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Letters to the Editor

Withdrawal of the Parenterally Applicable Form of Thyrostatic Drugs in Austria

Dear Editor:

The actual importance of thyrostatic drugs has recently been extensively reviewed by Cooper (1) in the *New England Journal of Medicine*. In spite of the fact that antithyroid drugs are rapidly absorbed from the gastrointestinal tract there remain few—but important—indications for the parenteral administration: patients who cannot swallow or patients who deny their poor compliance (a situation not so rarely encountered in hyperthyroid patients). In Austria methimazole was the only thyrostatic drug available in ampules until recently. To our regret, Novartis decided to withdraw the ampules from the market at the beginning of 2005. Because there is no competitor for this product we are left with the company's advice to apply methimazole via a gastric tube or to import ampules from Germany, where they are still being produced. Without commenting on the first advice one has to point out that the ampules should be readily available in case of need.

I admit that the case of need is relatively rare and that the production of the ampules will probably never be profitable. However, I feel that a company like Novartis could and should afford its production—and be it only for their reputation to care for patients and not for economics only.

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Propylthiouracil-Induced Lupus-Like Syndrome: Successful Management With Oral Corticosteroids

Dear Editor:

Recently, we read the interesting case of Calanas-Continente et al. (1) entitled "Necrotizing Glomerulonephritis and Pulmonary Hemorrhage Associated with Carbimazole Therapy." We would like to share our experience in a patient who developed propylthiouracil (PTU)-induced lupus-like syndrome. PTU, a thioureylene derivative, has been used for more than 50 years for the treatment of hyperthyroidism. Fever, arthralgia, rash, and leukopenia are the most common side effects, however, more serious complications such as agranulocytosis, vasculitis, hepatitis, and lupus-like syndrome may occur (2,3).

A 61-year-old woman was referred to our hospital in April 2004. She had been complaining of arthralgia, fever, myalgia, anorexia, dispnea, and fatigue for the preveious 3 weeks. She had been taking PTU, 50 mg daily, for a toxic multinodular goiter since 1995. In fact, 1 month before admission, PTU dosage was increased to 300 mg daily because of hyperthyroidism. Physical examination at the time of presentation revealed a temperature of 38.7°C, 1+ bilateral pretibial edema, and palpable, nodular, nontender goiter. Bilateral basal crackles on the chest examination and erythematous, ulcerated skin lesions on the abdomen and right popliteal region were also present. Laboratory investigations were as follows: Hemoglobin (Hb) 9.3 g/dL; white blood cell count (WBC) 2×10^9/L; platelets 353×10^9L; urea 71 mg/dL; creatinine 1.1 mg/dL; protein 6.3 g/dL; albumin 2.3 g/dL; thyrotropin (TSH) 0.01 mU/L; and thyroxine (T_4) 90 nmol/L. Urinalysis was normal. Acute phase reactants (erthyrocyte sedimentation rate [ESR] 130 mm/hr; C-reactive protein [CRP] 117 mg/L) were elevated. Antinuclear antibody (ANA) (titer 1/1000) and antineutrophil cytoplasmic antibody with c-ANCA pattern (titer 1/10) were positive. Anti-double–stranded DNA, antihistone antibody, and rheumatoid factor were negative. Serum complements (C3, C4) were within normal ranges. Immunoglobulins were polyclonally increased; immunoglobulin (Ig) G 3080 mg/dL, IgA 421 mg/dL, and IgM 344 mg/dL. PTU was withdrawn and she was put on antibiotherapy. Gram-stained smear and cultures

of punch biopsy material of the skin lesions for bacteria and fungi were negative as blood cultures. Histologic examination of biopsy material revealed pyoderma gangrenousum. Thorax computed tomography (CT) scan revealed pericardial and bilateral pleural effusions. Pleural fluid, obtained by diagnostic thoracentesis, was exudates and cultures for bacteria and fungi were negative. At this time no change in her clinic presentation was observed despite continuation of antibiotherapy for 2 weeks. The diagnosis of PTU-induced lupus-like syndrome was made on the bases of clinical and laboratory findings. She was started on prednisone 20 mg 3 times daily, and antibiotherapy was discontinued. Temperature decreased to within normal ranges after the second day of treatment. At the end of the first month of therapy, total thyroidectomy was performed and the patient began taking T_4. Oral corticosteroid therapy was gradually tapered after surgery, and completed to 3 months, at which time she had already been discharged from the hospital. At the end of 3 months of therapy, she was clinically well. Investigations revealed: Hb 14 g/dL; WBC 6.2×10^9/L; platelets 223×10^9/L. ESR and CRP were 25 mm/hr, 12 mg/L, respectively. ANA and ANCA were negative. Thorax CT scan was normal except diffuse pericardial thickening.

In summary, our patient has developed lupus-like syndrome associated with PTU therapy. Systemic side effects of antithyroid drugs may be examined in three major clinical manifestations: polyarthritis, hypersensitivity vasculitis and lupus-like syndrome. Clinical features of lupus-like syndrome include arthralgia, pericarditis, pleuritis, fever, and cutaneous photosensitivity. Antinuclear antibodies are positive in most of the cases and native anti-DNA antibodies are reported. Duration of therapy prior to onset of symptoms ranges from weeks to years and there is no evidence of dose effect (4,5). Although symptoms generally disappear several days after withdrawal of the drug, early institution of immunosuppressive drugs would be necessary to minimize the risk of permanent organ damage if the efficacy of the drug withdrawal is incomplete (4). If a patient has had an adverse reaction with PTU, the next step in the management of hyperthyroidism should be radioiodine or surgery, because of cross-reactivity between antithyroid drugs. Therefore, lupus-like syndrome is a rare, and may be life-threatening complication of PTU. Our findings should alert physicians who are dealing with patients receiving PTU, although the exact mechanism(s) of the sideeffects remain unclear.

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Reference Values for Thyrotropin

Dear Editor:

The definition of thyroid function and its potential influence on other body systems relies on the interpretation of laboratory determinations based on valid reference values for the population in question. In the March 2005 issue Völzke et al. (1) have defined reference intervals for thyroid function tests for a northeast German population. It is interesting that their upper normal level for thyrotropin (TSH) is 2.12 mIU/L. While this value appears to fit perfectly in western Pomerania, any extrapolation to other population might be misleading. Following this line of thought we would like to present an analysis of our current data regarding the upper limit of TSH values for Austria. This analysis contains both the definition of the upper range of basal TSH and the evaluation of this limit in patients attending our Outpatient Thyroid Service.

The definition of the upper normal range for TSH was based on biologic information arising from intravenous thyrotropin-releasing hormone (TRH) stimulation tests. The data for 2143 female patients seen between 1996 and 1998 were analyzed. They attended the Endocrinology Outpatient

Unit, Department of Gynecology (HM). A normal response was defined as a maximal TSH level of 20 mIU/L. Using ROC analysis (SPSS for Windows, release 11.0.1, SPSS, Inc., Chicago, IL), a basal TSH level of 3.5 mIU/l had a specificity value of 0.9928 for predicting a normal TSH response.

During the period of time between January 2001 and December 2003 a further series including 12,838 subjects was studied. There were 10,036 females and 2802 males, ranging in age from 20 to 89 years. The subjects were attending the Thyroid Outpatient Unit of the Clinical Department of Nuclear Medicine, Innsbruck Medical University (RM, IV). Thyroid hormone determinations, TSH, free triiodothyronine (FT_3) and free thyroxine (FT_4), were done using the ACS:180 System (Bayer Health Care, Leverkusen, Germany). Using the statistically evaluated level of basal TSH of 3.5 mIU/L, 88.2% and 85.3% of female and male patients, respectively, were considered euthyroid. Using the reference intervals from Völzke et al., only 71% of females and 64.1% of males would be considered euthyroid.

The effects of reducing the upper level of TSH values would lead to the false diagnosis of either overt or latent hypothyroidism. Fatourechi et al. (2) have evaluated the impact of lowering the upper value to for 5 to 3 mIU/mlL They found an additional proportion of 15.4% of patients would fall into the category of decreased thyroid function. In our population the use of an "external" reference interval would also increase the number of false positives by 17.2% and 21.2% of females and males, respectively. We conclude that although there is indeed a trend toward lower TSH reference values in this millennium, there are still regional differences. These differences have to be kept in mind for a correct interpretation of thyroid function tests.

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Disseminated Medullary Thyroid Cancer After Early Thyroid Surgery in Multiple Endocrine Neoplasia Type 2A

Dear Editor:

Currently, DNA analysis for the detection of germline mutations in the *RET* (*RE*arranged during Transfection) proto-oncogene is the gold standard in the assessment of individuals at-risk for multiple endocrine neoplasia (MEN) type 2A, 2B and familial medullary thyroid cancer (FMTC). A positive result is the single indication for prophylactic thyroid surgery, which tends to be less aggressive with minimal morbidity ahead of the development of a malignant stage (1). Timing of treatment for MTC can be based on the type of *RET* mutation in patients with MEN 2A, MEN 2B, and FMTC (2,3). In the May 2005 issue of this Journal, Van Santen et al. (4) described a case history of a boy diagnosed with MEN 2A in whom prophylactic thyroidectomy failed. The authors address the difficult issue of detectable tumor markers without anatomic substrate. Multiple unsuccessful diagnostic procedures resulted in substantial emotional burden to the patient. The authors conclude that when prophylactic thyroidectomy in MEN 2A has failed, it may be best to withdraw from further interventions to prevent more damage. However, they do not discuss the fact that initial surgical management of patients with MTC is crucial for disease-free survival (5,6). We would like to take the opportunity to comment on that.

In the patient described by Van Santen et al., both basal and stimulated serum calcitonin levels were elevated indicating C-cell pathology, but in 1994 it was considered safe to postpone thyroidectomy until the serum calcitonin levels became abnormal. At age 7.0, a total thyroidectomy without lymph node dissection was performed. Despite surgery, the calcitonin levels failed to return to normal indicating, residual C-cell disease.

Currently, preventive thyroidectomy is recommended before the age of four to five years or even earlier when calcitonin levels are elevated (2,4). Since 1994, we perform a central lymph node dissection or at least an exploration of the tracheoesophageal groove with dissection of enlarged nodes at the time of total thyroidectomy in case of abnormal tumor markers (4). Although lymph node metastases rarely are present before the age of 10 in patients with MEN 2A, there is a lack of consensus regarding additional lymph node dis-

section (2,4). Even though there is no consensus, when serum calcitonin levels do not return to normal after thyroidectomy an elective central and bilateral lymph node dissection has to be performed as soon as possible (5,6). Elevated calcitonin and carcinoembryonic antigen are reliable determinants of residual MTC and MTC primarily metastasises to lymph nodes in the central compartment of the neck. Therefore, despite the great efforts made to visualize residual MTC, elective neck dissection probably would have demonstrated micrometastases and could have offered this patient a chance of cure (5,6).

The case reported by Van Santen et al. illustrates that when calcitonin levels are elevated, a central compartment dissection should be added to total thyroidectomy as a one-stage procedure in carriers of a *RET* germline mutation. In experienced hands, this procedure can be performed safely even in very young children (3). Initial (elective) lymph node dissection can improve loco-regional control and prevent multiple surgical procedures. We agree with Van Santen et al. that a "wait-and-see" policy shifting the goal of treatment from cure to palliation is warranted in this patient. However, in case of postoperative elevated calcitonin levels, one must not hesitate to perform central and bilateral lymph node dissection in addition to total thyroidectomy.

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Authors' Response

Dear Editor:

We would like to thank de Groot and colleagues for their reactions to our case report, published in *Thyroid* in May 2005.

We agree fully with the authors that successful management of medullary thyroid cancer (MTC) in patients with multiple endocrine neoplasia type 2A (MEN 2A) can only be achieved by initial adequate surgical management.

The treatment strategy for patients with MEN has changed over time, for example, thyroidectomy is now advised at a younger age than in 1994 and the timing of treatment may even be based on the type of *RET* mutation. The current advice is to perform surgery before the age of 4 to 5 years. However, this consensus may even be discussed, considering the fact that MTC has already been diagnosed in children 1 and 2 years of age. In light of this it may even be indicated to perform thyroidectomy as early in life as soon as the diagnosis of MEN 2A is confirmed by DNA analysis.

Indeed, the past few years it has become clear that in case of MTC (positive markers) in a patient with MEN 2A, prophylactic total thyroidectomy should be combined with a central neck dissection. In contrast to 1994, this has now become our current strategy, which is in line with the guidelines of the Dutch working group for Endocrine Surgery of The Netherlands Association of Surgeons. In our patient, in 1994, additional lymph node surgery was not performed at that time mainly because the histologic evaluation of the thyroid tissue did not show any MTC. Only after two reevaluations of the thyroid tissue was MTC found. For this reason, the elevated calcitonin and carcinoembryonic antigen (CEA) levels were repeatedly measured and determined with different techniques to rule out there was a false-positive elevation of tumormarkers. After the thyroid tissue did prove to show MTC and a palpable lymph node was found, additional lymph node dissection was performed, as is described in the case report.

We agree that in retrospect, thyroidectomy should have been performed as soon as the diagnosis of MEN 2A was confirmed and that central lymph node dissection should be

performed if plasma calcitonin levels are elevated preceding or following soon after thyroid surgery. We thank de Groot and colleagues for their valuable comments that clarify this aspect of the treatment and the guidelines we currently follow in these patients. At this time in the course of the disease in the patient described, it may be best to wait for clinical symptoms of MTC and treat accordingly instead of searching for metastases at the cost of the quality of life of the patient.

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