ANNIVERSARY REVIEW

Antithyroid drug therapy: 70 years later

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Abstract

The thionamide antithyroid drugs were discovered in large part following serendipitous observations by a number of investigators in the 1940s who found that sulfhydryl-containing compounds were goitrogenic in animals. This prompted Prof. Edwin B Astwood to pioneer the use of these compounds to treat hyperthyroidism in the early 1940s and to develop the more potent and less toxic drugs that are used today. Despite their simple molecular structure and ease of use, many uncertainties remain, including their mechanism(s) of action, clinical role, optimal use in pregnancy and the prediction and prevention of rare but potentially life-threatening adverse reactions. In this review, we summarize the history of the development of these drugs and outline their current role in the clinical management of patients with hyperthyroidism.

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History

Prior to the 1940s, surgery was the only treatment for hyperthyroidism. In 1942, Edwin B Astwood began a series of investigations at Harvard and later at Tufts Medical Schools that would ultimately lead to the development of what he dubbed 'antithyroid drugs' (1) (Fig. 1). The experiments were based on earlier observations by two groups working independently at Johns Hopkins University School of Medicine, the Mackenzies (2) and Richter *et al.* (3). Both groups showed that certain substances (sulfaguanidine and phenylthiourea, respectively) were goitrogenic. Importantly, McKenzie *et al.* also demonstrated that the goiter was likely due to inhibition of thyroid hormone synthesis rather than an effect on iodine metabolism (4). Their work was echoed

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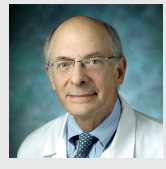

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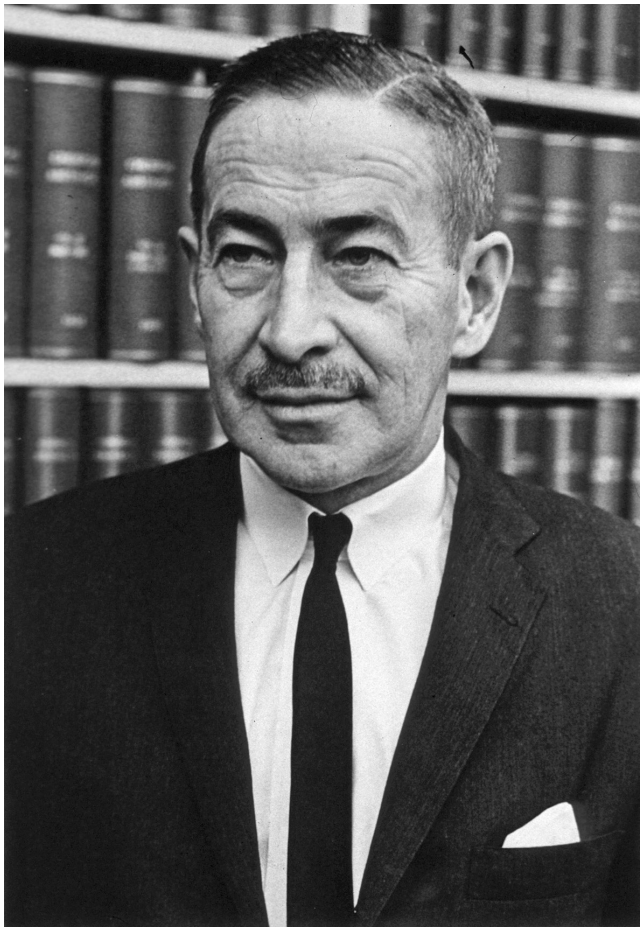

Figure 1
Edwin Bennett Astwood (1909–1976). Courtesy of the National Library of Medicine.

by Astwood who confirmed the effect of sulfaguanidine and thiourea on thyroid function (5). In addition, the pituitary was implicated in the goitrogenic effect of these compounds by showing that goiter was prevented by hypophysectomy (5). Astwood was also aware of the work of TH Kennedy in New Zealand, who had reported that thiourea, structurally similar to goitrogens in rape seed, caused goiter in rats (6).

In 1942, Astwood treated the first hyperthyroid patient with thiourea, in whom there was a remarkable clinical improvement. At the same time, he initiated a series of studies of over 100 synthetic thiourea analogs as potential goitrogens in rats, and came upon one compound, 2-thiouracil, that was particularly potent (7). In what has been republished as a 'landmark' paper in JAMA (8), Astwood reported the successful therapy of three hyperthyroid patients (one with thiourea and two with thiouracil). Although one patient developed agranulocytosis, he survived, and thus represents the first known instance of this important adverse reaction. In that original report, Astwood also noted that the drugs took days to weeks before a clinical effect was observed and that the drugs controlled hyperthyroidism well while they were being given, but that hyperthyroidism recurred when the drug was discontinued. He also noted that patients could become hypothyroid with overtreatment. A second paper published in 1944 expanded on observations of the efficacy (and toxicity) of thiouracil therapy (9). In 1946, after studying more than 300 compounds for their 'antithyroid' effect, the more potent 6-n-propylthiouracil (PTU) was introduced and approved by the U.S. FDA in 1947 (10). Methimazole (MMI) was discovered to be an even more potent and less toxic thiourea analog in 1949 (11). Subsequently, carbimazole, a 'prodrug' for methimazole was introduced in 1953, in the unrealized hope that it would have less toxicity than methimazole (12).

It is fascinating to note that many observations initially made by Astwood and his colleagues more than half a century ago continue to be topics of great debate in the 21st-century. For example, Astwood's group reported that after a prolonged course of therapy, some patients had long-lasting 'remissions' after antithyroid drug therapy was discontinued (13). This paper also introduced the terms 'relapse' to mean a return of hyperthyroidism within 3 months of antithyroid drug discontinuation and 'recurrence' to indicate hyperthyroidism developing after more than 3 months. Astwood and his associates were the first to report on the side effects of antithyroid drugs, particularly drug eruptions and agranulocytosis (8, 9), as well as the possibility of treating hyperthyroid pregnant women with these compounds (14); both topics continue to provoke controversy to the present day. The notion that Graves' disease could be treated 'indefinitely' with antithyroid drugs is also a topic of current controversy. This concept took root more than 50 years ago, again in a publication from Astwood's laboratory describing therapy for as long as 16 years in some patients (15).

Mechanism of action

Inhibition of thyroid hormone synthesis

The 'thionamide' antithyroid drugs are five- or six-membered ring structured sulfur-containing compounds that are thiourea derivatives. Contrary to popular belief, antithyroid drugs do not block thyroidal iodine uptake. Rather, their primary effect appears to inhibit

an early step in thyroid hormone synthesis, which is the 'organification' of inorganic iodine. The process is catalyzed by thyroid peroxidase (TPO) and requires endogenously generated hydrogen peroxide. During the initial steps of organification, iodide is oxidized and bound to heme residues within TPO (TPO-I_{ox}), prior to subsequent iodination of tyrosine residues in the thyroglobulin molecule. While antithyroid drugs can irreversibly inhibit TPO *in vitro*, *in vivo* (16), in the presence of iodine, the drugs appear to act as substrates for TPO-I_{ox} (17) and are probably iodinated themselves to form unstable sulfenyl-iodide intermediates, thus diverting TPO-I_{ox} moieties away from tyrosine iodination pathway (18). Others have suggested that methimazole, through its sulfur moiety (or after desulfuration) can interact directly with the iron (Fe(III)) atom at the center of the heme molecule (19). It has also been proposed that antithyroid drugs interfere with the coupling reaction, in which two iodotyrosine molecules form an ether link to yield the iodothyronines thyroxine (T4) and triiodothyronine (T3) (20). Other less well-documented proposed mechanisms to inhibit thyroid hormone synthesis include drug binding directly to thyroglobulin (21) or inhibition of thyroglobulin synthesis (22).

Propylthiouracil, but not methimazole or carbimazole, inhibits the selenoprotein type I iodothyronine deiodinase, thereby reducing T3 formation in peripheral tissues from T4. On the other hand, propylthiouracil does not inhibit the type 2 or type 3 deiodinases, which are also selenoproteins, suggesting that there are important steric considerations behind this disparity (23). The mechanism of inhibition of type I deiodinase appears to be formation of a stable selenyl-sulfide moiety, which prevents the formation of a key selenyl-iodide intermediate (24).

Effects on thyroid autoimmunity

Given the decline in thyroid-stimulating antibody titers with antithyroid drug therapy (25) as well as the possibility that patients treated with antithyroid drugs may undergo a remission after a course of treatment, there has been interest in whether antithyroid drugs may have direct or indirect effects on the immune system (26). Unfortunately, space does not permit a thorough discussion of the extensive data on the subject (27). Suffice it to say that there is *in vitro* evidence that thionamide antithyroid drugs may have direct effects on intrathyroidal T cells (28, 29) and HLA Class II expression by thyrocytes (30), as well as *in vivo* evidence for increased numbers of suppressor T cells and decreased intrathyroidal activated T cells (31).

On the other hand, others have argued that the putative direct effects of thionamides on thyroid autoimmunity are much less important than the indirect effects on the immune system that occur as a direct result of hyperthyroidism *per se*, and which are reversed after control of the hyperthyroidism by antithyroid drug therapy (32, 33). The extent to which either the direct or indirect effects of antithyroid drugs on the immune system predominate to achieve the observed reduction in antiTSH receptor antibody titers and resultant remissions remains uncertain.

Antioxidant activity

The increased basal metabolic rate associated with hyperthyroidism is believed to result in accelerated production of superoxide radicals as byproducts of electron transport (34, 35). Reactive oxygen species have also been implicated in the pathogenesis of Graves' orbitopathy (36, 37, 38). *In vitro* studies have shown that both MMI and PTU inhibit leukocyte production of oxygen radicals in a dose-dependent manner (39, 40) and appear to accelerate hydrogen peroxide scavenging in cultured thyroid cells (41). A clinical study in patients with Graves' disease found that plasma thiol levels and superoxide dismutase activity, both free radical scavengers, were reduced in patients presenting with thyrotoxicosis, but normalized following treatment with CBM (42). Another study found that indices of lipid peroxidation were elevated and the antioxidants vitamin E and coenzyme Q10 were reduced in untreated Graves' disease patients but normalized after treatment with either MMI or PTU (43). Similar findings of enhanced lipid peroxidation were found in two additional studies of hyperthyroid Graves' disease patients (44, 45), but improvement following treatment with PTU occurred in only one of these studies (45). Each of these clinical studies is flawed by an inability to distinguish the effects of the ATDs from the effects of correcting hyperthyroidism per se.

Clinical applications

Restoration of euthyroidism

Three antithyroid drugs are commercially available, including methimazole (MMI), propylthiouracil (PTU) and carbimazole (CBM). CBM is rapidly metabolized in the blood to MMI with 10 mg CBM yielding approximately 6 mg MMI (46). For most patients, CBM/MMI can be given as a single daily dose, whereas PTU, the least potent

antithyroid drug with shortest duration of action, is typically initiated three times daily. A PTU dose of 100 mg is approximately equivalent to 5–6 mg of methimazole (15–20:1). Initial dosing of CBM/MMI should depend on the severity of hyperthyroidism. The 2016 ATA Guidelines for the management of hyperthyroidism recommended that this dose be based on the degree of elevation in free T4, using 5–10 mg if free T4 is 1–1.5 times the upper limit of normal, 10–20 mg if free T4 is 1.5–2 times normal and 30–40 mg for free T4 elevation of 2–3 times the upper limit of normal (Table 1) (47). CBM/MMI is the preferred antithyroid drug due to superior efficacy, the ability to use once daily in most hyperthyroid patients and a lower adverse effect profile (47, 48). Recent surveys of clinical endocrinologists show that fewer than 5% would choose propylthiouracil as the initial antithyroid drug (49, 50). However, PTU is still preferred during the first trimester of pregnancy due to a lower prevalence and severity of drug-associated embryopathy than with CBM/MMI (51), and in the treatment of thyroid storm, where the additional inhibition of T4-to-T3 conversion may be critical to early reversal of this disorder (52, 53).

Both MMI and PTU are nearly completely absorbed following oral administration, with peak serum levels obtained within 1–2 h. Each drug is further concentrated within the thyroid. Intrathyroidal methimazole levels are approximately 2–5 times higher than peak plasma levels and the intrathyroidal levels remain high 20 h after ingestion (54). The restoration of euthyroidism occurs gradually, as existing thyroid hormone stores are released and T4 is converted to T3 both within the thyroid and in the peripheral tissues. A large Japanese study that randomized Graves' disease patients to either 30 mg MMI once daily or 300 mg PTU daily in divided doses found that at the end of 12 weeks of therapy, free T4 normalized in 96.5% taking MMI and 78.3% taking PTU, while free T3 normalized in 90 and 62.9% of those taking MMI and PTU, respectively (55). In the subset of patients very high baseline free T4 levels >7 ng/dL, free T4 values were normalized at 12 weeks in 66.9% of patients treated with MMI, compared to only 57.1% of those treated with PTU (55). In the European Multicenter Study Group on Antithyroid Drug Treatment prospective trial, euthyroidism was achieved after 6 weeks of therapy in 84.9% of patients receiving 10 mg MMI daily and 91.6% receiving 40 mg MMI daily, both supplemented with LT4 (56).

Table 1 Approximate starting doses of antithyroid drugs based on initial free T4 levels.

Free T4 elevation	CBM (mg)	MMI (mg)	PTU (mg)
1–1.5×ULN	10–15	5–10	100–200
1.5–2×ULN	20–30	10–20	200–400
2–3×ULN	50–70	30–40	600–800

Remission from Graves' disease

Remission from Graves' disease has been defined as a maintenance of biochemical euthyroidism for at least 1 year after stopping antithyroid drugs (47). Approximately one half of patients receiving ATDs for 1 year will enter a period of drug-free remission, but there is clinical and geographical variability, with remission rates ranging from as low as 30% to as high as 60–70% (57). While hyperthyroidism subsequently recurs in one-third of patients initially achieving a remission, approximately one in three patients treated may achieve a permanent remission. Numerous studies have evaluated patient features and ATD dosing regimens predictive of remission following a course of ATDs (58). The most consistent features showing predictive value include a small goiter, lesser degrees of thyrotoxicosis, and TSH receptor antibody titers that are minimally elevated before ATD therapy or normalize on therapy (48). Additional features with possible negative influence on remission rates include tobacco smoking (59, 60), age <30 (58) and the postpartum state (61). The optimal duration of antithyroid drug therapy is between 12 and 18 months, with a high recurrence rate after only 6 months and no apparent additional benefit by extending therapy beyond 18 months (48, 62). The mechanisms responsible for remission while taking ATDs are not certain. As noted earlier, in addition to possible direct immunologic effects of ATDs, achievement of euthyroidism even without antithyroid drugs, such as after perchlorate or thyroid surgery, seems to have beneficial immune effects, as indicated by reductions in TSAb levels (33).

Antithyroid drugs in pregnancy

Prior to the introduction of antithyroid drugs, surgery was the only treatment for thyrotoxic pregnant women, with high rates of fetal loss. After radioiodine was found to be concentrated in the fetal thyroid, it was obvious that it could be used to treat women before, but not during pregnancy (63). It soon became clear that antithyroid drugs were safe in pregnancy. In one of the earliest reports, Astwood described the use of PTU 100 mg every 8 hours to treat 13 pregnant women (14), and other drugs including

methimazole to treat an additional six women. He noted that often the dose of medication could be tapered during the latter half of pregnancy, and in some cases, the drug could be discontinued because of clinical improvement. Subsequent studies suggested that PTU was the preferred drug in pregnancy because, compared to methimazole, it was highly protein bound and therefore less likely to cross the placenta (64). However, research using isolated perfused human placentas revealed that both drugs cross the placenta equally well (65). A study in pregnant women showed a strong correlation between cord blood PTU levels and fetal thyroid function, consistent with the notion that PTU crosses the placenta (66). Finally, a cohort study in which fetal thyroid function was assessed at delivery following exposure to either PTU or methimazole, showed that both drugs appeared to affect fetal thyroid function equivalently (67). Despite this, reports showing that methimazole exposure was associated with aplasia cutis, as well as other more severe birth defects (so-called 'methimazole embryopathy') (68, 69, 70, 71), led to the general recommendation that PTU be used in the first trimester during the period of organogenesis. However, analysis of insurance claims data from the United States revealed that birth defects were also linked to PTU use (72). This finding was confirmed by data from Denmark, showing that PTU was also associated with birth defects, albeit less obvious and clinically less significant (51, 73). Based on the totality of the data, the American Thyroid Association recommends the use of PTU in pregnant women in the first trimester and then either maintaining PTU or switching to methimazole for the duration of pregnancy (74). There is, however, no consensus about which drug would be preferred in women with Graves' disease who are desirous of becoming pregnant (49). Women taking antithyroid drugs while pregnant should be closely monitored with monthly thyroid function tests using the lowest dose of drug possible to maintain normal thyroid function. Since autoimmunity in general tends to decrease progressively in pregnancy, the dose of antithyroid drugs can often be reduced as pregnancy continues. Approximately one third of women can discontinue therapy completely during the third trimester. However, postpartum recurrence of Graves' disease is common, especially 6–12 months after delivery, so that close monitoring is required for a full year after delivery. Both antithyroid drugs are safe in lactating women, and both are approved by the American Academy of Pediatrics (75). Doses of methimazole of up to 20 mg a day and up to 450 mg of PTU a day do not affect neonatal thyroid function (76, 77). Methimazole would be preferred, however, because of the higher risk of adverse reactions in the mother with PTU therapy. There are no case reports of adverse reactions to infants exposed to antithyroid drugs via the breast milk.

Orbitopathy neutrality

Three RCTs and additional meta-analyses comparing the effects of either radioactive iodine (RAI) therapy or ATDs on the development or progression of Graves' orbitopathy have shown better outcomes using ATD therapy (78, 79, 80, 81, 82). These differences have been largely attributed to adverse effects of RAI on TSH receptor autoimmunity, as evidence by sustained increases in TSAb titers after RAI, compared to gradual decreases during a prolonged course of ATDs (83). A study examining long-term use of ATDs in patients with concurrent Graves' orbitopathy noted no exacerbations of eye disease during a mean duration of 3.4 years (84). The demonstrated TSH receptor expression in retroocular tissue has fueled the speculation that enhanced autoimmunity against this protein leads to new or worsened eye inflammation and retroocular fibroblast proliferation (85). While this theory suggests that ATDs play a neutral role relative to the pathogenesis of Graves' orbitopathy, it is possible that beneficial immune effects of ATDs also contribute to the difference between these two nonsurgical approaches.

Preparation for definitive therapy

ATDs serve a key role in preparing patients for definitive therapy with either thyroidectomy or RAI therapy. There is a consensus that GD patients should be rendered euthyroid prior to thyroidectomy to avoid the risk of postoperative thyroid storm (47, 49, 50). The introduction of antithyroid drugs in the late 1940s led to a sharp decrease in the risk of postoperative thyroid storm (52, 86). Preparation with beta adrenergic blocking agents alone is insufficient to prevent this complication (87). Conversely, the use of ATDs in preparation for RAI ablation of the thyroid is subject to geographical variation (49, 50). In a US-based international survey of practicing endocrinologists, only 37.7% of respondents reported routinely pretreating most patients with ATDs before giving RAI ablation (49), whereas a European-based survey showed that 61% of respondents routinely utilized ATD pretreatment (50). The 2016 American Thyroid Association Guidelines recommend selective pretreatment with ATDs before RAI therapy, particularly in the elderly, and those

with extensive comorbidities or coronary artery disease, who can ill-afford an acute worsening of thyrotoxicosis after RAI therapy (47). Since abrupt discontinuation of ATDs leads to a rapid increase in circulating thyroid hormone levels (88, 89), a discontinuation period of only 2–3 days was recommended (47). Some experts recommend resumption of ATD therapy 5–7 days after RAI administration to maintain better control of thyroid function in the ensuing weeks (90).

Thyroid storm management

ATDs represent a keystone in the management of life-threatening thyrotoxicosis/thyroid storm. Typical starting doses of ATDs in thyroid storm are PTU (when available) 200–250 mg every 4 h (1200–1500 mg daily) or MMI 20 mg every 4 h (120 mg daily) (86). The Japanese Thyroid Association recommends the use of MMI 60 mg daily to treat thyroid storm (91). PTU has the benefit of reducing T4-to-T3 conversion (unlike CBM/MMI), which leads to lower T3 levels in the first 24 h after initiation, compared to that seen with methimazole (92). This would seem to be advantageous in the early management of thyroid storm (47). However, there are no randomized trials comparing the outcomes with these two drugs in patients with thyroid storm.

Augmenting ATDs with iodine

The possible synergy between thionamides and KI has been a subject of investigation for many years, but short-term KI use was not shown to be effective (93, 94). On the other hand, more chronic use of KI was shown to significantly improve the effectiveness of PTU (95). A recent randomized controlled trial of longer-term therapy with KI showed that the effects of methimazole could be augmented by concomitant use of this drug (96). In this study, patients with Graves' disease were randomly assigned to one of four regimens: MMI 30 mg alone; MMI 30 mg + 50 mg KI (administered as a tablet containing 38 mg of iodide); MMI 15 mg alone and MMI 15 mg + KI. Over 12 weeks, thyroid function improved in all four groups, but the number of patients with normal free T4 and free T3 was higher in the two groups receiving KI augmentation. Importantly, the rate of normalization with 15 mg of MMI plus KI was similar to 30 mg of MMI alone. Thus, this study raises the possibility that lower doses of MMI could be used in association with KI augmentation, which would decrease MMI toxicity, which is dose related (18).

Block-and-replace regimens

Early advocates of the 'block-and-replace' regimen, in which levothyroxine is added to ongoing ATD therapy in patients with GD, suggested a higher remission rate with combined therapy (97). Multiple subsequent studies failed to reproduce these results (98, 99, 100, 101, 102, 103, 104). Subsequently, it was proposed that the block-and-replace regimen provided greater stability in thyroid hormone levels compared to ATDs alone (105), but a large retrospective case series did not confirm this hypothesis (106). A meta-analysis showed a higher incidence of adverse effects with the block-and-replace regimen, logically a result of the higher ATD doses utilized in this regimen (62, 107). These results were subsequently challenged, and it was suggested that either regimen gives comparable results and remained viable options (108). A recent survey of European thyroidologists found that block-and-replace regimen was used routinely by 25.7% of respondents and selectively by an additional 37.9% of respondents (50). The rationale for this treatment choice was not explored.

Long-term ATD therapy

Chronic ATD therapy is considered a reasonable alternative to ablative therapy (surgical or RAI) for Graves' disease patients failing to achieve a remission after an initial course of antithyroid drugs. Proponents of this approach note that patients increasingly report a preference for non-ablative therapy (109). There is a lower incidence of adverse effects on a low (maintenance) dose of MMI (56, 110), and most cases of agranulocytosis occur within the first 3 months of ATD therapy (111). Conversely, chronic ATD therapy requires serial reassessment of dosing adequacy, surveillance for possible overtreatment due to patient remission and monitoring for rare late-occurring adverse effects related to ATDs, such as vasculitis (112). A study comparing 10-year outcomes in patients randomized to either radioiodine or further ATD therapy after initially failing to achieve a remission on ATDs found costs of management were similar or slightly lower with chronic ATD therapy, and episodes of hypothyroidism occurred more frequently after RAI therapy than with chronic ATDs (113). Another study assessing long-term ATD therapy, using a block-and-replace regimen in patients with Graves' orbitopathy, found that 90% of patients stayed continuously euthyroid during a mean follow-up of 6.7 years, and the remainder had brief periods of hyperthyroidism either spontaneously or due

to recent ATD dose reduction (112). Adverse effects were rare, including five patients with cutaneous reactions to MMI, and one patient who developed vasculitis on PTU (112). A third study assessing long-term ATD therapy in GD patients treated for a range of 2–11 years and then followed for an average of 4.5 years after stopping ATDs, found a remission rate of 63% (84). A meta-analysis including six studies of GD patients treated with ATDs for a minimum of 2 years found an overall adverse effect rate of 19.1%, consisting mostly of rash, gastric intolerance or arthralgia, with only 1.5% of patients experiencing severe reactions at any point, including initial ATD therapy, such as agranulocytosis and unspecified hepatotoxicity (60). A retrospective analysis of patients treated with either continued low-dose ATDs or radioiodine following an initial relapse after ATD therapy showed that low-dose ATD-treated patients had better maintenance of euthyroidism, less weight gain, less orbitopathy deterioration and similar quality of life compared to those treated with radioiodine (114). The 2016 American Thyroid Association (ATA) Guidelines note that ATD therapy beyond 12–18 months is an acceptable alternative to ablative therapy in patients who prefer this approach (47).

Adverse effects

Rash

Minor cutaneous allergic reactions, including rash, pruritis and urticaria represent the most common adverse effects ascribed to ATDs, particularly MMI. In a meta-analysis that included 5136 patients treated with either MMI (77%) or PTU (23%), rash occurred in 6% of those treated with MMI and approximately 3% of those treated with PTU. An additional 2–3% of patients complained of pruritis without rash (115). In a randomized trial from Japan, 22% of patients treated with either 30 mg MMI or 300 mg PTU developed a cutaneous reaction, compared to 6% of those treated with 15 mg MMI (55). Cutaneous reactions to ATDs generally occur within the first few weeks of therapy (55). A study examining the effects of switching to the alternate ATD after developing minor reactions (mostly cutaneous) on the first ATD found that approximately one-third of patients who switched developed minor adverse effects on the second ATD, but this rate was lower than that seen when first starting either ATD (116). Current ATA guidelines recommend consideration of antihistamine therapy without stopping ATDs in patients with mild skin reactions, consideration of definitive therapy or the alternate ATD in the case of moderate reaction and avoidance of ATDs all together in patients with more severe cutaneous reactions (47).

Agranulocytosis

As noted earlier, agranulocytosis as an adverse reaction to antithyroid drugs was observed early on and has been an ever present fear for prescribing physicians and their patients. Agranulocytosis is usually defined as a granulocyte count $<0.5\times10^9$/L, but most patients with antithyroid drug-related agranulocytosis have granulocyte counts that are close to zero. This complication occurs in approximately 0.2–0.5% of patients taking antithyroid drugs (117). The onset is typically abrupt from a clinical point of view, presenting with the sudden onset of high fever, malaise and severe pharyngitis due to a streptococcal infection (118). In some prospective studies, however, the decline granulocyte counts is gradual, rather than precipitous, leading to the recommendation by some that monitoring of the white blood cell count can detect the development of agranulocytosis before the patient manifests it clinically (117). However, the ATA guidelines found insufficient evidence to recommend for or against routine white blood cell count monitoring (47). Advocates of a non-monitoring approach point to the relative rarity of this side effect, the fact that the onset is precipitous in most patients, and the lack of cost-effectiveness (18). Patients should be told to contact their physicians if they develop fever or pharyngitis while taking antithyroid drugs. Disturbingly, a recent study found that 61% of antithyroid drug-treated patients were unfamiliar with this the symptoms of agranulocytosis (119), emphasizing the need for physicians to educate patients about the potential for agranulocytosis, preferably in writing, and to emphasize this on an ongoing basis during follow-up (47).

The majority of cases of agranulocytosis occur within the first 90 days of treatment, although there are exceptions (111). Also, agranulocytosis can develop after prior use and discontinuation of an antithyroid drug, followed by a resumption of the drug after a period of months to years (120). Agranulocytosis is dose-related with respect to methimazole (121), but not with PTU.

The exact etiology of drug-induced agranulocytosis is still uncertain, but it appears to be due to immune targeting of the granulocytic lineage in the bone marrow rather than a direct toxic effect (122, 123, 124, 125). Antithyroid drugs are concentrated within granulocytes, and metabolized by myeloperoxidase (126), which may lead to alterations of the cell membrane. Studies in different ethnic groups have observed that patients with

specific HLA types may be more susceptible to antithyroid drug-induced agranulocytosis in Asians (127) and Caucasians (128), leading to exciting idea of using HLA genotyping as 'personalized medicine' to select the safest treatment for patients with Graves' disease.

In addition to cessation of the offending drug, the treatment of antithyroid drug-induced agranulocytosis typically involves supportive measures, broad-spectrum antibiotics, and granulocyte colony-stimulating factor (G-CSF) (129). Full recovery of white blood cell counts typically occur over 7–14 days. While most patients survive, the mortality rate remains about 5%, with older age, comorbidities, septicemia, granulocyte count $<0.1\times10^9$/L at the time of diagnosis being risk factors for mortality (129). The management of hyperthyroidism in a patient with antithyroid drug-related agranulocytosis can be challenging and typically involves radioiodine or surgery. A recent case series presented data on rapid preparation of such patients for surgery using potassium iodide, glucocorticoids and beta-blockers (130).

Hepatic dysfunction

Hepatotoxicity from ATDs ranges from mild transaminase elevation to hepatic necrosis resulting in death. Historically, severe hepatocellular disease has been described predominantly with PTU, with a cholestatic picture typically associated with MMI (131). In the United States, for example, as of 2009, there have been no MMI-related deaths or liver transplants reported to the FDA. In contrast, between 1990 and 2007, between one and three liver transplants from PTU exposure were reported annually (132). However, this view has been challenged by two large studies performed in Asia (133, 134). Among 71 379 patients newly prescribed ATDs in Taiwan and followed for a median of just over 6 months, hepatotoxicity occurred in 139/46 436 (0.3%) patients exposed to MMI and 38/24 941 (0.15%) of those given PTU (133). MMI was associated with non-infectious hepatitis in 0.25% of cases, which was significantly higher than the rate of 0.08% with PTU (133). The rates of cholestasis were similar with PTU and MMI in this study. However, the rates of hepatic failure were higher with PTU than with MMI. A study from China reported 90 patients with severe ATD-related hepatotoxicity, defined according to the degree of elevation in transaminases, bilirubin and prothrombin time as well as the presence of symptoms (134). The mean doses of MMI and PTU were approximately 20 mg and 200 mg, respectively. The onset of severe hepatotoxicity was within 12 weeks for 81.1% of patients, and the type of hepatotoxicity (cholestatic vs hepatocellular injury pattern) were similar with MMI and PTU (134). Finally, a Danish study found similar frequencies of hepatic failure, presumably a result of hepatic necrosis, although this was not specified, at 0.03% of CBM/MMI exposed patients and 0.05% of PTU-treated patients (135).

Since up to one-third of patients with thyrotoxicosis have baseline transaminase elevation (136), it is important to obtain liver function testing before starting ATDs and to avoid ATDs if baseline transaminase values are more than five times the upper limit of normal (47). Likewise, if patients are discovered to have new transaminase elevation greater than three times the upper limit of normal or experience further increases from baseline elevation during a course of antithyroid drug therapy, continuation of therapy should be seriously reconsidered (47). Serial monitoring of liver function during a course of antithyroid drug therapy was reported by 54% of respondents to a US-based survey of endocrinologists (49) and by 42.3% of a survey of European Thyroid Association Members (50), though the ability of monitoring to detect early liver failure in this setting has not been studied. The ATA guidelines found insufficient evidence to recommend for or against routine monitoring of liver function tests in patients on ATDs, but noted that patients should be informed about possible hepatotoxicity and should discontinue the offending drug and contact their physician immediately with the onset of jaundice, malaise, dark urine or clay-colored stools (47).

Vasculitis

Antithyroid drug-induced lupus erythematosus was first reported in 1970 (137). More recent work has made it evident that such cases were really manifestations of drug-induced vasculitis, typically associated with perinuclear anti-cytoplasmic neutrophil antibody (pANCA) (138). In contrast to what is seen in antithyroid drug-related agranulocytosis and hepatotoxicity, vasculitis often occurs after years of treatment (138). Adding confusion to the situation is the fact that some patients with Graves' disease may have ANCA positivity in the absence of antithyroid drug therapy (139), as well as reports that ANCA positivity can develop in patients treated with antithyroid drugs who remain asymptomatic (140).

Patients typically present with fever, malaise, arthralgias and may have clinical findings of cutaneous, pulmonary and renal vasculitic involvement. Most patients are of Asian descent, with PTU being the offending drug in most but not all cases. The syndrome resolves with

drug discontinuation, but some patients have required immunosuppressive therapy as well as hemodialysis (138). This contrasts with non-antithyroid drug ANCA-related vasculitis, which appears to have a worse prognosis and a poorer response to treatment (127). Routine screening for ANCA positivity is not recommended (47).

Arthralgias/arthritis

Arthralgias occur relatively commonly during the use of antithyroid drugs. One study found that joint pain occurred in 8 (1.6%) of 500 patients treated with antithyroid drugs (141). These patients developed severe arthralgias of the hands, shoulders, hips, knees or ankles requiring analgesic use for 1–3 weeks to control pain. Joint swelling and erythema were rare (141). A patient with severe arthralgias occurring less than 1 month after starting MMI was recently reported (142). The patient developed pain, swelling, erythema and warmth over multiple small and large joints and required corticosteroid therapy for pain relief. MMI was switched to PTU, without recurrence of symptoms (142).

Summary

Medical therapy of hyperthyroidism, rather than ablative treatments such as RAI therapy and surgery, was Astwood's and his colleagues' major contribution to medicine and endocrinology. Nevertheless, antithyroid drugs continue to provoke controversy regarding their proposed mechanisms of action, their clinical role, including optimal use in pregnancy, and the fact that they can cause potentially lethal side effects. Despite these continuing uncertainties, they are the preferred treatment in most parts of the world. While novel pharmacologic approaches that target the autoimmune basis of Graves' disease may be on the horizon (143, 144), such therapies will likely be available only to future generations of physicians. In 1945 in his Harvey Lecture (1) Astwood predicted: 'The time will not be long before the common practice of ablating the thyroid will pass into history'. One wonders how much longer it will take for this hopeful statement to be fully realized.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review. The views expressed in this article are those of the authors and do not reflect the official policy of the National Institutes of Health or the United States Government. One of the authors (HB) is an employee of the U.S. Government. This work was prepared as part of his official duties. Title 17 U.S.C. 105 provides the 'Copyright protection under this title is not available for any work of the United States Government.' Title 17 U.S.C. 101 defines a U.S. Government work as a work prepared by an employee of the U.S. Government as part of that person's official duties. We certify that all individuals who qualify as authors have been listed; each has participated in the conception and design of this work, the analysis of data (when applicable), the writing of the document and/or the approval of the submission of this version; that the document represents valid work; that if we used information derived from another source, we obtained all necessary approvals to use it and made appropriate acknowledgments in the document and that each takes public responsibility for it.

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