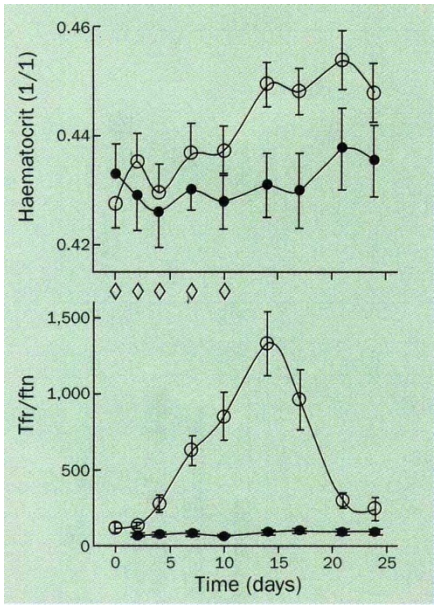
Erythropoietin abuse in athletes

SIR — The availability of recombinant human erythropoietin (rHuEpo) has made it a drug of choice for athletes looking for an artificial performance enhancer. The lay press still represents the main reporting vehicle for such illicit use of erythropoietin, the most dramatic picture having been portrayed in the German weekly magazine *Der Spiegel*: 18 deaths related to erythropoietin administration among racing cyclists[1].

Although it is on the list of banned substances issued by the medical commission of the International Olympic Committee, the non-medical use of erythropoietin remains uncontrollable. No reliable analytical technique[2,3] is available to detect its use as an ergogenic agent. The kinetic constraints (for example, short half-life, delayed erythropoietic effects) of an approach based on the electrophoretic mobility measurement of erythropoietin[4] prompted us to investigate a new marker of erythroid activity, the soluble transferrin receptor, released predominantly from haematopoietic progenitors, in healthy athletes receiving either placebo or rHuEpo administration. Our data indicate that erythropoietin induces striking changes in the serum soluble transferrin receptor (Tfr) content. These observations could eventually be considered in the design of a probe to detect erythropoietin misuse.



Haematocrit (upper panel) and soluble transferrin receptor/ferritin[7] (Tfr/ftn; lower panel) values in blood samples collected repeatedly (days 0, 2, 4, 7, 10, 14, 17, 21, 24) in healthy, trained, adult males (age ± s.d. 21.4 ± 0.3 yr) given 5 subcutaneous injections (◊) of placebo (●; $n=10$) or 200 U kg^{-1} commercial (Eprex, France) recombinant human erythropoietin (○; $n=19$).

Because rHuEpo administration stimulates erythropoiesis and induces the redistribution of storage iron into erythroid elements, Tfr as an index of both tissue iron deficiency and expanded erythroid progenitor mass has been expressed in relation to serum ferritin (ftn), a measure of body iron store, thus giving the serum Tfr/ftn index. This approach is particularly appealing, as the expression of such a ratio obviates problems related to the variable effects of hydration, as is the case with haematocrit readings. Moreover, changes in this Tfr/ftn index could reflect rHuEpo abuse, as well as any other manoeuvres that accelerate erythropoiesis[5].

Analysis of variance performed on the data in the figure indicates that no significant change ($P=0.53$) in serum Tfr/ftn occurred over the entire observation period in the placebo-treated subjects, while striking increases were induced by the rHuEpo treatment. The rHuEpo-induced increases were statistically different ($P<0.05$) from basal values (pooled placebo group Tfr/ftn values) for serum Tfr/ftn values measured on days 4, 7, 10, 14, 17 and 21. This relatively low-dose rHuEpo treatment yielded no significant ($P>0.05$) increase in haematocrit values. One can speculate that the magnitude of a Tfr/ftn increase observable with a rHuEpo dose sufficient to yield an ergogenic haematocrit increase would be even more dramatic.

Notwithstanding the discriminative power of low haematocrit values observed in anaemia, patients presenting an increased serum Tfr concentration associated with primary or non-pharmacological secondary polycythaemia, or with iron-deficient or megaloblastic anaemia, are not likely to yield false-positive results, as they generally do not achieve élite-level physical performances. Physical exercise *per se* does not seem to be associated with increased Tfr/ftn serum values[6], thus precluding a false-positive identification of erythropoietin from blood sampled at the competition site.

Hence, observation of concomitant changes in haematocrit and Tfr/ftn values could permit the discrimination of pathological from physiological conditions, and thus distinguish between rHuEpo abusers (or even athletes who had undergone blood transfusions) and those competing fairly. The most recent technological developments already allow measurement of these discriminating variables from a few microlitres of capillary blood sampled from the fingertip or ear lobe. This first breach in athletes' immunity to detection of their use of engineered hormones as performance enhancers is a pledge in favour of the blood matrix to detect and deter sophisticated abusers.

Raynald Gareau
Department of Chemistry-Biology, University of Québec at Trois-Rivières, PO Box 500, Trois-Rivières, Québec G9A 5H7, Canada
Michel Audran
Biophysics Laboratory, Department of Pharmacy, University of Montpellier 1, Montpellier 34060, France
Roy D. Baynes, Carol H. Flowers
Department of Internal Medicine, Division of Hematology, University of Kansas Medical Centre, Kansas City, Kansas 66160-7233, USA
Alain Duvallet
Faculty of Medicine Cochin Port-Royal, Université René-Descartes, 75014 Paris, France
Louis Senécal, Guy R. Brisson
Montréal Anti-doping Laboratory, INRS-Santé, Pointe-Claire, Québec H9R 1G6, Canada

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Derivative of the hyperbolic cotangent

SIR — The derivative of the hyperbolic cotangent is a standard result which appears in essentially every compilation of mathematical formulas[1]. Here we point out that this result is incomplete; there is, in fact, an additional term which is proportional to the Dirac delta function. We present the correct formula, outline its proof and give an example of its importance in the analysis of a physical problem.

The correct formula is

$$\frac{\mathrm{d}}{\mathrm{d}y}\coth y = -\operatorname{csch}^2 y + 2\delta(y) \qquad (1)$$

where $\delta(y)$ is the Dirac delta function. The usual derivation of the first term does not properly handle the fact that $\coth y$ has, in addition to the obvious $1/y$ singularity, a discontinuity at $y=0$. A better approach is to write

$$\coth y = \pm\left\{1 + \frac{2}{\mathrm{e}^{2|y|}-1}\right\} \qquad (2)$$

where the + and – signs refer to $y>0$ and $y<0$, respectively. Regardless of the sign