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This Week's Citation Classic®

Adamson J W. The erythropoietin/hematocrit relationship in normal and polycythemic man: implications of marrow regulation. *Blood* **32**:597-609, 1968.
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This paper compared the erythropoietin (Ep) response to bleeding in normal subjects with that in patients having various forms of polycythemia. Patients with polycythemia vera had unmeasurable levels of Ep, in contrast to normals and to patients with secondary polycythemias. These results allowed a physiological classification of the polycythemias based on Ep levels. [The *SCI*® indicates that this paper has been cited in over 135 publications.]

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When I began working with C.A. Finch at the University of Washington, I assumed responsibility for an erythropoietin (Ep) bioassay that had been initiated by a former Fellow. By current standards, the assay, which employed groups of polycythemic mice, was unacceptably time-consuming and labor-intensive (as well as imprecise and crude) and was directed toward a hormone whose existence was somewhat disputed even then.

Nevertheless, we were able to demonstrate a level of sensitivity somewhat better than that previously reported and could reliably measure Ep excretion in the urine of normal people.[1] The most useful wrinkle was the use of concentrated urine as the test material. We also hyperfractionated the injection schedule (probably unnecessarily) in order to take advantage of the fact that divided doses of Ep had been shown to be more effective than single doses in stimulating hemoglobin synthesis. The schedule called for injections every 12 hours for four consecutive days, and I can remember leaving dinners and parties to return to the hospital to inject large numbers of unappreciative mice.

Despite the limitations of the assay, the insights provided by the studies were correct. We were able to establish the levels of excretion of Ep for normal subjects.[1] Then we turned our attention to the more difficult situation—that of patients with polycythemia. The prevalent assays could demonstrate elevated Ep levels in patients with anemia; however, the distinction between normal and suppressed Ep levels had not yet been reported.

Our studies not only measured Ep excretion in the basal state but also in response to phlebotomy. In addition, we autohypertransfused normal volunteers to monitor the change in Ep excretion and correlated that with a decline in reticulocytes. We showed that patients with polycythemia vera and an elevated hematocrit had decreased or absent levels of measurable Ep in their urine. We inferred from these experiments that we were dealing with a neoplasm of the hematopoietic stem cell and that red cell production was likely outside the normal mechanisms of regulation. The neoplastic and presumably clonal nature of polycythemia vera was shown by us several years later.[2]

Equally pertinent was the fact that, with phlebotomy, Ep became detectable in the urine of these patients. We postulated, therefore, that the Ep/hematocrit relationship was the same for normal individuals and for patients with polycythemia vera, and we were clearly able to distinguish them from patients with secondary forms of polycythemia. We found that patients with hypoxic polycythemia had normal or increased levels of Ep excretion, even at high hematocrits, and that Ep production increased further with phlebotomy. Patients with tumor-associated polycythemia had a fixed level of Ep excretion. These findings led to a physiological classification of the polycythemias that we find useful even today. Although new assays have been developed for Ep,[3] the basic principles established nearly 20 years ago remain, and the findings provided values against which studies of other conditions could be compared.

1. **Adamson J W, Alexanian R, Martinez C & Finch C A.** Erythropoietin excretion in normal man. *Blood* 28:354-64, 1966. (Cited 85 times.)
2. **Adamson J W, Fialkow P J, Murphy S, Prchal J F & Steinmann L.** Polycythemia vera: stem-cell and probable clonal origin of the disease. *N. Engl. J. Med.* 295:913-16, 1976. (Cited 215 times.)
3. **Garcia J F, Ebbe S, Hollander L, Cutting H O, Miller M & Cronkite E P.** Radioimmunoassay of erythropoietin and circulating levels in normal and polycythemic human beings. *J. Lab. Clin. Med.* 99:624-35, 1982.

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