LUC, What Is That?

To the Editor:

LUC, an acronym for "large unstained cells", is displayed on our automatic cell counter (Technicon H3) when large peroxidase-negative cells cannot be characterized further as large lymphocytes, "virocytes", or stem cells. Each year, we report ~30 000 laboratory results with LUC, of which 11% are abnormally high. (reference interval $\leq 0.2 \times 10^9$/L). We report ~65 000 blood leukocyte results, 90 000 blood hemoglobin results, and 1.6 million laboratory results per year. We have used the name LUC on the laboratory result-reporting scheme for 4 years. The automatic cell count is followed by a manual cell count in the daytime if the LUC value is abnormal.

On rare occasions, physicians have asked about the meaning and interpretation of LUC, but we have not known whether the term has been widely understood. We therefore asked 22 randomly selected doctors from three medical departments to answer a questionnaire while attending a morning conference on a certain day. The questionnaire consisted of a copy of a laboratory result-reporting scheme followed by questions concerning the doctor's education and interpretation of the LUC result.

Thirteen of the 22 doctors were specialists in internal medicine. All had ordered a cell count. Nineteen of the 22 doctors [86% (95% confidence interval, 65–97%)] did not know exactly what the abbreviation LUC meant. Seventeen of the 22 doctors [77% (95% confidence interval, 55–92%)] did not know how to interpret a high LUC; of the remaining 5, only 2 had a thorough knowledge. Nine of the 22 doctors [41% (95% confidence interval, 21–64%)] remembered specific clinical situations in which they had been unsure of the interpretation. Their actions in these situations differed (e.g., "nothing", "looked at the patient", "asked a colleague, who said it meant nothing"), but no one asked the laboratory department. Eight of the 22 doctors [36% (95% confidence interval, 17–59%)] had not encountered LUC in specific situations, but did not know what LUC meant when answering the questionnaire.

If all 30 000 LUC results reported by our laboratory each year were seen by a clinician, calculations show that 23 000 results per year (of which 2500 are abnormal) could not be interpreted. After this was revealed, the laboratory made a footnote saying "lymphocyt? virocyt? Stem cell? (Peroxidase-negative cells (Large unstained cells = LUC))" to explain the meaning and to remind clinicians of both viral disease and leukemia as possibilities.

The understanding of abbreviations in medical journals has been found to be incomplete *(1)*; therefore, it is not surprising that this same difficulty occurs with reports from the clinical laboratory. The presentation of the test results in a configuration that is easily perceived by the clinician, therefore, will facilitate interpretation of laboratory reports *(2)* and probably will improve patient outcome *(3, 4)*.

The laboratory cannot rely on clinicians to complain about nonunderstandable results, but must make the interpretation of laboratory results quick, easy, and user-friendly—features that should be evaluated before IUPAC or technical terms are delivered to clinicians.

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Serum γ-Glutamyltransferase Isoform Complexed to LDL in the Diagnosis of Small Hepatocellular Carcinoma

To the Editor:

Up to one-third of cirrhoses evolve into hepatocellular carcinoma (HCC), with ~90% of these cases developing on a preexisting cirrhosis *(1)*. However, the detection of early-stage neoplastic transformation remains a challenge. In a recent series of studies, we reported that multivariate discriminant functions based on the serum concentrations of various biochemical indexes efficiently discriminate between chronic hepatobiliary diseases at different stages of their natural history *(2–4)*. The multivariate analysis also allowed us to detect the neoplastic evolution in five of six cirrhotic patients ~6 months earlier than instrumental approaches *(2)*. This result prompted us to evaluate the efficiency of serum biochemical indexes in detecting small HCC, i.e., <3 cm *(5)*, developed on cirrhosis. We studied 21 new patients with small HCC diagnosed by ultrasound-guided fine-needle biopsy. The control population consisted of 51 cirrhotic patients diagnosed by histology. The latter patients were monitored for signs of HCC for at least 2 years after biopsy. The following biochemical indexes were analyzed on freshly collected serum from patients: alpha-fetoprotein (AFP), carcinoembryonic antigen, lactate dehydrogenase (LD), LD isoenzymes, alkaline phosphatase and alkaline phosphatase isoenzymes, γ-glutamyltransferase (GGT) and the GGTL isoenzyme (i.e., GGT complexed to LDL and VLDL), 5′-nucleotidase, leucine aminopeptidase, cholinesterase, copper, iron, ferritin, and pseudouridine, using previously described procedures *(2)*.

Serum LD5 (mean, 8.1 U/L in cirrhosis, 43.5 U/L in HCC; $P < 0.0001$), GGTL (mean, 24.6 U/L in cirrhosis, 44 U/L in HCC; $P < 0.005$), and AFP (mean, 55.9 μg/L in cirrhosis, 1440.9 μg/L in HCC; $P < 0.002$) concentrations were significantly higher (Student *t*-test) in patients with small

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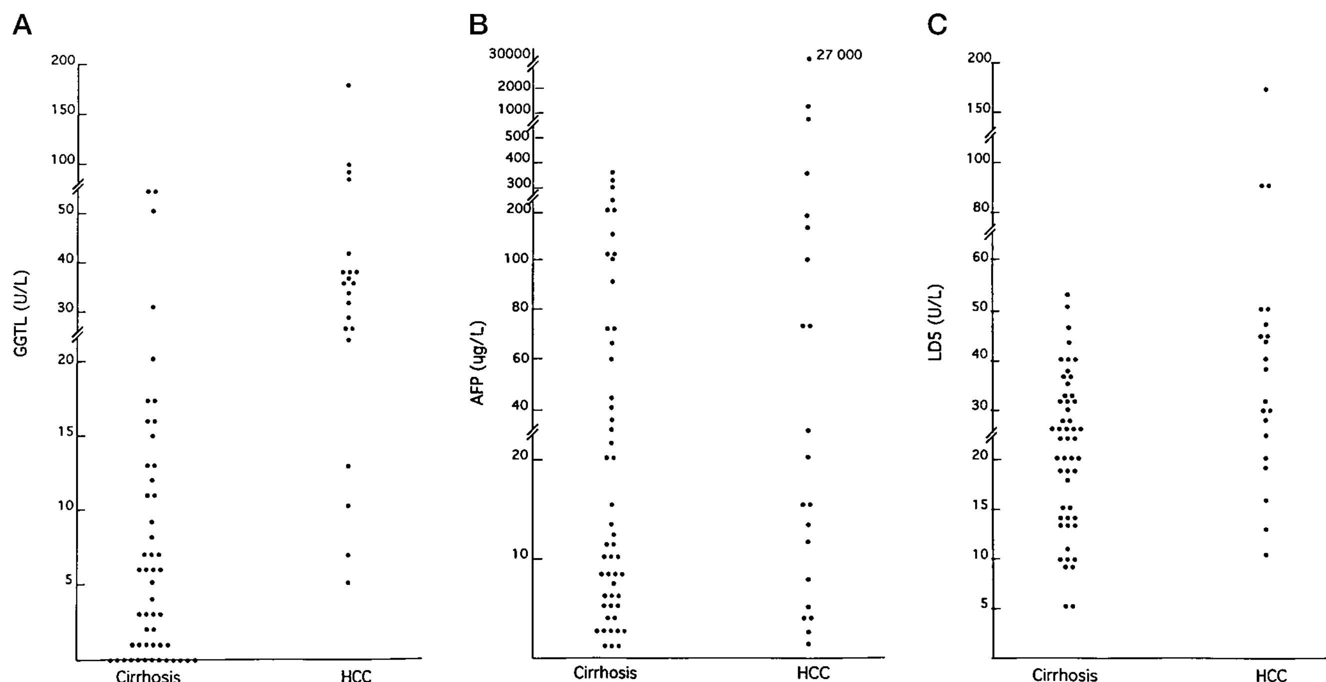

Fig. 1. Serum concentrations of GGTL (*A*), AFP (*B*), and LD5 (*C*) in cirrhotic patients and in patients with small (<3 cm) HCC.

HCC than in controls. As shown in Fig. 1A, at a cutoff of 20 U/L, GGTL had a diagnostic sensitivity of 80% and a diagnostic specificity of 92% for the diagnosis of small HCC, similar to those reported for ultrasound-guided biopsy *(6)*. The same cutoff (i.e., 20 U/L) is the upper reference limit in healthy subjects *(7)*. On the other hand, only 4 of 21 patients (19%) had serum AFP concentrations predictive for HCC (>400 μg/L; Fig. 1B). Similarly, LD5 values overlapped in the two populations (Fig. 1C). The receiver-operating characteristic plot analysis *(8)* confirmed that the area under the curve for GGTL (0.901) is significantly higher (P <0.001) than those for LD5 (0.708) and AFP (0.639). The multivariate discriminant analysis *(2)* failed to identify any function that increased the diagnostic efficiency of GGTL. This can be attributed to the fact that the other biochemical indicators included in the multivariate discriminant analysis *(2)* are less sensitive compared with GGTL for detecting small HCC (e.g., AFP and LD5 in Fig. 1).

GGT, overexpressed by liver neoplastic cells, forms complexes with LDL and VLDL. Complexes between GGT and LDL occur in serum as a consequence of the biliary impairment typical of the neoplastic liver *(7)* and produce the GGTL isoform. Serum GGTL analysis is rapid, noninvasive, and inexpensive. Our data suggest that this assay should be included (together to AFP and ultrasound scanning) in the protocol for the monitoring of cirrhotic patients.

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Prostate-specific Antigen Expression in Normal Human Bone Marrow Cells

To the Editor:

Improved procedures for measuring prostate-specific antigen (PSA) protein and mRNA have demonstrated that this kallikrein-like serine protease is present in many nonprostatic sources, indicating that PSA production/secretion is not tissue- or sex-specific, but rather is a steroid hormone-dependent phenomenon *(1)*. Reports on PSA-positive cells in bone marrow (BM) and peripheral blood mononuclear cells are contradictory *(2–6)*. The elucidation of this controversy might be of clinical utility to establish the nonspecificity of PSA as an indicator of micrometastases *(7, 8)*.

Belonging to a large study project on the extraprostatic expression of PSA, we undertook the present study to evaluate the presence of PSA in human BM hematopoietic stem/progenitor cells from a healthy adult donor, who gave written informed consent. He was without clinical findings referable to the prostate and did not take any medication during the preceding 6 months. The BM sample was enriched in mononuclear cells, and the CD-34$^+$ or CD-34$^-$ subpopulations were purified by immunomagnetic separation *(9)*. The BM cells were then lysed immediately, and the supernates were assayed for PSA content and analyzed by Western blot *(10)*. The ultrastructural immunolocalization of PSA in BM cells was performed as described previously *(10)*. The results, reported as the mean ± SE of at least three independent experiments performed in triplicate, were analyzed statistically with the Stat-View, Ver. 4, package (Abacus Concepts) on a Macintosh Power PC (Apple). Significance was established as P <0.05.

The total-PSA content in extracts from CD-34$^-$ cells was significantly higher than that found in CD-34$^+$ cells (0.208 ± 0.024 ng/10^7 cells and 0.072 ± 0.006 ng/10^7 cells, respectively; n = 9; P <0.0001, paired *t*-test). The subpopulations of BM cells also showed a marked difference for free PSA (77% vs 18% for CD-34$^+$ and CD-34$^-$ cells, respectively). The linear correlation between PSA concentration and dilution (r^2 = 0.96) demonstrated that the cell matrix did not affect PSA analysis.

Western-blot analysis confirmed the quantitative results. The electron microscopic examination of immunolabeled CD-34$^-$ cells displayed a specific cytoplasmic PSA distribution, localized mainly on small vesicles, whereas CD-34$^+$ cells showed only a negligible signal.

The different patterns of PSA expression in CD-34$^+$ or CD-34$^-$ cells may reflect different characteristics of these cell subpopulations; in fact, BM cells represent a quite heterogeneous cell population *(9)*.

Our present findings are in agreement with the previously reported PSA detection in BM and peripheral blood mononuclear cells from healthy subjects *(2–4)*, confirming that these cells can express PSA and that PSA in BM may not represent hematogenous micrometastases *(3, 6)*. Similarly, human leukemic cell lines have been demonstrated to produce/secrete PSA *(2, 11)*.

Although the biological and physiological roles of PSA in BM progenitor/stem cells remain unknown, the presence of PSA in these cells of nonprostatic origin further supports the hypothesis about possible extraprostatic functions of this protease in nonpathologic conditions and should be taken into consideration when using methods to detect hematogenous micrometastases *(7, 8)*.

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