

Erslev A. Humoral regulation of red cell production. *Blood* 8:349-57, 1953.
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Large amounts of plasma from rabbits rendered anemic by bleeding were injected into normal rabbits. A rise in the number of reticulocytes was observed followed by an increase in red blood cell count and hematocrit. Control rabbits receiving the same amount of plasma from normal donor rabbits failed to show any significant change in the reticulocyte count. It is concluded that plasma from rabbits rendered anemic by bleeding contains a factor capable of stimulating red-cell production. [The *SCI*® indicates that this paper has been cited in over 175 publications since 1955.]

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In 1951, during a frustrating Damon Runyon Fellowship at Yale University School of Medicine, I got sidetracked from my primary project of hyperimmunization into a study of aplastic anemia. Stimulated by Reismann's paper on parabiotic rats¹ and subsequently by Grant and Root's review on erythropoiesis,² I hypothesized that red-cell production was controlled by a hemopoietic factor and, specifically, that aplastic anemia is caused by the absence of this factor.

With the abandon of a young investigator in the days before informed consent, and to the horror of the house staff, I bled my patients with pernicious anemia or blood-loss anemia and injected their plasma into two highly cooperative patients with aplastic anemia. There was, of course, no sustained response, but the reticulocyte counts were erratic enough to keep my enthusiasm alive and to

force me, somewhat belatedly, to go to the literature and to physiologic animal experiments.

I discovered then that French investigators had already made such experiments in 1906 and had found that small amounts of plasma from anemic rabbits will cause a dramatic, almost instantaneous increase in red-cell counts when injected into normal rabbits.³ Unfortunately, these somewhat fantastic results could not be reproduced in other laboratories and certainly not in my early studies in New Haven.

The reticulocyte counts (I must have done thousands) had their ups and downs, and as I increased the amount of "anemic" plasma administered to rabbits, the ups became more frequent. Driven by these ups and a certain native stubbornness, I finally injected 50 ml of "anemic" plasma intravenously once a day to normal rabbits, and, on the day before a carefully planned family vacation in Canada, I observed a clear-cut reticulocyte response. Rarely have I had a more miserable vacation, wishing every day that I was back in the laboratory with my rats and reticulocytes. After returning, I finished the study, wrote my first experimental paper, and received a great boost from William Dameshek, editor of *Blood*, who accepted my paper unchanged despite some critical comments by the reviewers.

Since the publication of this paper in 1953, the erythropoietic factor, later named erythropoietin, has been studied intensively, culminating in 1985 with its identification, cloning, and mass production.⁴ In my 1953 paper I wrote, "Conceivably, isolation and purification of this factor would provide an agent useful in the treatment of conditions associated with erythropoietic depression, such as chronic infection and chronic renal disease." It is with some pride that I note that the clinical trial in 1986 using recombinant erythropoietin will be directed primarily at the treatment of these two anemias.

1. Reismann K R. Studies on the mechanism of erythropoietic stimulation in parabiotic rats during hypoxia. *Blood* 5:372-80, 1950.
2. Grant W C & Root W S. Fundamental stimulus for erythropoiesis. *Physiol. Rev.* 32:449-98, 1952. (Cited 160 times since 1955.)
3. Carnot P & DeFlandre C. Sur l'activité hémopoïétique du sérum au cours de la régénération du sang. *C. R. Acad. Sci.* 143:384-6, 1906. (Cited 150 times since 1955.)
4. Jacobs K, Shoemaker C, Rudersdorf R, Neill S D, Kaufman R J, Mufson A, Seehra J, Jones S S, Hewick R, Fritsch E F, Kawakita M, Shimizu T & Miyake T. Isolation and characterization of genomic and cDNA clones of human erythropoietin. *Nature* 313:806-9, 1985.