"Half-Life" Is Erroneously Used to Describe the Disappearance of Erythrocytes and Hemoglobin from the Circulation

To the Editor:

Several reports (e.g., 1–4) have incorrectly used "half-life" to characterize the disappearance of erythrocytes and hemoglobin from blood. Although clinicians may have benefited over the years from their use of this term (each gaining some understanding of what the other was trying to communicate), they have played rather loose with scientific vocabulary. What these writers have done is to casually assign "half-life" to the time period equal to half of the life span of the entity, whether erythrocytes, hemoglobin, or something else. Thus, in a clinical setting, the nominal half-life facilitates the interpretation of increased or decreased clinical laboratory results. Both erythrocytes and hemoglobin have a mean in vivo life span of 120 days; the term half-life incorrectly characterizes the kinetics of their removal from circulation. This difference in use of terminology can be particularly confusing relative to the laboratory medicine of glycated proteins.

"Half-life" describes the disappearance of a molecule or other entity such that half of the molecules present at time zero disappear during the first half-life, half of what remains disappears during the second half-life, and in future half-lives one-half of what remains disappears. The fractions of the original entity that remain after 1, 2, 3, 4, 5, and 6 half-lives are 1/2, 1/4, 1/8, 1/16, 1/32, and 1/64, respectively. Half-life accurately portrays the decay of unstable isotopes of elements. In addition, half-life is an appropriate term to describe the disappearance of albumin; labeled plasma albumin has been shown to disappear in vivo with a half-life of 19 days (5). The amount of plasma albumin in vivo is nearly constant because albumin is continuously being synthesized as other albumin molecules are catabolized, primarily to supply amino acids to tissue cells. Consumption of albumin molecules is a random or first-order process that occurs with no regard as to how long the individual molecule has been in circulation.

Formation of hemoglobin is continuous and occurs primarily within the nucleated erythrocytes; the hemoglobin then remains in the mature erythrocyte until the erythrocyte dies and the hemoglobin and other cell components are broken down. Landaw's (6) excellent discussion of erythrocyte life span explains that senescent erythrocytes are selectively removed from circulation in a gaussian fashion between ~90 and 150 days, with a maximum rate of cell death after ~120 days. In addition, a random mode of erythrocyte destruction (not age-related) occurs in normal humans but at a rate of only ~0.04–0.50% per day or less. If we assume that random hemolysis is negligible, then after ~60 days one-half of the erythrocytes and hemoglobin present on day 1 are gone; however, after another 60 days none (or very little) of the hemoglobin or erythrocytes from day 1 remain—as opposed to the one-fourth that should remain if half-life accurately characterized their disappearance. Hemoglobin is selected sequentially for disposal, based primarily on the senescence of the erythrocyte. The life spans of erythrocytes and of hemoglobin are best stated as 120 days.

Our recommendation is that authors and articles use the term "half-life" carefully and appropriately. This attention to terminology is especially important for articles comparing the clinical utility of fructosamine (or glycated albumin) with that of glycated hemoglobin. The issue is more clearly represented by referring to the interval of glycemic control reflected in the results rather than by trying to apply the term "half-life" everywhere.

References

Rapid Diagnosis of Mitochondrial Mutation at Position 11778-Associated Leber Hereditary Optic Neuropathy

To the Editor:

Leber hereditary optic neuropathy is a maternally inherited disease associated with mutations of mitochondrial DNA (1, 2). A G to A substitution at position 11778 converts a highly conserved arginine to histidine in the fourth subunit of NADH dehydrogenase (EC 1.6.99.3). This mutation causes the loss of an SfaNI restriction site (1) and creates a new Mae III restriction site (3).

We developed a rapid detection of this mutation by a simplification of DNA extraction followed by polymerase chain reaction (PCR) amplification (4) and digestion with restriction enzymes, SfaNI or Mae III.

Frozen EDTA-anticoagulated blood samples (20 μL) were treated three times with 1 mL of a solution of 10 mmol of Tris·HCl and 1 mmol of EDTA per liter (pH 8.0) at 4°C. After centrifugation at 11,000 × g for 2 min, the pellet was frozen at −70°C for 5 min, then heated at 95°C for 5 min, after which PCR amplification was performed without delay.

Primer sequences used for this purpose were 11618-11637 (light strand; 5′-GCATACTTCTCAATCGCCA-3′) and 11883-11874 (heavy strand; 5′-TTCTCCAGTAGGTTAATAAG-3′). The following solution was prepared per liter: 200 μmol of each deoxynucleotide triphosphate (dATP, dGTP, dCTP, and dTTP), 0.10 μmol of each oligonucleotide primer, 50 mmol of potassium chloride, 1.5 mmol of magnesium chloride, 0.1 g of gelatin, and 10 mmol of Tris·HCl (pH 8.3). We added 50 μL of this solution and 1 U of Taq DNA Polymerase (from Perkin Elmer Cetus, Norwalk, CT, or Boehringer) to the blood pellet and subjected the mixture to 25 cycles of PCR in a DNA thermal cycler (PTC-100; MJ Research Inc., Watertown, MA), with each cycle consisting of denaturation at 94°C for 1 min, annealing at 52°C for 1 min, and extension at 72°C for 2 min. For the last cycle, annealing was carried out at 52°C for 1 min and extension at 72°C for 5 min. After PCR, 10-μL samples from the PCR mixture were digested for 2 h with 1.5 U of restriction enzyme, SfaNI (New England Biolabs, Beverly, MA) or Mae III (Boehringer).

The digested products were separated by electrophoresis, either agarose or 5% polyacrylamide gel. Agarose electrophoresis was performed as described by Wallace et al. (1). Polyacrylamide gel electrophoresis (PAGE) was performed in 20 mmol/L Tris, 180 mmol/L glycin buffer (pH 9.0) for 4 h at 180 V. PCR products stained with ethidium bromide were made visible by transillumination in an ultraviolet light box. Figure 1 illustrates the PAGE patterns obtained with mitochondrial DNA from two patients with Leber disease and from one normal individual. By agarose electrophoresis, the separation between the 119- and 124-bp fragments was not so sharp (data not shown), but the separation took only 1 h.

References


Viviane Dumur
Guy Lalau
Pascal Boone
Philippe Rousset
Dépt. de Biochim.
Hôpital Calmette, CHRU de Lille
59037 Lille, France

Pierre Francois
Jean-Claude Hache
Bernard Hemery
Bernard Puech

Ophthalmologie
CHRU de Lille
59037 Lille, France

Multiple Serum Protein Abnormalities in Carbohydrate-Deficient Glycoprotein Syndrome: Pathognomonic Finding of Two-Dimensional Electrophoresis?

To the Editor:

We wish to report that high-resolution two-dimensional polyacrylamide gel electrophoresis (2DE) and silver staining yields a potentially pathognomonic profile of multiple serum protein anomalies in carbohydrate-deficient glycoprotein syndrome (CDGS). CDGS is a recently described chronically debilitating autosomal recessive neurometabolic disorder that affects multiple organ systems (1–5). One of the hallmarks of this disease is the occurrence of cathodal, carbohydrate-deficient isoforms of serum transferrin (CDT) that lack between one and four sialic acid-containing terminal triacylcholines (6). The methods used to detect CDT have been isoelectric focusing with or without immunofixation isocratic anion-exchange chromatography, and carbohydrate analysis after isolation of transferrin by immunoaffinity chromatography (6). In all cases of CDGS, the increased concentration of the cathodal CDTs exceeds that usually seen in alcoholism or severe liver disease (7).

We undertook the present study to determine whether these CDT isoforms could be qualitatively detected with 2DE in serum from a 24-month-old girl whose clinical findings of "floa