A Limited Sampling Strategy for Estimating Sirolimus Area-Under-the-Concentration Curve, Bruce Kaplan,1* Herwig-Ulf Meier-Kriesche,2 Kimberly Napoli,2 and Barry D. Kahn1 (1Div. of Renal Dis. and Hypertension, Dept. of Internal Med., and 2Div. of Immunol. and Organ Transplant., Dept. of Surgery, The University of Texas Medical School at Houston, 6431 Fannin, Suite 4.163, Houston, TX 77030; *author for correspondence and reprint requests: fax 713-794-1197)

Sirolimus (SRL), a promising new immunosuppressive macrolide [1–3], displays unpredictable pharmacokinetic properties in humans. Measurement of a single trough concentration may reflect total drug exposure for drugs with consistent bioavailability and elimination properties, but not for drugs such as SRL that have variable bioavailability and unpredictable elimination characteristics. For such agents, area-under-the-concentration–time-curve (AUC) measurements have been used to estimate total drug exposure because they often correlate with pharmacodynamic effects [4–6]. Although the relation between SRL AUC, the therapeutic effects of SRL, and toxicity has not been investigated, such a study might help elucidate the optimal therapeutic regimen for the drug.

Sampling regimens for full pharmacokinetic profiles are frequently not clinically feasible because of both time and cost restraints. Therefore, limited sampling strategies have been devised to obtain reasonable estimates of drug exposure. Limited sampling AUC strategies have been used to monitor the exposure of patients to oil-based (Sandimmune®; Sandoz, Basel, Switzerland) [7, 8] or microemulsion (Neoral®; Sandoz) [9] formulations of cyclosporine (CsA) and to chemotherapeutic agents such as cyclophosphamide [10]. The present report describes a clinically reliable sampling strategy to predict the AUC values for SRL to more efficiently evaluate the clinical significance of total exposure.

In our study, 27 renal transplant recipients underwent a total of 77 full SRL pharmacokinetic profiles during the first year after the transplant procedure; 7 patients underwent pharmacokinetic profiling before the transplant procedure. SRL was administered once daily in an aqueous mixture (Rapamune®) provided by Wyeth–Ayerst Research, Princeton, NJ. The clinical protocol for pharmacokinetic monitoring was approved by our institutional Committee for the Protection of Human Subjects. The whole-blood samples were assayed with a validated HPLC method to quantify SRL concentrations [11].

The linear trapezoidal rule [12] was used to calculate the AUC values for each patient profile from the concentrations in the full set of blood samples drawn before dosing as well as 1, 2, 4, 6, 10, 14, and 24 h thereafter. Simple linear regression models were applied to assess the correlation between the AUC value and single sample concentrations. A nonlinear relation between the variables was excluded by using multiple curve estimation procedures (quadratic, cubic, power, inverse, “s,” and log). The relative ability of single vs multiple sample concentrations to predict the AUC value was assessed with a stepwise forward selection multiple regression technique [13]. This method called for the independent variables to be added to the regression equation sequentially in order of diminishing importance, and for the coefficient of determination ($r^2$) and the regression coefficient to be calculated at each step. We developed multiple linear regression models in which two, three, or four concentration time points served as the independent variables. The relative fit of each model was determined on the basis of the $r^2$ value. The models were then validated by comparing the predicted AUC with the value calculated from the full pharmacokinetic profile. We used the concentration data from several combinations of samples to generate model linear regression equations. The prediction error for each set of values for a given patient was calculated as $\left(\text{predicted AUC} - \text{full AUC} \right) \times 100$. In addition, the mean prediction error and the standard deviation values among all patient data were displayed in frequency histograms that were evaluated for the presence of a normal distribution.

Simple and multiple linear regression and ANOVA analyses were performed to investigate the importance of other factors that might influence the prediction error, such as time after transplantation, absolute AUC values, demographic characteristics, and CsA pharmacokinetic parameters. A power analysis was performed to investigate the likelihood of a type-II error. The statistical analyses were performed with SPSS software (Version 7.0 for Windows 95; SPSS, Chicago, IL) [13] and NCSS software (for the power analysis; PASS, Version 1.0 for DOS) on an IBM-compatible personal computer with a Pentium processor.

Table 1 shows the correlation between the SRL AUC value calculated from the full pharmacokinetic profile and concentrations obtained at several time points. The concentration values for the samples obtained at 24 h ($C_{24}$) correlated better with the full AUC values and showed lower prediction error values than $C_0$ values, presumably because the $C_{24}$ sample was obtained at the precise time.
Serum Neuron-Specific Enolase in Patients with Pitu- 
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of Biochem., Pitie’ School of Medicine, 75013 Paris, France; 
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Neuron-specific enolase (NSE) is an isomer of the widely 
distributed glycolytic enzyme 2-phospho-d-glycerate hy 
drolase (EC 4.2.1.11), composed of two subunits, α and γ. 
NSE is localized in neurons and in peripheral and central 
neuroendocrine cells [“amine precursor uptake and de 
carboxylation” cells (APUD)] [1]. Tumors arising from 
APUD cells may contain high amounts of NSE detectable 
by both immunostaining of tumor cells and radiomu 
rographic techniques for measurement of whole blood rapamycin con 

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usefulness of serum measurement of NSE in patients with functioning and nonfunctioning (NF) pituitary adenomas.

We studied 36 patients (24 women, 12 men, ages 20–84 years, mean 47 years) with pituitary adenomas. Nineteen tumors secreted prolactin (PRL) and six growth hormone (GH), and 11 were NF adenomas. Control subjects (28) included 9 females and 19 males, ages 12–69 years (mean 36 years) without known pituitary disorders. The procedures followed for the use of these subjects were in accordance with the Helsinki Declaration of 1975, as revised in 1983.

Tumor patients were given a complete pituitary function test, including measurements of serum PRL, GH, corticotropin and (or) cortisol, thyrotropin, free thyroxine, luteinizing hormone, testosterone or estradiol-17β, and follicitropin. For serum NSE determination, venous blood samples were drawn without hemolysis from the antecubital vein, and centrifuged after 30 min. Each serum aliquot was stored frozen at –20 °C until assayed with a commercial kit (Pharmacia, Saint Quentin en Yvelines, France). Normal NSE values were 0.45–16.5 μg/L.

Statistical analysis was performed with the nonparametric Mann–Whitney U-test and Spearman rank correlation. A P value < 0.05 was considered significant.

The mean (±SD) serum NSE concentration was significantly higher in tumor patients than controls [7.5 ± 2.9 μg/L (range 1.0–16.5 μg/L) vs 5.0 ± 1.5 μg/L (range 2.3–9.9 μg/L) (P < 0.001)]. In patients with tumors, serum NSE concentrations were within the reference interval in all but one subject. The mean serum NSE concentration was also significantly higher (P < 0.003) in each subgroup of pituitary tumor group when compared with the control group. In patients with PRL, GH, and NF tumors, values were 6.9 ± 2.6 μg/L (range 1.0–12.0 μg/L), 8.1 ± 1.7 μg/L (range 5.7–10.0 μg/L), and 8.3 ± 3.2 μg/L (range 4.5–16.5 μg/L), respectively. Mean serum NSE concentrations were similar among the three subgroups of tumor patients. No significant correlation was found between serum PRL and NSE concentrations in patients with PRL adenoma.

We conclude that serum NSE is not a useful marker of pituitary adenomas and cannot distinguish among PRL, GH, and NF tumors.

We are indebted to the nurses of the Department of Endocrinology, Pitié Hospital, Paris, France, for valuable assistance.

References

Age- and Sex-Related Changes of S-100 Protein Concentrations in Cerebrospinal Fluid and Serum in Patients with No Previous History of Neurological Disorder, Øystein Nygaard, Bodil Langbakk,1 and Bertil Ronner* (Depts. of Neurosurgery and 1Clin. Chem., Univ. Hosp. of Tromsø, 9038 Tromsø, Norway; *author for correspondence: fax + 47 77 62 70 52)

S-100 is a calcium-binding protein synthesized in astroglial cells in all parts of the central nervous system (CNS). It is present in the body in different subchains, of which the beta form (96%) predominates in the brain [1]. S-100 protein is normally not detectable in serum [1], but previous studies have demonstrated that increased S-100 concentrations in cerebrospinal fluid (CSF) are an index of the active phase of cell injury in patients with acute multiple sclerosis exacerbations, intracranial tumors, acute encephalomyelitis, and spinal cord compression [2]. High CSF concentrations of the S-100 protein have also been demonstrated in patients with glioblastoma, cervical compression, polyneuropathy, hydrocephalus, subarachnoid hemorrhage, encephalitis, meningitis, and cerebral infarction [3–8]. A previous study demonstrated age-related reference values for S-100 protein in CSF in children and adults with distinct neurological disorders [9].

We sampled serum and CSF from 75 men and 35 women undergoing various surgical procedures in spinal anesthesia. The patients had no actual or previous history of neurological disease. The study was performed to establish reference intervals of S-100 protein in CSF and serum.

From August 1995 to June 1996, serum and CSF samples were obtained from 110 patients undergoing surgery in spinal anesthesia. Before inclusion in the study, the patients answered a questionnaire concerning known neurological symptoms or diseases, and their hospital records were investigated. The inclusion criteria were as follows: no history of previous neurological symptoms or disease, no previous investigation in a neurological department, no present symptoms indicating any neurolog-
ical disease, no evidence of malignant disease, age between 20 and 89 years, and signed informed consent form. The patients were divided into three age groups: 20–39 years, 40–59 years, and 60–89 years.

To determine S-100 protein concentration, 1 mL of CSF was taken from the spinal needle (gauge 25) immediately before the spinal anesthesia was performed. Simultaneously, 5 mL of serum was taken from a venous cannula. The samples were stored at −70 °C within 10 min for later analysis.

The concentrations of S-100 protein in CSF and serum were analyzed by using a commercially available two-site IRMA kit (Sangtec Medical, Bromma, Sweden). Calibrators (1, 5, 10, and 20 μg/L), controls (high and low), and diluent (also used as zero calibrator) were delivered from Sangtec Medical. CSF and serum samples were diluted with phosphate buffer and subsequently incubated with a plastic bead coated with monoclonal anti-S-100 antibody. After a 1-h incubation, the beads were washed to remove any unbound material. 125I-labeled anti-S-100 antibody was added, and after a 2-h incubation and subsequent washing, the amount of radioactive label bound to immobilized S-100 was measured in a gamma counter.

The sensitivity was 0.13 μg/L S-100 protein, and the precision (CV) was: low concentration, 10%; high concentration, 5%.

The same calibration curves were used for CSF and serum, and each sample was analyzed in duplicate.

The procedure of collecting CSF from the 110 patients undergoing surgery in spinal anesthesia was approved by the ethical committee at the University Hospital of Tromsø.

The scatter diagrams of S-100 protein contained one clear outlier (10.2 μg/L), which was excluded, resulting in a normal distribution of values. P-values for sex dependency were calculated by using a two-tailed Student’s t-test. The relation between age and S-100 protein in CSF in men and women was evaluated by using simple regression analysis. The median values and distribution percentiles in three age groups of men and women were estimated.

The mean age for men (n = 75) was 48 ± 15 years and for women (n = 35), 47 ± 15 years. The frequency distribution of age in men and women was equal.

S-100 protein was not detectable in any serum samples. There was a significant difference between men and women in S-100 protein concentrations in CSF (mean 1.9 ± 0.7 vs 1.5 ± 0.5 μg/L, P = 0.0026). Fig. 1 illustrates the S-100 protein concentrations as a function of age (years) in both sexes. Concentrations of S-100 protein in CSF increased with age in both sexes, but this relation was less pronounced in women.

Table 1 lists age-related percentiles for the distribution of S-100 protein concentrations in men and women.

This is the first report of reference values of S-100 protein in CSF in patients with no previous history of neurological disorder. In 1992, van Engelen et al. [9] reported age-related changes of S-100 protein concentrations in CSF from children and adults undergoing neurological examination but without evidence of an organic neurological disease. The present report confirms their results, demonstrating an increase of S-100 protein concentrations in CSF with age from 21 to 84 years. Furthermore, we found sex-related dependency of S-100 protein in CSF, with significantly higher concentrations in men than in women.

There are several explanations for an age-related increase in S-100 protein in CSF: (a) The age dependency reflects increasing myelin loss with age; (b) the S-100 protein concentrations in the cells increase with age, whereas the turnover of the cells remains constant; or (c) the increase could be a result of increased half-life attributable to a reduced CSF bulk flow at older age [9–12].

S-100 protein was not detectable in serum in the present material including only neurologically healthy patients. Detectable serum S-100 protein indicates damage to glial cells and a reduced integrity of the blood–brain barrier (BBB). Ingebrigtsen et al. [13] reported increased serum concentrations of S-100 protein in patients with minor
head injury. The protein was detectable in serum within 12 h after the injury, indicating a BBB dysfunction.

Persson et al. [6] demonstrated increased CSF concentrations of S-100 protein in ischemic stroke patients between 18 h and 4 days after the stroke. Thus, normal values of S-100 protein in CSF or serum do not exclude neurological disease, and serial measurements can elucidate the dynamics of the pathological process in relation to therapy.

The commercially available IRMA kit for analysis of S-100 protein in CSF and serum estimates values as low as 0.2 μg/L with an acceptable precision. In one sample, the calibrators and controls showed higher concentrations of the protein than described from the manufacturer. Consequently, a consistent use of local laboratory controls in addition to the ordinary delivered calibrators and controls is recommended.

Recently, Lamers et al. [7] evaluated the value of neuron-specific enolase, S-100 protein, and myelin basic protein in CSF in patients who underwent a diagnostic lumbar puncture for a clinical indication such as CNS infection or another neurological disorder. In patients with cerebrovascular accidents such as minor cerebral infarcts, a significant increase in S-100 protein in CSF was demonstrated. The authors conclude that the concentrations of proteins in CSF depend on several factors, such as the distance between the affected brain area and the CSF compartment, the severity and extent of brain damage, the regional variability of these proteins in the brain, and the possible degradation of these proteins by macrophages and (or) proteinases either locally or in the CSF. Consequently, normal or increased concentrations of CSF-specific proteins in individual patients must be evaluated with caution. Although S-100 protein and other nervous system-specific proteins are very sensitive indices of pathology [14], normal serum or CSF values do not exclude CNS disease.

The present study underlines the importance of considering both age and sex when S-100 protein concentrations in CSF are evaluated in patients with different neurological disorders.

We thank Sangtec Medical, Bromma, Sweden, for supporting analyzing kits.

References

Table 1. Percentiles for the distribution of S-100 protein concentrations (μg/L) in CSF in three age groups of patients with no previous history of neurological disorders.

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Men</th>
<th>Women</th>
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<tr>
<td>20–39</td>
<td>P10</td>
<td>P25</td>
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<tr>
<td>1.0</td>
<td>1.1</td>
<td>1.4</td>
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<td>1.2</td>
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<td>1.8</td>
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<td>1.4</td>
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10th to 90th percentiles (P = percentile).

Serum Osteocalcin in 1634 Healthy Children, Michele Cioffi,* Anna Maria Molinari, Patrizia Gazzero, Bruno Di Finizio, Mario Fratta, Angela Deufemia, and Giovanni Alfredo Puca (Ist. di Patol. Generale e Oncol., Seconda Univ. degli Studi di Napoli, Larghetto S. Aniello a Caponapoli, 2, 80138 Napoli, Italy; *author for correspondence: fax +81/566-5695)

Osteocalcin or bone Gla protein (BGP) is a vitamin K-dependent, low-molecular-mass (5800 Da), 49 amino acid peptide synthesized by osteoblasts [1, 2]. Osteocalcin con-
tains three residues of γ-carboxyglutamate, which provide the point of interaction between the BGP and hydroxyapatite in the extracellular bone matrix. The 19–20 and 43–44 residues provide sites for the tryptic hydrolysis; the resulting peptides may be the products of liver, kidney, and plasmatic breakdown of the molecule. The physiological role of these fragments is unknown.

Osteocalcin is an important marker of bone turnover in physiological and pathological conditions [3]. Physiologically, serum osteocalcin was increased in children, particularly during the first year of life and during puberty, when the evolution of the concentration was related to the rapidity of physical growth. The significant correlation between BGP and testosterone and serum insulin-like growth factor 1 is consistent with the important role of this protein in the skeletal growth [4]. Some authors have reported a decrease of serum osteocalcin in growth hormone-deficient children and normalization after hormone treatment [5, 6]. The aim of this study was to determine serum osteocalcin in a large group of children according to their age.

We selected for recurrent controls for the study 1634 healthy children (801 girls, 833 boys), ages 1–16 years, arriving at the Department of Paediatrics. None of the subjects was receiving any medication and all were ambulatory. All children with evidence of endocrine, hepatic, renal, or other diseases known to affect bone metabolism were not considered. A single venous blood sample was obtained and the serum was extracted and frozen until assay. The procedures followed for human investigations were according to the ethical standards of the institution’s responsible committee, in accord with the Helsinki declaration of 1975 (as revised in 1983).

Serum osteocalcin was measured by the same solid-phase “sandwich” IRMA used in our laboratory (OsteoELSA; CIS bio international, Gif sur Yvette, France). The first antibody was coated on the ELSA solid phase; the second, radiolabeled with 125I, was used as a tracer. The precision was tested by using four samples at different concentrations (between 32.5 and 88.2 μg/L) 30 times in the same assay (CV = 3.5–4.9%, mean 4.2%) and 15 times in successive assays (CV = 3.7–6.2%, mean 4.9%). The minimum detectable concentration (0.4 μg/L) was obtained by repeating in duplicate 20 times the zero calibrator and calculating 3 SD on average.

The median results are shown in Fig. 1 and interquartile ranges in Table 1. For children between ages 1 and 11 years, median values were in narrow intervals. In all healthy children, median osteocalcin concentrations were ≤88.5 μg/L. In girls, serum osteocalcin decreased significantly (P ≤0.05) after the 12th year, reaching the values of healthy adult women at the age of 14. In boys this happened 2 years later, at 16, and the result decreased significantly (P ≤0.001) after the 15th year. P values are calculated with a statistical nonparametric (Friedman) test for paired groups.

Previous studies showed increased serum osteocalcin in diseases with increased bone turnover, e.g., renal osteodystrophy, hyperparathyroidism, hyperthyroidism, and Paget disease [7–10], and decreased concentrations with low bone turnover, e.g., hypoparathyroidism, hypercalcemia resulting from bone metastasis, and long-term cortisone therapy. The decreased serum osteocalcin during prolonged cortisone therapy reflects a decrease of the osteoblastic activity [11]. In primary osteoporosis, such as in the postmenopausal form when the phosphocalcic balance is normal, the assay of serum osteocalcin allows classification of the disease according to regeneration rate (high or low remodeling) [12–14]. In contrast, little information is available on serum osteocalcin in children. Some authors have reported higher values in healthy children than in adults; the increase happens at the age at which puberty usually occurs [15].

The decreases of osteocalcin at ages 12 and 15 in girls and boys, respectively (Fig. 1), may reflect the later occurrence of puberty in boys.

The observed median values for osteocalcin in boys and girls ages 1–12 are two or three times those in healthy adults.

![Fig. 1. Median serum osteocalcin in boys and girls.](image-url)
We acknowledge Marisa Punzo, Angela Sglavo, and Anna Maria Palmieri for excellent technical assistance in the assay procedure.

References


Elecsys® Thyrotropin (TSH) Assay Evaluated, Rémy Sapin,1*, Françoise Gasser,1 Michèle d’Herbomez,2 Jean Louis Wemeau,3 Christoph Ebert,3 and Jean Louis Schlenger4 (1Lab. Univ. de Phys. Biol., URA CNRS 1173, Service de Méd. Interne, CHRU, Strasbourg, France; 2Service Central de Méd. Nucléaire, Clin. Marc Linquette, CHRU, Lille, France; and 3Boehringer Mannheim, Tutzing, Germany; address for correspondence: Inst. de Phys. Biol., Faculté de Méd., F-67085 Strasbourg Cedex, France; fax 33 3 88 14 48 79, e-mail sapin@alsace.u-strasbg.fr)

Immuoassays on the fully automated Elecsys® 2010 analyzer (Boehringer Mannheim, Meylan, France) involve the electrochemiluminescent reaction of Ru(II) Tris(bipyridyl) with tripropylamine combined with a magnetic microparticle separation after short incubation times with low sample volumes [1]. The thyrotropin (TSH) assay, which requires a high sensitivity [2], has an 18-min incubation time and 50-μL sample volume. In the present study we assessed the analytical and clinical performances of this TSH assay during 5 weeks in June and July of 1996. Assays were performed in singleton according to the manufacturer’s instructions with two different lot numbers. Results were compared with those of the Immulite TSH3G assay (Behring Diagnostic, Rueil Malmaison, France). The procedures were performed in accordance with the Helsinki Declaration of 1975, as revised in 1983.

Interassay reproducibility was assessed by repeated analysis (n = 12) of 12 patients’ frozen sera and of the
TSH$^3$G Immulite control serum. CVs were $<5\%$ at TSH $>0.06$ mU/L, $10.4\%$ at TSH of $0.018$ mU/L, and $14.9\%$ at TSH of $0.014$ mU/L. “Functional sensitivity” (CV = 20%) was $<0.014$ mU/L; therefore Elecsys TSH can be considered a third-generation TSH assay [3]. Carryover might be a problem with such an assay [4]. Two samples with low TSH concentrations ($<0.005$ mU/L) were assayed immediately after a sample of high TSH concentration (191 mU/L). Carryover was $<0.3:10,000$ and so should not affect the precision profile [4]. For practical purposes we adopted a lower working limit for the Elecsys TSH of 0.01 mU/L.

One serum (TSH = 100 mU/L) was diluted from twofold to 512-fold in universal diluent (Boehringer Mannheim) and one serum (1 mU/L) from twofold to 64-fold in a sample from a hyperthyroid patient ($<0.005$ mU/L). The linearity was satisfactory with found values 97–106% and 100–107% of expected, respectively.

Elecsys TSH results ($y$) from 318 samples were related to those obtained with the Immulite method ($x$) over the range 0.005–100 mU/L according to the equation: $y = 1.18x - 0.08$ ($r = 0.981$, $S_{y|x} = 2.81$). Over the range 0.005 to 1 mU/L ($n = 153$) the equation was: $y = 1.15x + 0.005$ ($r = 0.974$, $S_{y|x} = 0.09$). Results were significantly higher by the Elecsys method ($P <0.001$, Wilcoxon’s matched pairs signed rank test).

Clinical results are shown in Fig. 1. TSH was assayed in sera obtained from 102 euthyroid control patients (51 ambulatory, 51 hospitalized; age range 16–75 years). Log transformation of the data yielded a reference range (mean $\pm 2SD$) of 0.50–4.36 mU/L. TSH was $>4.36$ mU/L in 41 sera from patients with hypothyroidism (35 overt and 6 subclinical) and $<0.30$ mU/L in 46 sera from patients with hyperthyroidism (33 overt and 13 subclinical). We propose a reference range from 0.30 to 4.36 mU/L that, without decreasing sensitivity for dysthyroidism, includes low normal TSH values [5]. In 31 euthyroid patients between 75 and 92 years of age, TSH was increased in two and decreased in three. Severe nonthyroidal ill (NTI) patients ($n = 68$) may have transiently high or low TSH [6, 7]. In these samples Elecsys and Immulite showed similar and satisfactory performances. Specificities were respectively 100% vs 99% in euthyroid control patients, 84% vs 81% in old patients, and 84% vs 85% in NTI patients; sensitivities were 100% vs 100% in hyperthyroid patients and 100% vs 97.5% in hypothyroid patients. In 13 patients receiving l-thyroxine (l-T$_4$) suppressive doses for thyroid cancer treatment, TSH values were $<0.30$ mU/L by both kits and well correlated ($r = 0.964$, $S_{y|x} = 0.029$).

In six sera from hyperthyroid patients, of which three contained heterophile antibodies, showing falsely increased TSH values as measured by another immunometric assay, Elecsys TSH was low, consistent with the clinical status of the patient. Interference seems to be very rare with this assay, which involves a chimeric (mouse/human) labeled antibody. In a serum from an euthyroid patient containing anti-avidin antibodies, Elecsys TSH was normal (2.0 mU/L), in agreement with the Immulite value (1.5 mU/L). Contrary to other methods also involving a streptavidin-coated solid phase [8], Elecsys TSH seems not to be disturbed by these antibodies. These lacks of interference are worth noting since, according to Laurberg [9], nonspecific TSH values are the most common cause of nonsuppressed TSH in hyperthyroidism and should be considered before other causes such as pituitary tumors or pituitary resistance to thyroid hormones.

In conclusion, the Elecsys TSH assay showed a high degree of reproducibility (third-generation TSH assay). It provided a clear separation between eu-, hyper-, and hypothyroid patients. Its specificity was also very satisfactory: lack of interference from heterophile antibodies or from less specific origin, no carryover. These characteristics tend to give to the Elecsys TSH a very good diagnostic potential and reinforce TSH as a cost-effective front-line thyroid function test.

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**Fig. 1.** Elecsys TSH results in different groups of patients: A, 102 control euthyroid patients; B, 35 overt hypothyroid; C, 6 subclinical hypothyroid; D, 33 overt hyperthyroid; E, 13 subclinical hyperthyroid; F, 31 old persons (>75 years old); G, 68 severe NTI patients; H, 13 patients receiving suppressive l-T$_4$ therapy for thyroid cancer treatment. Horizontal lines indicate the limits of the reference range (0.30–4.36 mU/L).
We thank S. Doffoel from the MGEN Laboratory in Strasbourg for providing us the ambulatory control samples and Boehringer Mannheim France for the Elecsys 2010 analyzer as well as the corresponding reagents.

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