with a signal/background, parameter for judging immunometric assay (IMA) sensitivity from the rhTSH response data shown in Fig. 2 [1]. Although this is a valid criticism, recalculation of the data as the ratio only changes the sensitivity ranking of the Pasteur method from fifth to fourth with respect to both patients. Further, their comment regarding a concern for using an isotopic tracer close to its expiration date only emphasizes the advantages of nonisotopic signals.

Minimum detection limits and clinical cutoffs cannot be compared in absolute terms (μg/L) unless Tg assays are standardized on the new International Reference Preparation (CRM 457) [2]. Calzolari et al. discuss minimum detection limits based on analytical sensitivity (95% confidence limits of the signal for the zero calibrator). Analytical detection limit is a clinically meaningless parameter when compared with functional sensitivity based on low range intersay precision—a concept now firmly established for serum TSH measurements [3]. It is especially important for a Tg assay that functional sensitivity be used to establish the lower reporting limit since the typical clinical interval for using Tg to monitor patients with thyroid cancer is 6 to 12 months.

Calzolari et al. appropriately question the use of 131I scintigraphy as the "gold standard" for judging the clinical sensitivity and specificity of serum Tg measurements. Disparities between imaging and serum Tg do not usually reflect differences in TSH secretory status rather than differences in scan dose [4, 5] and the sensitivity of the Tg assay method [1]. Indeed, studies now suggest that negative 131I uptakes in patients with detectable serum Tg usually represent falsely negative scans since post-treatment scans will often reveal disease in many patients [4, 5]. Current concepts dictate that a detectable serum Tg is expected whenever a patient has unequivocal metastatic thyroid cancer, even when serum TSH is suppressed [6]. The Mariotti study of the Pasteur Tg IRMA [7] included only TgAb-positive patients in the high TSH state before imaging. The failure to detect serum Tg by IRMA in such a patient is more likely to be due to TgAb interference causing underestimation of the serum Tg measurement than a submaximal TSH increase.

The epitope selection approach used to develop the Pasteur IRMA is an attractive concept. The question of whether the Tg epitope fingerprint typical of thyroid cancer is the same as that of autoimmune thyroid disease is not as important as the question of the clinical validity of serum Tg measurements made in TgAb-positive patients. Calzolari et al. conclude their remarks by claiming that their epitope selection approach leads to a significant reduction in autoantibody interference as compared with "conventional" IMAs. Tg recovery cannot support this claim in view of the gross discordance between the RIA and IMA serum Tg results for TgAb-positive patients with unequivocal evidence of persistent disease (33.1, range 1.2–92 vs <0.3, range <0.3–1.1 μg/L, RIA vs IMA respectively [1]) despite "appropriate" (>80%) recoveries with both the RIA and IMA methods.

Clearly the clinical reliability of serum Tg measurements made in TgAb-positive sera by IMA methodologies remains a major concern, whether or not an epitope selection approach is used. It behooves manufacturers to show that their methods provide serum Tg values in TgAb-positive patients that are concordant with clinical status and prompt an appropriate clinical response. Patients with persistent TgAb detected on long-term follow-up usually have persistent disease and have a higher risk of recurrences [8, 9]. For such patients, the use of a Tg IMA method prone to TgAb interference causing underestimation could potentially have serious medicolegal consequences, as an inappropriately low serum Tg result may lead to a delay in the diagnosis and treatment of recurrent or metastatic disease. Because recoveries cannot be used to validate the reliability of serum Tg measurements made in TgAb-positive sera, we should question the current practice whereby laboratories continue to report serum Tg values for such patients.

References


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Apparent Positive Interference from an Etoposide Metabolite, but Not Etoposide, in Measuring Urinary Vanillylmandelic Acid

To the editor:
For 15 years, we have determined urinary vanillylmandelic acid (VMA) by a method [1] that relies on the reaction of extracted VMA with the diazo derivative of p-nitroaniline to give a pink chromophore; the chro-
etoposide added in the final stage of the procedure, (B) etoposide metabolite from patient's urine. (C) VMA from normal urine.

Etoposide undergoes extensive hepatic metabolism and excretion by the kidneys [3]. Allen et al. [4] isolated the major urinary metabolite of etoposide and identified it by mass spectrophotometry as 4-demethyl-epipodophyllinic acid. The features of this compound make it a good candidate for reaction with a diazo derivative: an aromatic phenolic residue as possible site for reaction and a carboxyl group to carry the molecule through the extraction steps of our procedure. Other metabolites excreted in smaller amounts, i.e., picroetoposide and the aglycone, are for purely structural reasons not expected to react positively in the assay. The patient's urine gave a normal VMA spectrum 10 days after therapy with etoposide was stopped.

Several metabolites as well as xenobiotics interfere with many diazo methods used in the determination of VMA [5]. The reaction of a diazo derivative with carboplatin is highly unlikely, this simple organo-metallic compound being devoid of activated aromatic residue. Further work is under way to isolate and test the major metabolite.

We recommend that VMA analysis by use of any diazo derivative such as ours or some other [6] be interpreted with caution in patients receiving etoposide. Alternatively, methods with high resolving powers such as thin-layer chromatography [7] or HPLC [8] should be considered.

References

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Serum Cardiak Troponin I, Creatine Kinase (CK), and CK-MB in Early Posttraumatic Rhabdomyolysis

To the Editor:

Early diagnosis of posttraumatic cardiac injury is important for patient outcome [1] but a concomitant rhabdomyolysis may impede its detection by biochemical means. Cardiac troponin I (cTnI) might be a useful tool to specifically assess myocardial damage in trauma patients. We re-