DOI: 10.1111/apha.13709

EDITORIAL

ACTA PHYSIOLOGICA

"So is science …"[1]: No evidence for *neocytolysis* on descending the mountains (Response to Rice and Gunga)

> "…our belief in any particular natural law cannot have a safer basis than our unsuccessful critical attempts to refute it."
>
> (Sir Karl R. Popper: Conjectures and Refutations; 1963)

"So is science" commented Rice and Gunga[1] pointing to the fact that science is the interpretation of results, where it is easily possible to explain an experimental observation with different hypotheses. The more supporting parameters are measured, the more likely a hypothesis reflects the actual mechanism. Rice and Gunga[1] commented on a study by Klein et al (not Mairbäurl et al!)[2] set out to provide more stringent evidence and mechanisms causing the decrease in total Hb mass after descent from a 19-day stay at 3450 m at the Jungfraujoch Research Station in Switzerland to test and strengthen the hypothesis of *neocytolysis*, that is, the selective destruction of the fraction of young erythrocytes, when EPO levels drop. This hypothesis, first proposed by Alfrey et al,[3,4] was based on an upward deflection of survival curves of ^{51}Cr-labelled erythrocytes after astronauts returned from space missions. It was concluded that this relative increase in the proportion of ^{51}Cr-labelled erythrocytes, which at that time point represented a rather senescent erythrocyte population, had to be caused by selective removal of those erythrocytes produced after the labelling with ^{51}Cr, that is, the "younger" fraction of cells (*neocytes*).[3,4] The alternate hypothesis, lack of young erythrocytes due to a decreased rate of erythropoiesis subsequent to a decrease in blood EPO levels, had been put aside because it was thought to be "interminably slow,"[1] whereas destruction would provide a means for rapid change.

To our big surprise, our results indicated that the young erythrocytes produced prior to the decrease in EPO after descent from high altitude had not been destroyed but were well detectable in circulating blood. However, the fraction of the very young reticulocytes was missing. We concluded therefore that the quite rapid decrease in total haemoglobin mass upon descent from high altitude cannot be explained by *neocytolysis* (i.e., lysis, destruction), but might as well be explained by decreasing the erythropoietic rate.[2] Our assumption appeared justified because a decrease in the erythropoietic rate follows the rapid drop in EPO levels after descent,[5] and the change in parameters could be modelled well by an algorithm that excluded *neocytolysis*. One would therefore expect that maintaining EPO levels high after descent (in normoxia) would prevent the decrease in total Hb mass because of continued enhancement of erythropoiesis, similar to the "prevention of neocytolysis by EPO treatment" as indicated by Rice and colleagues.[6] Unfortunately, in this publication, relevant data were not shown and the number of subjects was very small.[6]

We now applied our model[2] to estimate, how much the total Hb mass could decrease over time after EPO levels sharply decrease and erythropoiesis comes to a halt. Figure 1A summarizes these results and shows that this "interminably slow response"[1] should result in an approximately 10% reduction of total Hb mass within 10 days after complete suppression of the erythrocyte production, and by approximately 5% if the production rate would be decreased by one half. Assuming a high degree of suppression of erythropoiesis appears justified since EPO is required for several proliferation and maturation steps of erythroid progenitors in the bone marrow.[7] The predictions of our model are well within the range of the data shown by Alfrey et al in 1996.[4] Along this line, the model can also be used to estimate the time course of the decay of ^{51}Cr-labelled erythrocytes assuming an erythrocyte-age independent labelling intensity and no situation-specific elution of the ^{51}Cr label.[8] Figure 1B shows that a reduction of the erythropoietic rate produces an upward deflection from the normal decay of ^{51}Cr-labelled erythrocytes in the semi-logarithmic plot, very similar to what Alfrey and colleagues had reported.[4] Taken together, our model and the curves shown by Alfrey et al[4] on the deflection of ^{51}Cr decay are both consistent with their statement saying "*the survival curve created the appearance that the labelled cells were surviving longer than normal*",[1] and that this could only be explained by the fact that labelled cells *"were not being diluted by the expected number of unlabelled cells"*[1] indicating missing young erythrocytes. As a possible explanation, Alfrey et al[3] proposed destruction of these cells (*neocytolysis*), and we proposed a reduced erythrocyte production rate.[2] Neocytolysis is thus not *"the only plausible*

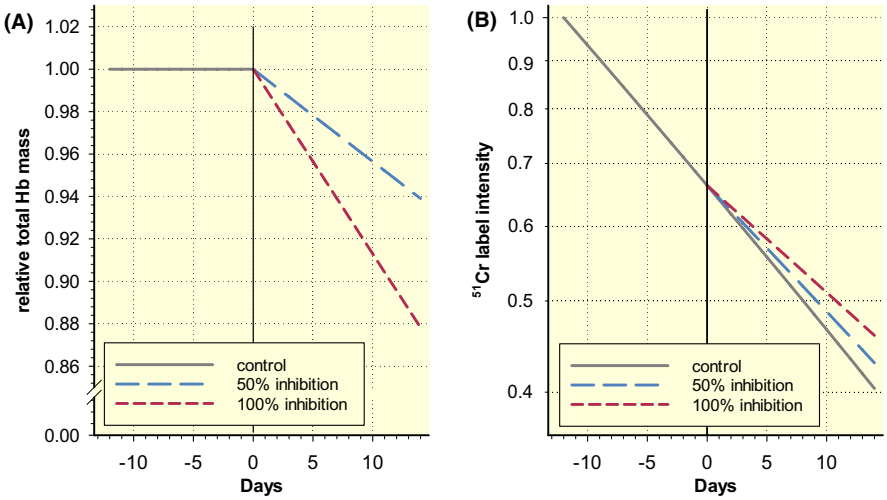

FIGURE 1 Modelling consequences of decreasing the rate of erythropoiesis. Effects on total haemoglobin mass (A) and on the evolution of the ^{51}Cr label (B). The erythrocyte production rate is normalized with respect to before EPO levels decrease, for example, entering space flight or descent from high altitude, where at day = 0 the erythrocyte production rate drops to either 50% or 0% of the initial rate as indicated by the vertical lines

possibility".[1] Resolving this discrepancy is only possible by measuring supportive parameters, as we did, showing with several techniques that these neocytes were still present in circulation after descent[2] but not removed. Therefore, the "lacking dilution with newly produced cells" seems to be caused by a decreased erythrocyte production rate.[2]

Do we "want to create scepticism about the existence of *neocytolysis*"[1]? Yes, of course we challenge this hypothesis, "by broadening and deepening the discussion"[1]! Age-cohort labelling and measuring parameters of erythrocyte senescence (as we did) very well allow studying the fate of erythrocytes of different age after a drop in EPO. Results seem to disprove the existence of *neocytolysis*. Is this a general phenomenon? We believe "yes" because the erythropoietic rate decreases whenever EPO levels drop rapidly and remain decreased for several days. This has implications for changes in total Hb mass after descent from high-altitude sojourns, acute relative erythrocyte plethora as in space, termination of EPO treatment in clinical settings and in doping, prolonged oxygen therapy, and the many other situations where a rapid decrease in EPO may occur. This needs to be proven experimentally, of course. Should the decrease in total Hb mass be avoided in the sense of "beneficial influencing on earth and in space"[1]? This depends on its clinical implications such as the degree of anaemia, tissue hypoxia and impairment of performance. We are not sure whether using EPO is the only and most promising treatment because in many situations this would counteract the natural regulation of total erythrocyte mass and blood volume.

CONFLICT OF INTEREST

No conflict of interest to declare.

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