greater than right), lid retraction, neck vein distension, and a slightly enlarged (20–25 g) thyroid. Although bilateral pleural effusions were present on the chest x-ray, interstitial edema was absent. A myocardial infarction was ruled out. His ventricular response was difficult to control despite escalating doses of β-blockers. Laboratory studies are summarized in Table 1.

His 20-min 99m pertechnetate uptake was low at 0.19% (normal range, 0.5–3.75). AIT was diagnosed, possibly secondary to Graves’ disease. He was begun on methimazole (10 mg, po, tid), prednisone (40 mg, po, daily), iopanoic acid (500 mg, po, bid), lopressor (75 mg, 4 id), verapamil (20 mg, tid), lasix (20 mg, po, qd), and coumadin. Prednisone was discontinued after June 24.

On July 2, he was in atrial fibrillation with a ventricular response of 104–108; his blood pressure was 90/60. He had lost 12 lbs since his hospital admission and noted less exertional shortness of breath. Mild proptosis, left greater than right, was noted (Hürthle exophthalmometer: left, 20 mm; right, 19 mm). TSH-binding inhibitory immunoglobulin titers (TBII) had been completed and were weakly positive. Graves’ disease was considered likely.

On July 22, his pulse was 120 (AF). His dyspnea was unchanged, but he had a single episode of angina relieved by nitroglycerine. He noted increased fatigue and heat sensitivity. Methimazole was increased to 20 mg three times daily. Iopanoic acid was continued. On August 6, his radial pulse was 116–120. His ventricular rate on electrocardiogram was 139, increased compared with his previous electrocardiogram, and worsening ST segment depression was present. Although his dyspnea was stable, edema had increased to the mid-calf. His cardiologist considered hospital admission, but careful outpatient observation was the final recommendation.

On August 17, thyroidectomy was recommended, in part, based on a serum T4 of 25.9 μg/dL, although his serum T3 had fallen to 140 ng/mL.

A bilateral thyroidectomy was performed on September 10 without incident or complications. Pathological examination revealed an enlarged thyroid gland (right lobe, 5 × 2.5 × 1.5 cm; left lobe, 4.5 × 2.5 × 3 cm), but no weight was recorded. The final pathology report read: “Enlarged thyroid with fibrosis and mild chronic inflammation. There is no evidence of malignancy.” We asked to have the pathological material re-assessed. An addendum was reported: “The thyroid is diffusely affected with the lesions described as follows. Approximately half of the areas contained islands of dilated thyroid follicles that were lined by attenuated follicular epithelial cells. These islands are separated by areas of collapsed thyroid follicles admixed with fibrosis and prominent vasculature. Nonspecific findings including histocytes and eosinophilic bodies were present. These changes are consistent with those described in amiodarone-associated thyrotoxicosis” (2).

Subsequent hypothyroidism was treated with levothyrox-
Amiodarone is an iodinated benzofuran derivative that is approved for the therapy of life-threatening recurrent ventricular arrhythmias (3) but is also used to treat angina, paroxysmal supraventricular tachycardia, and atrial fibrillation and to maintain normal sinus rhythm after cardioversion for atrial fibrillation (4).

Amiodarone contains 75 mg iodine per 200-mg tablet and releases ~10% of the iodine as free iodide daily (5). Amiodarone is highly lipophilic and is concentrated in adipose tissue, cardiac and skeletal muscle, as well as the thyroid (6). With prolonged use, amiodarone has an elimination half-life as long as 100 days (6). Amiodarone effects on thyroid function result from iodine release and intrinsic drug properties (7).

Pharmacologic iodide administration to euthyroid individuals with intrinsically normal thyroid glands results in transient inhibition of thyroid hormone synthesis and release, decreased thyroidal iodide trapping, and enhanced T₄ (3,3',5,5' tetraiodothyronine) rather than T₃ (3,3',5 triiodothyronine) production by the thyroid, so-called autoregulatory functions (8). The net effect is a slight serum TSH increase that occasionally exceeds the normal range (9, 10). With chronically higher iodide intake, the prevalence of Hashimoto's thyroiditis increases in genetically susceptible human and animal populations (11–13). In addition, pharmacologic iodide administration may precipitate hyperthyroidism in patients with Hashimoto's thyroiditis (14). Approximately 6% of patients receiving amiodarone develop iodine-induced hypothyroidism; the prevalence is higher in areas of iodine sufficiency and lower in iodine-deficient areas (15). Hypothyroidism may develop as soon as 2 weeks and as long as 39 weeks after starting amiodarone (7).

Iodide supplementation in iodine-deficient endemic goiter populations triggers epidemics of hyperthyroidism in a minority of the population, the so-called Jod-Basedow phenomenon (16). Eighty-five percent of these hyperthyroid patients have nodular goiters. Autonomous areas within the nodular thyroid gland overproduce thyroid hormone when exposed to excess substrate (iodide) but are relatively impervious to the autoregulatory effects of iodine (17). However, some hyperthyroid patients have diffuse thyroidal uptake suggestive of Graves' disease (18). As in the Hashimoto's thyroiditis example above, excess iodide seems to trigger or facilitate an immunological attack on the thyroid (19). Additionally, borderline iodine-deficient patients with Graves' disease in remission commonly relapse after adding 500 µg iodide daily (20), an amount comparable with the daily iodide intake in many iodide-sufficient areas. Pharmacologic doses of iodide may also precipitate hyperthyroidism in euthyroid individuals with nodular thyroid glands in iodine-sufficient regions (21). Case reports (22) and the amiodarone experience suggest that iodine excess may also precipitate Graves' hyperthyroidism in iodine-sufficient areas, but this conclusion is uncertain.

Amiodarone also has powerful effects on thyroid hormone metabolism (7). Amiodarone inhibits the peripheral conversion of T₄ to T₃ and may inhibit T₃ receptor binding and action (23–25). In euthyroid individuals, T₄ and free T₄ concentrations increase by 42% due to decreased T₄ clearance (7). Reverse T₃ (3,3',5' triiodothyronine) concentration rises by 172%. Efficacy and toxicity of amiodarone may be proportional to reverse T₃ concentration (26). Serum T₃ concentrations initially decline by 20–25%, subsequently an average 16% below baseline, but may be frankly low in some patients (7, 27). Serum TSH rises, occasionally out of the normal range, but with chronic administration generally remains in the normal to high normal range. It is uncertain whether TSH elevation in the 10–20 µU/mL range represents peripheral subclinical hypothyroidism or is a pituitary specific effect of amiodarone. Some authors accept subnormal serum TSH concentrations with normal T₃ concentrations as compatible with the euthyroid state. However, I interpret these findings as evidence of amiodarone-induced subclinical hyperthyroidism. The 24-h radioiodine uptake decreases to low levels (<4%) in euthyroid individuals taking amiodarone (28). This is to be expected because 15 mg inorganic iodide daily, after a loading dose of 30 mg, decreases mean 24-h radioiodine uptake to less than 2% after 12 days (10).

When added to antithyroid drugs, amiodarone facilitates the treatment of severe hyperthyroidism (29), by inhibiting T₄ to T₃ conversion, thyroid hormone release, and possibly T₃ receptor binding and action. Unfortunately, 3% of patients exposed to amiodarone develop hyperthyroidism (30), with a higher prevalence in iodine-deficient regions (15). AIT may have a male predominance (31), reflecting the higher cardiovascular disease prevalence in men. Hyperthyroidism may occur 4 months to 3 yr after initiating therapy or after drug withdrawal (28) and is not related to cumulative drug dosage (7).

Knowledge of three distinct types of AIT is required to understand this case (1, 30).

Amiodarone-induced toxic nodular goiter, a form of io-
dine-induced thyrotoxicosis, was described in Europe where large nodular goiters are more prevalent than in the United States. Despite antithyroid drug therapy, some patients demonstrated refractory hyperthyroidism (28). The addition of perchlorate to antithyroid drugs decreased the time to euthyroidism in uncontrolled trials (32, 33). Perchlorate inhibits the thyroidal iodide pool and permits the back diffusion of free (nonorganified) iodide from the thyroid gland, so-called perchlorate “discharge” (34). Doses of perchlorate higher than 1.5 g per day may cause aplastic anemia, whereas doses of 1 g per day used in these studies are apparently safe. Emergency thyroidectomy was required in some patients, a courageous approach in these critically ill patients.

The mechanism of refractory hyperthyroidism is uncertain. Thyroidal iodine stores are much higher in hyperthyroid compared with euthyroid patients receiving amiodarone (34a). The expanded iodide pool is invoked to explain refractory hyperthyroidism, because antithyroid drugs prevent thyroid hormone synthesis but not hormone release. However, pharmacologic iodide inhibits thyroid hormone release from autonomous nodular thyroid glands when new hormone production is blocked by antithyroid drugs (35). Although amiodarone was often discontinued at the onset of thyrotoxicosis, a continued high iodide environment persisted due to its long half-life.

A second group of patients treated with amiodarone developed Graves’ hyperthyroidism characterized by diffuse thyroid enlargement, a prolonged course, and the presence of thyroid autoantibodies (30). T-cell populations specific for Graves’ disease have been demonstrated as well (36). Most authors infer that “latent” Graves’ disease was made overt by an iodine-stimulated immune attack on the thyroid. Proof of this assumption requires specific markers for genetic Graves’ disease. Toxic nodular goiter and Graves’ disease comprise Type I AIT, hyperthyroidism in patients with preexisting or “latent” thyroid disease.

Type II AIT is a form of “destructive thyroiditis” (37), which develops in patients with baseline normal thyroid glands. Hyperthyroidism is due to release of stored thyroid hormone. The thyroid is usually nontender, but pain may occur. The sedimentation rate is generally within normal limits. Amiodarone, its metabolites, and intrathyroidal iodide have all been implicated in cellular toxicity, however, amiodarone is also toxic to cells that do not incorporate iodine (38, 39). Hyperthyroidism lasts for 1–3 months, until thyroid hormone stores are depleted, but resolves more quickly after glucocorticoid therapy. Transient and rarely permanent hypothyroidism may ensue, but the prevalence is uncertain (37).

Subacute lymphocytic thyroiditis (“silent thyroiditis”) and subacute granulomatous thyroiditis (“painful subacute thyroiditis”, de Quervain’s thyroiditis) are worthy of study as other examples of destructive thyroiditis that follow a similar course (40). Hyperthyroidism with a nil 24-h radioiodine uptake is often followed by hypothyroidism. Subacute lymphocytic thyroiditis is an autoimmune disorder with a predilection for the postpartum period (postpartum thyroiditis). Thyroid autoantibodies are generally present, diffuse lymphocytic infiltration is found on biopsy, and permanent hypothyroidism occurs in a significant minority of patients. Subacute granulomatous thyroiditis is characterized by intense thyroid pain, a very high sedimentation rate, severe thyroid follicle disruption, and multinucleate giant cells. Permanent hypothyroidism is rare (41). Amiodarone-induced destructive thyroiditis seems not to be an autoimmune disorder because antithyroid antibodies are generally absent. Hypothyroidism, when it occurs, is usually transient. Although limited numbers of such thyroids have been examined, follicular disruption, zones of fibrosis, and mild inflammatory changes are usually present, but dense lymphocytic infiltration and multinucleated giant cells are usually absent (2, 38). Type II AIT was diagnosed on histological examination of our patient’s thyroid gland; hyperplastic changes of Graves’ disease were absent. Type II is the most common variety of AIT in our clinic. Type I AIT is more common in Europe; the geographic differences likely reflect the higher iodine intake in the United States. Many patients with AIT II demonstrate minimal transient hyperthyroidism, diagnosed by fully suppressed TSH alone (personal observation). Permanent hypothyroidism is rare, even when amiodarone is continued (personal observation). Some episodes of Type II AIT may represent subacute lymphocytic thyroiditis precipitated by amiodarone (42). Occasional patients develop repeated cycles of hypothyroidism, followed by hyperthyroidism (43).

Appropriate therapy of AIT requires a clear distinction between Type I and Type II AIT. How can this be accomplished (Table 2)?

Given the high iodine content of amiodarone, a nil 24-h radioiodine uptake might be expected in all patients taking this drug. However, detectable or normal 24-h radioiodine uptake is found in 80% of patients with amiodarone-associated hyperthyroidism in Europe (44). Furthermore, in Europe type I AIT is accompanied by low, normal, or high 24-h radioiodine uptake, a possible consequence of baseline borderline low iodide intake (45, 46). The radioiodine uptake is near zero in all patients with Type II AIT. A normal or high radioiodine uptake effectively excludes Type II AIT, however, a nil uptake cannot distinguish between Type I or Type II. All patients with Type I and Type II AIT seen in our Thyroid Clinic have a nil uptake. Systemic radiodiode studies of Type I AIT are needed in the United States. If confirmed, our observations suggest that 24-h radioiodine uptakes are superfluous in AIT in the United States. A low (0.19%) 20-min 99m pertechnetate uptake was measured in our patient. In contrast to the 24-h radioiodine uptake, this test can be performed while receiving antithyroid drugs, allowing therapy to begin immediately.

Thyroid ultrasonography may allow us to discriminate between Type I and Type II AIT. Thyroid nodules are easily diagnosed by ultrasound and in their absence toxic nodular goiter is effectively excluded. However, destructive thyroiditis may coexist with a nodular thyroid (38). Thyroid ultrasound with color flow Doppler sonography (CFDS) can qualitatively estimate thyroid blood flow. Type I AIT with Graves’ disease has normal or increased blood flow whereas Type II AIT demonstrates a heterogenous pattern with decreased flow. In Italian studies, CFDS clearly distinguished patients with Type I from Type II AIT (47). Many ultrasonographers routinely perform flow studies on thyroid
nODULES BUT NOT NONNODULAR TISSUE. WHEN ORDERING ULTRASONOGRAPHY IN PATIENTS WITH AIT, THYROID GLAND FLOW STUDIES SHOULD BE SPECIFICALLY REQUESTED. THYROID CFDS HOLDS PROMISE AS THE DEFINITIVE DISCRIMINATING TEST, BUT ADDITIONAL EXPERIENCE IN IODINE-SUFFICIENT AREAS SUCH AS THE UNITED STATES MUST BE REPORTED BEFORE IT CAN BE FULLY ACCEPTED.

ARE OTHER STUDIES HELPFUL? ANTITHYROID PEROXIDASE ANTIBOIES ARE PRESENT IN AT LEAST 70% OF PATIENTS WITH GRAVES’ HYPERTHYROIDISM AND ARE GENERALLY ABSENT IN AIT II. THYROID-STIMULATING ANTIBODIES (TSI AND TBII) ARE CONSIDERED SPECIFIC FOR GRAVES’ DISEASE. WHEN THYROID AUTOANTIBODIES ARE ABSENT, NO CONCLUSIONS CAN BE DRAWN. WEAKLY POSITIVE TBII WERE FOUND IN OUR PATIENT, POINTING TOWARD GRAVES’ DISEASE. SERUM INTERLEUKIN 6 (IL-6) IS A MULTIFUNCTIONAL CYTOKINE THAT INFLUENCES B-CELL DIFFERENTIATION AND T-CELL ACTIVATION. IL-6 IS MARKEDLY ELEVATED IN TYPE II AIT AND NORMAL TO AT MOST SLIGHTLY ELEVATED IN TYPE I. MEAN IL-6 VALUES IN TYPE II AIT ARE 573.5 ± 78.7 FMOL/L (MEAN ± SE) (RANGE, 149.4–1145.1) AND IN TYPE I AIT ARE 152.7 ± 46.3 FMOL/L (RANGE, <25–505.6) (49). HOWEVER, WE HAVE SEEN EXTREMELY LOW IL-6 CONCENTRATIONS IN PATIENTS WITH TYPE II AIT, PERHAPS REFLECTING VARIABLE RELIABILITY OF DIFFERENT COMMERCIAL IL-6 ASSAYS. IL-6 WAS NOT MEASURED IN OUR PATIENT.

PREFERENTIAL T3 SECRETION IS A CHARACTERISTIC OF GRAVES’ HYPERTHYROIDISM. THE RATIO OF SERUM T3 TO T4 CONCENTRATION (NG/μG) IS A CRUDE INDEX THAT CAN BE HELPFUL IN DISTINGUISHING GRAVES’ HYPERTHYROIDISM FROM Destructive thyroiditis, particularly when radiiodine uptakes cannot be performed. In one study, 87% of patients with uncomplicated Graves’ hyperthyroidism had a T3 to T4 ratio greater than 20, whereas only 15% of those with “destructive thyroiditis” and 6% of euthyroid individuals were in this range (50). This ratio has not been studied in AIT. A low value is unlikely to be helpful because amiodarone inhibits T3 to T4 conversion, however, a high value would favor AIT I. Euthyroid patients receiving amiodarone have a mean T3 to T4 ratio of 8, whereas AIT patients have a mean ratio of 12 (7). Subgroup analysis of Types I and II AIT have not been performed. Our patient’s initial T3 to T4 ratio of 23.7 favored the diagnosis of Graves’ hyperthyroidism.

CLINICALLY, TYPE I AIT WITH GRAVES’ DISEASE AND TYPE II AIT PRESENT WITH A NORMAL SIZE TO DIFFUSELY ENLARGED THYROID. Active opthalmopathy or a thyroid bruit favor Graves’ disease. However, pharmacologic doses of iodide (60 mg/day) decrease thyroidal blood flow in Graves’ disease (51), and a bruit may disappear within days of iodide administration (personal observations). In our patient, thyroid palpation was thought to exclude nodularity. Graves’ hyperthyroidism was diagnosed based on eye findings and positive TBII, although this ultimately proved to be incorrect. We did not perform an ultrasound or measure IL-6 in our patient, studies that in retrospect might have been helpful. The role of fine-needle aspiration biopsy is uncertain because pathological changes in Type II AIT are often patchy.

Table 2 contrasts the therapy of Types I and II AIT.

Therapy of iodide-induced toxic nodular goiter includes methimazole or propylthiouracil; perchlorate may be necessary. With prolonged hyperthyroidism, clinical deterioration, or continued amiodarone requirement, surgery should be considered (52, 53). The role of radioiodine therapy in patients with normal or high 24-h radiiodine uptake is uncertain. Type I AIT due to Graves’ disease is treated in a similar fashion. Recently, 12 consecutive patients with Type I AIT (10 with toxic nodular goiters and 2 with Graves’ disease) were treated with a combination of methimazole (30 mg) and perchlorate (1 g). All achieved normal free T3 concentrations by 4 weeks (54). A tentative diagnosis of Graves’ hyperthyroidism was made in our patient. Methimazole was started, and iopanoic acid was added to decrease hormone release and inhibit T4 to T3 conversion, functions also shared by amiodarone. The 24-h urine iodide was only mildly increased, and, therefore, perchlorate was not added. It is reasonable to consider continuing amiodarone for several weeks after starting antithyroid drugs in typical Type I AIT patients, but this is of unproven efficacy. Although amiodarone serum half-life is known, the duration of T4 to T3 inhibition after drug cessation is unknown.

Hyperthyroidism in Type II AIT is self-limited, but some patients become critically ill with cardiovascular deterioration. Glucocorticoid therapy rapidly reverses the hyperthy-

### Table 2. AIT-differential diagnosis and therapy

<table>
<thead>
<tr>
<th>Baseline thyroid condition</th>
<th>Type I AIT</th>
<th>Type II AIT Destructive thyroiditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxic nodular goiter</td>
<td>Nodular thyroid</td>
<td>“Latent” Graves’ disease</td>
</tr>
<tr>
<td>Normal size or diffuse goiter</td>
<td>Normal size or diffuse goiter</td>
<td>Normal thyroid</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>One or more nodules</td>
<td>Diffuse goiter</td>
</tr>
<tr>
<td>CFDS</td>
<td>Normal or increased flow</td>
<td>Normal or increased flow</td>
</tr>
<tr>
<td>Thyroid autoantibodies</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>IL-6</td>
<td>Normal or high</td>
<td>Normal or high</td>
</tr>
<tr>
<td>24-h radiiodine uptake</td>
<td>Low, normal, or high</td>
<td>Low, normal, or high</td>
</tr>
<tr>
<td>Therapy</td>
<td>Methimazole or Propylthiouracil</td>
<td>Methimazole or Propylthiouracil</td>
</tr>
<tr>
<td>Percloate may be necessary</td>
<td></td>
<td>Perchlorate may be necessary</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Based on European experience (see text).*
roidism of Type II AIT and may be life saving. Bartelana et al. (54) treated 12 consecutive Type II AIT patients with prednisone (40 mg/day) for 7–14 days, with a subsequent taper over 3 months. Free T\textsubscript{3} and IL-6 normalized after an average of 8 and 6 days, respectively. In our experience, many patients remain euthyroid after several weeks of prednisone. However, if hyperthyroidism recurs, then prednisone should be reinitiated. A rapid response to glucocorticoid therapy is an additional differential point in difficult cases.

Until a diagnosis seems certain, therapy directed at both Type I and Type II AIT should begin, including methimazole, prednisone, and, when indicated, perchlorate. Results from IL-6 and thyroid-stimulating antibodies measurements often take days to weeks to return. Our patient was severely ill on admission. Amiodarone had already been discontinued. Although Graves' disease was the initial diagnosis based on his exophthalmos, prednisone, methimazole and iopanoic acids were all prescribed. When the TBII results returned, prednisone was discontinued. The initial clinical improvement was attributed to iopanoic acid but may have been due to prednisone therapy. In retrospect, a longer course of prednisone therapy would have been prudent and surgery might have been avoided. A decision for surgery was made when the patient was still clinically unstable. When admitted for surgery, the patient was clinically improving, but the patient and his physicians wanted a definitive resolution. The diagnosis was still in question, and long-term therapy with antithyroid drugs might have been necessary. In retrospect, more patience with a systematic diagnostic approach might have been rewarded.

Should amiodarone be discontinued in all cases of AIT? When the cardiac situation allows, we ultimately stop amiodarone in AIT I, but sometimes continue therapy for several weeks after starting antithyroid drugs. Many authors recommend stopping amiodarone in Type II AIT, however, this is unnecessary if the diagnosis is established. Recurrent cases of Type II are rare. Our patient had been off amiodarone for 9 months, yet Type II occurred.

Is thyroid prescreening necessary before starting amiodarone? The drug is usually begun in an emergent or semurgent setting by cardiologists without concern for underlying thyroid disease. However, a prudent approach would be to take a family history of autoimmune thyroid disease and measure serum TSH and antithyroid peroxidase antibodies. These studies might be particularly helpful in predicting amiodarone-associated hypothyroidism and possibly allow preliminary identification of “latent” Graves’ disease. Thyroid ultrasound would discover patients with nodular thyroid glands at risk for AIT I, but its use might be more cost-effective in Europe where AIT I is more common.

AIT continues to challenge our clinical acumen. Although clear guidelines are available, diagnosis and therapy for an individual patient may be problematic. Systematic studies in the United States using CFD$ and IL-6 in AIT are needed. Radioiodine or 99m pertechnetate uptake is currently recommended but may be superfluous in the United States. Although atypical in some ways, this case illustrates the clinical dilemmas that one encounters with AIT.

**References**

31. Reichert L, De Rooy HA. 1989 Treatment of amiodarone induced hyperthyroidism by on April 4, 2010

34. Wyngaarden JB, Wright BM, Ways P. 1952 The effect of certain anions upon the accumulation and retention of iodide by the thyroid gland. Endocrinology. 30:537–549.


