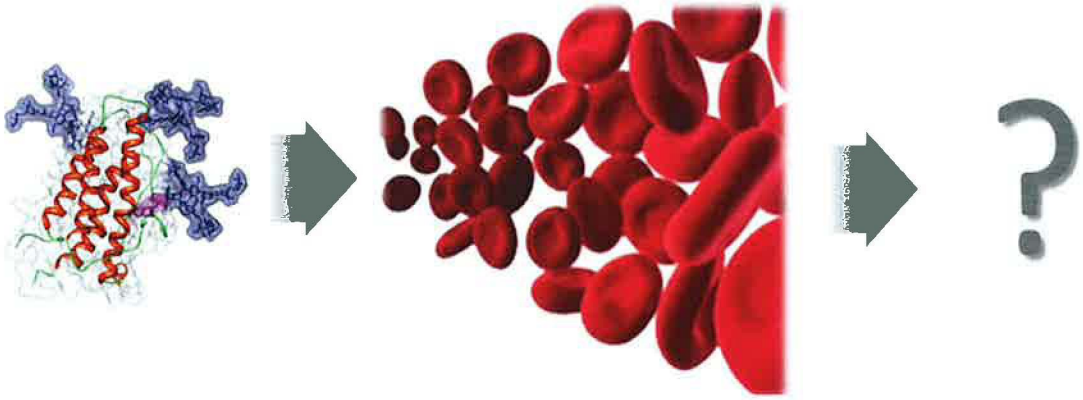
Medical Grand Rounds
October 22, 2010

After twenty years of erythropoietin prescriptions: What do we really know about this drug?



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Research:
Epithelial Biology of solute transport and cell metabolism
Acid-base electrolyte disorders, nephrolithiasis, renal failure

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Conflict:
None

The speaker will discuss off-label use of the drug erythropoietin.

AGENDA

- Case:Pre-erythropoietin era
- How we arrived at the present stage
- Illegitimate Abuse
- Legitimate Misuse
- Erythropoietin Biology

Patient:

Mr. GL July 1986

31 yo white male with ESRD from reflux
Hemodialysis since age 12
Anephric
Failed 3 transplants, 100% panel reactivity

HCT 14
Transfusion dependent
Iron overload

Premature atherosclerosis
Indication for transfusion
Angina at rest

November 1986
Died in his sleep

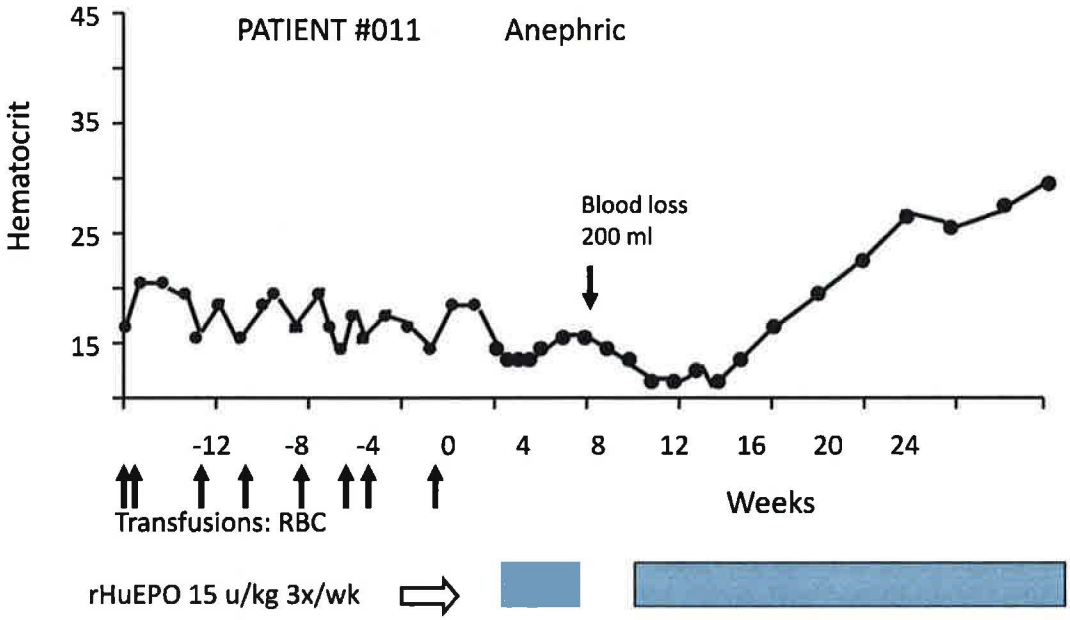
This was the status of a dialysis patient in June 1986. Mr. GL was a 31 year old Caucasian male on hemodialysis for 18 years. He was anephric from previous bilateral nephrectomies. He failed two cadaveric and one living-related allograft and now has 100% panel reactive antibodies rendering him close to an impossible candidate for transplant. He was surviving rather than thriving on dialysis.

A typical hematocrit for this patient was about ~14% which periodically drifted down even further. It was not that unusual to have hematocrits of this magnitude in dialysis units back in those days. The only way to raise his HCT was by blood transfusion which has caused severe iron overload and mandated chelation therapy. To minimize iron overload, indication for transfusion was set rather stringently. The threshold was not a number but angina at rest.

He died peacefully in his sleep in November of 1987. The diagnosis was presumed to be myocardial infarction. An autopsy was not performed.

Plenary session: American Society of Nephrology Washington DC Nov 1987

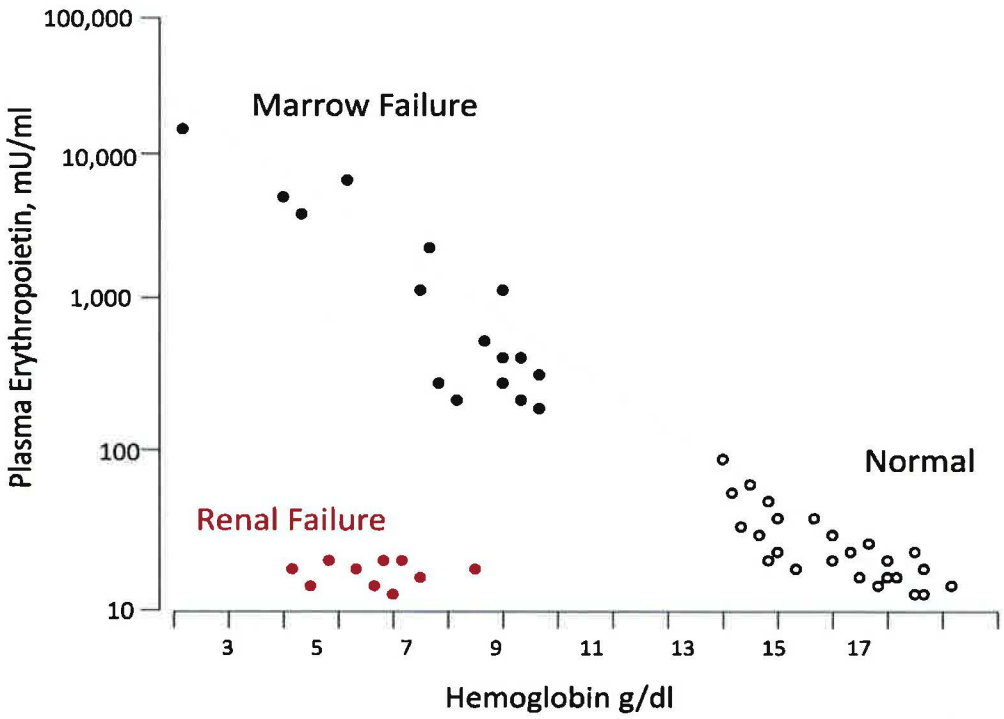
John Adamson, Seattle, WA



N Engl J Med 1987

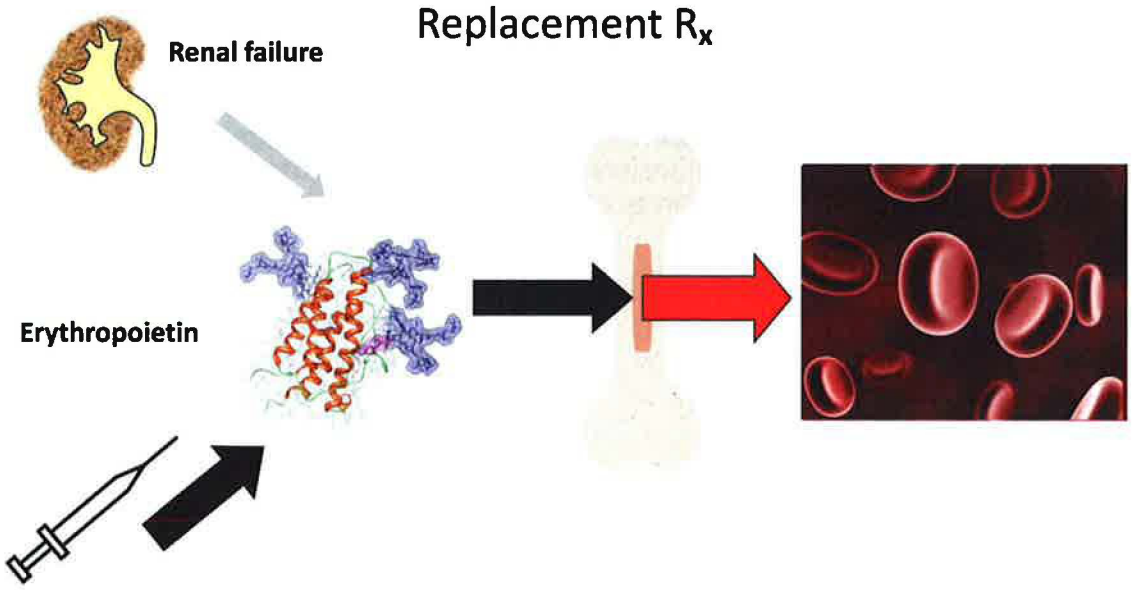
In the American Society of Nephrology meeting in the subsequent year. John Adamson gave a plenary lecture which nothing short of revolutionary. He showed that parenteral administration of recombinant erythropoietin alone can restore the hematocrit back to normal levels. This NEJM paper was universally considered a landmark paper in the history of nephrology; one for the archives (Eschbach 87). This drug would have saved the life of Mr. GL.

Indeed, anemia of chronic kidney appears to be a disease from a bygone era. All trainees and practicing physicians see this as a transient state when the CKD patient first comes to medical attention; a condition that will soon vanish as soon as the physician intervenes.



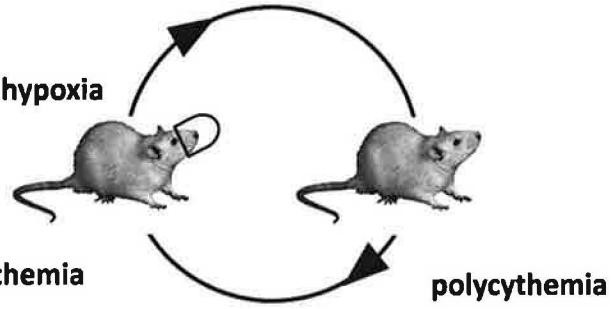
The anemia of bone marrow failure is accompanied by high erythropoietin levels because the kidneys are intact. The anemia of renal failure has a hemoglobin level comparable to bone marrow failure but erythropoietin levels are low. This is the foundation for classifying anemia of renal failure as an endocrine deficiency of erythropoietin.

By the principal of replacement therapy for an endocrine disorder, the failure of endogenous production of a hormone can simply be bypassed by the administration of that same hormone by the physician. This is the simplest view possible but as one will witness, the situation with erythropoietin is far more complicated.



Biomedical Milestones

1950



Reissman KR. Studies on the mechanism of erythropoietic stimulation in parabiotic rats during hypoxia. Blood 5:372-380, 1950

1957

Bilateral nephrectomy abolished erythropoietin production

Jacobson LO, Goldwasser E, Fried W, Pizak L. Role of the kidney in erythropoiesis. Nature 179:633-634, 1957

1977

Purification of erythropoietin from human urine

Miyaki T, Kung CKH, Goldwasser E. Purification of human erythropoietin. J Biol Chem 252:5558-5564, 1977.

1985

Cloning of human erythropoietin gene

Lin FK, Suggs S, Lin CH, Browne JK, Smalling R, Egrie JC, Chen KK, Fox GM, Martin F, Stabinsky Z, Badrawi SM, Lai PH, Goldwasser E. Cloning and expression of the human erythropoietin gene. Proc Nat Acad Sci USA, 82:7580-7583, 1985.

1989

FDA approval of erythropoietin to treat anemia of ESRD under the Orphan Drug Act

The history of erythropoietin can be traced back to the 1800's (Bert 78, Hufner 90, Viault 90). The major milestones are shown. Reisman performed a critical parabiosis experiment showing that "erythropoietic activity" is endocrine in nature (Reisman 50). Several seminal papers were associated with Dr. Eugene Goldwasser at the University of Chicago. Using systematic organ ablation, the source of endocrine erythropoietic activity was narrowed to the kidneys (Jacobson 57). Goldwasser and colleagues went on to purify this polypeptide to homogeneity (Miyaki 77) and cloned the human gene (Lin 85). It did not take long before this was transformed to a product with FDA approval of recombinant human erythropoietin to treat anemia of ESRD.

Pharmaceutical and Policy Milestones

1985 — **Amgen and Ortho enters into licensing agreement**

1986 — **Amgen received orphan drug designation for ESRD-dialysis**

June 1987 — **Genetic Institute patent granted**

Aug 1987 — **Ortho received orphan drug designati nfor predialysis CKD**

Oct 1987 — **Amgen patent granted**

July 1988 — **Ortho receives orphan drug designation for preterm infants**

Mar 1989 — **Ortho receives orphan drug designation for HIV patients**

1989 — **FDA approval of erythropoietin to treat anemia of ESRD**

Approval expanded to
- CKD (pre-dialysis)
- Chemotherapy-induced anemia
- HIV patients
- Pre-term infants
- Reduction of post-operative transfusion needs

A plethora of off-label uses

Products

Amgen patent
- Amgen – Epogen, Aranesp
- Amgen-Ortho- Procrit
- Hoffman La Roche- Micera
- Johnson & Johnson- Eprex
- Kirin- ESPO, NESP

Genetics Institute patent
Chugai-Upjohn-Marogen
Chugai- Epogin
Boehringer-Manheimp Recorman

2001 — **•Sales in billions**

2004 — **• FDA forms panel to scrutinize safety of ESA**

2007 — **• FDA changed labeling. Inserted a boxed warning**
• Avoid Hb > 12 to avoid death and cardiac events

2010 — **• FDA took the position that aggressive use of ESA increases risk to myocardial infarction, stroke, and acceleration of cancer growth**
• Physicians required to receive a training session
• Patients needs to be educated and receive literature with physician documentation
• Registration and prior approval not recommended

Orphan Drug Act of 1983
(Public Law 97-414)

Intent

Increase market incentives and decrease regulatory barriers for products used to treat rare disease

Rare disease

- 10-20 American suffering from 5,000 rare diseases
- For ODA <200,000

Provisions

- Market Exclusivity
- Tax Credits
- Regulatory Process Clarification

Erythropoietin was approved by the FDA in 1989 under the Orphan Drug Act (ODA) (Ashbury 91, Rin-Laures 91)). The ODA was meant to encourage the industry to develop drugs that benefit only a few and hence has little or no commercial value. The basis for the ODA is that the government and tax payers will provide the incentive and finances necessary to develop drugs that theoretically no one wants to develop. After the initial approval for treatment of dialysis patients with anemia, the target population was soon expanded to other approved indications plus many other off-label uses. The sale of erythropoietin reached billions within two years after its approval.

There have been ODA-supported products that called for questions as to whether the ODA led to unintended results; i.e. providing incentives to products that really do not need help. The two leading compounds that lead to queries as to whether they fit the spirit of the ODA are human growth hormone and erythropoietin and by far, erythropoietin is the most controversial. While no one has accused any party of any wrong doing and in fact everything has indeed been legitimate, some facts should be brought to light.

For a drug that no one wants to produce, erythropoietin sales exceed 100 million within the first 6 months with multiple millions of dollars invested into legal disputes between two industrial entities over this product. In the first year alone, federal expenditure cost 2.7 billion and recurrent annual costs ran hundred of million dollars. This basically catapulted a little known biotechnology company in the West Coast to an industrial giant overnight. Awhile there were several amendments of the ODA, an attempt by Congress to control loopholes in 1990 was prompted primarily by erythropoietin. However, this was vetoed by the president. The interested reader is directed to a superb article written by John Coster who was then serving on a Special Senate Committee (Coster 92).

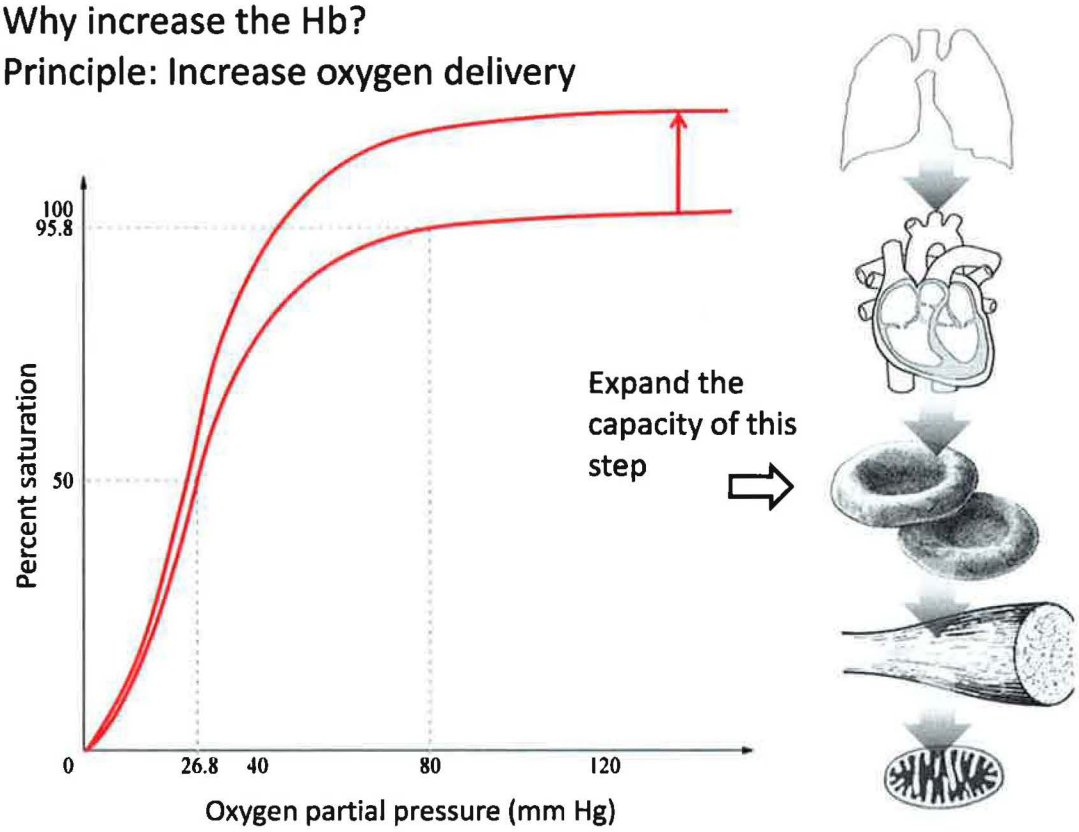
- A drug that no manufacturer wants to produce
  Federal government aided its development
- Sales exceeded $100 million in the first 6 months
  Multi-millions were invested into legal disputes
- In 1989, the program cost 2.7 billion federal dollars
  Costing hundreds of millions to Medicare
  A new biotech company was catapulted into an industrial giant
- Prompted the Waxman Amendment in 1990

In response to multiple clinical studies that indicated possible ill effects of erythropoietin therapy, the FDA formed a panel to evaluate the drug in 2004 and in 2007 issued a warning in indicate that one needs to avoid exceeding a Hb of 12. In 2010, a more vigorous policy was set where FDA took a more definitive position stating that aggressive use of ESA increases risk to myocardial infarction, stroke, and acceleration of cancer growth. Physicians are required to receive a training session before prescribing the drug. Patients need to be educated and receive literature with physician documentation. The FDA has not recommended registration of use nor requiring prior approval.

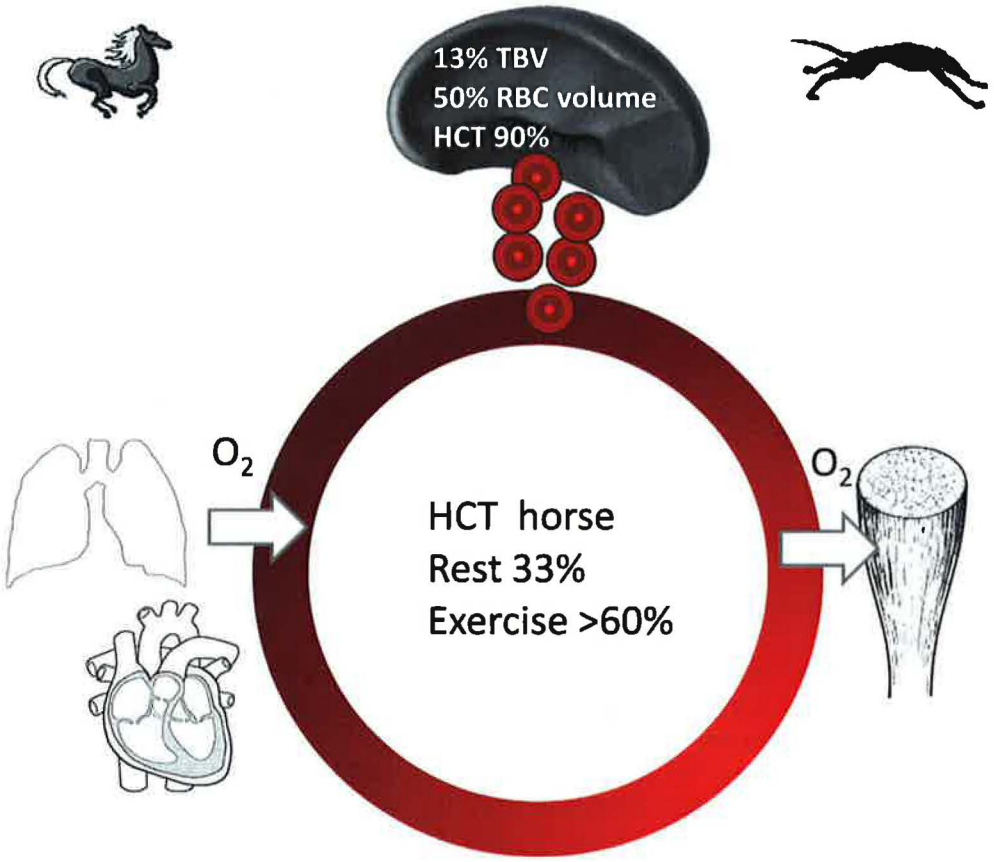
Illegal abuse

Transport of oxygen from the exterior to its final destination in the mitochondria requires multiple tandem steps. Oxygen carrying capacity of the circulating red cells is only one of a series of steps where diffusion, convection, and chemical reactions are involved. In a normal healthy individual, increasing the oxygen carrying capacity of the blood has been shown to improve maximal oxygen consumption ($V_{O2}max$) and also exercise performance.

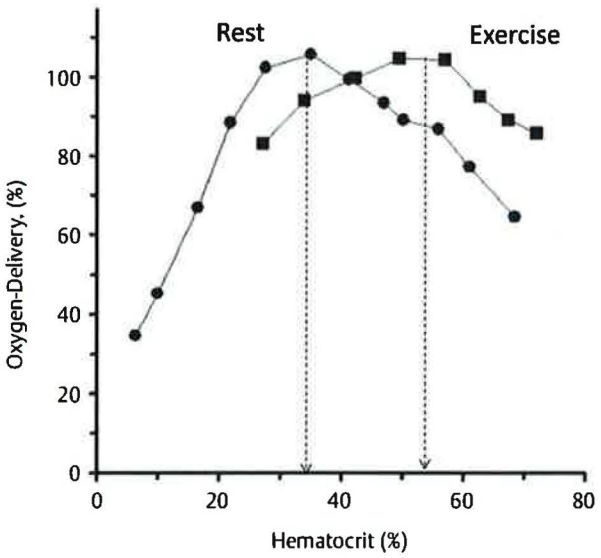
Why increase the Hb?
Principle: Increase oxygen delivery



When the hemoglobin in the red cell is fully saturated with oxygen, the only option left to increase oxygen carrying capacity is to increase the red cell mass, or hemoglobin concentration and hematocrit.

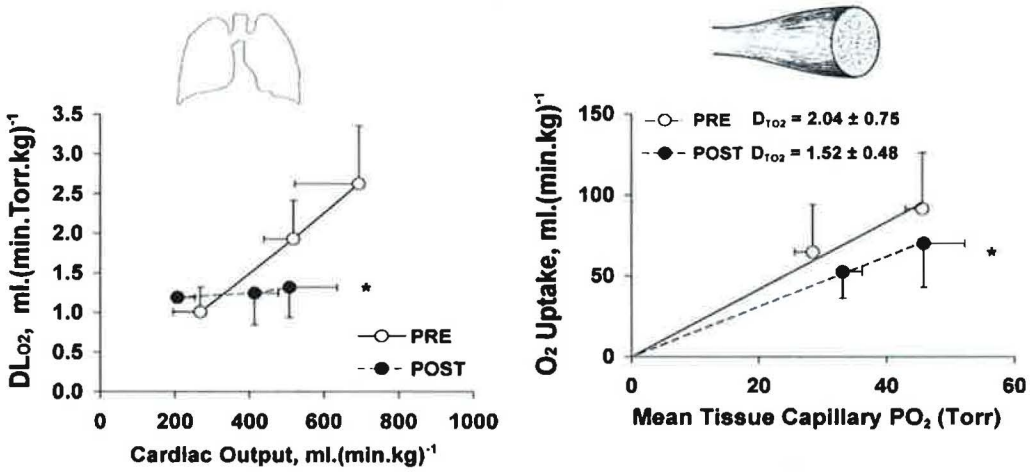


This is well known in athletic animals such as dogs, seals and horses, their spleen functions as a RBC reservoir, constituting 3% of body weight and sequestering ~50% of erythrocyte volume (~13% total blood volume) with a local hematocrit of 85-90% (Hsia 10).Under exercise-induced sympathetic stimulation in these animals, splenic contraction increases circulating blood volume, hematocrit and O_2 carrying capacity up to 50% above that pre-exercise. Splenic contraction-mediated erythrocyte release enhances pulmonary and peripheral (muscle) diffusing capacities by enlarging the hemoglobin pool, and by improving the matching of diffusion interfaces. Upon cessation of exercise, the erythrocytes return to the spleen and resting blood hematocrit, viscosity and vascular resistance normalize. A high hematocrit while good for oxygen carrying-capacity, is detrimental to oxygen delivery because it increases viscosity of the blood. There is a HCT where the two strike a compromising balance and that has been termed the "optimal HCT". In the exercising animal, the optimal HCT is transiently increased to match the splenic release of erythrocytes.



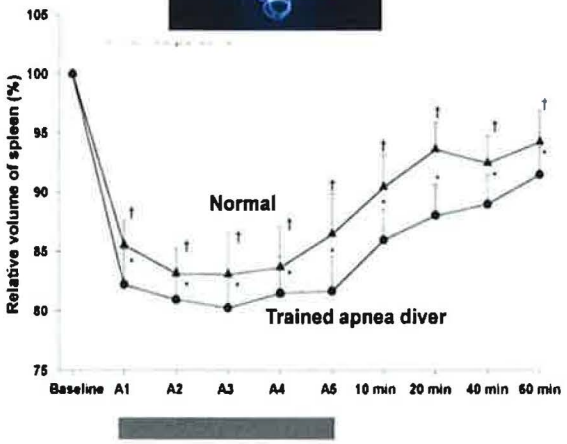
The functional significance of splenic release of RBC's in exercising mammals is best illustrated by the fact that splenectomy in dogs impairs the increase in diffusing capacity in the lung with increasing cardiac output as well as peripheral diffusion of oxygen (Hsia 10).

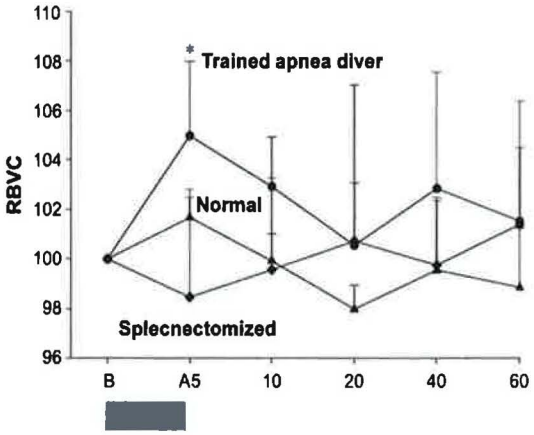
Pre and post splenectomy in foxhounds



Unlike, the athletic mammals, this splenic response in humans although exists, but is rather limited. The human spleen can sequester (generous estimate) 250 ml of RBC's and half of that can be released which can theoretically increase [Hb] by 1 gm/dl and HCT by 3% by calculation. This can be visualized by a smaller spleen during exercise but the increase in circulating RBC volume is rather modest (Bakovic 03, 05).

Human spleen 150-250 ml RBC's
~50% is released during exercise
Δ [Hb] = 1 gm/dl
Δ HCT 3%





Transfusion
Erythropoietin

1970
1980
1990
2000

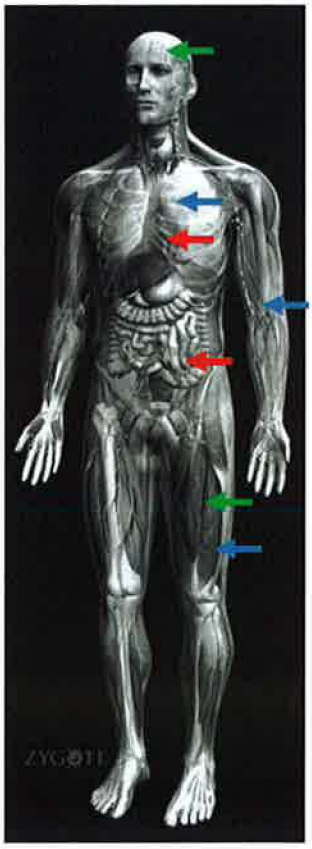
Popular

Decline

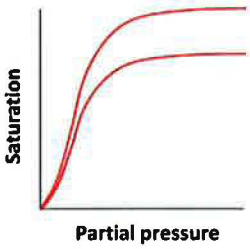
Re-emergence

1980 Widely used
1984 Widely used
1988 Banned

The only way to increase Hb or HCT in humans is via either blood transfusion or erythropoiesis stimulating agents (ESA) such as erythropoietin. Blood transfusions were widely used in the seventies and eighties until it was banned in 1988 Olympics (Giraud 10). The decline of blood transfusion was contemporaneous with the availability of ESA following FDA approval. However, it is important to note that erythropoietin is not equivalent to blood transfusion because it has a multitude of effects that can all contribute to enhancement of athletic performance (Boning 10).



Erythropoietin effects



GAS TRANSPORT
Increase diffusion capacity in the lung
Increased buffer capacity
Increased proportion of young erythrocytes
Increase diffusion capacity in peripheral tissue

CIRCULATION
Increased blood volume and pressure
Increase cardiac mechanical power for a given cardiac output
Constriction of mesenteric and renal vessels

OTHERS
Shift of muscle phenotype from glycolytic to oxidative
Improve mood

Detection

Transfusion Homologous

Minor RBC antigens

C, c, E, e, K

P_1, Fy^a, Fy^b

Jk^a, Jk^b, S, s

Transfusion Autologous

No established test

Exogenous substance during blood storage
- Plasticizers from plastic bags,
- Solvent for cryogenic preservation

Metabolites
- 2,3-bisphopshglycerate

Red blood cellular features
- Membrane changes
- Morphologic changes

Amount of Hb
- HCT
- Total red cell mass or Hb content

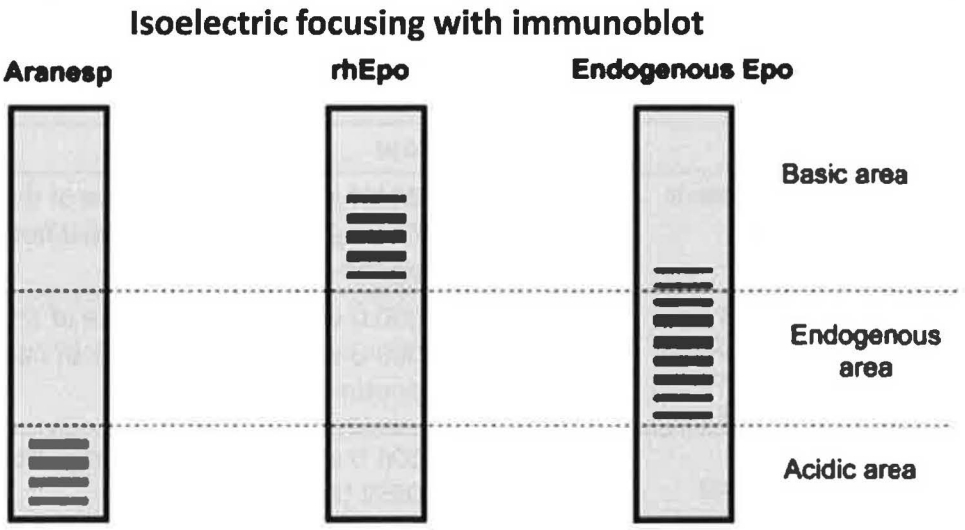
The detection of blood doping is challenging. To achieve the desired result of not missing any abuser, one needs a very sensitive test. Inherent with high sensitivity is a significant false positive rate. The stakes are very high because one can theoretically strip a gold medal from an innocent athlete and anger not one person but an entire country. Another difficulty is the nature of third abuse that renders detection very difficult.

Homologous transfusions using ABO and Rh compatible blood is no longer practiced. Part of the reason is that the homologous red cells are readily detectable using minor red cell antigens which are polymorphic and with twelve antigens, the probability of false positive is near zero. Autologous transfusions are much harder to detect and it relies on not one but a series of tests (Lippi 06, Arndt 08, Giraud 10). Since the banning of erythropoietin, autologous transfusions are becoming more popular again. The detection of exogenous erythropoietin has been a matter of intense debate and is still evolving (Franz 09, Lamon 09). There are indirect assays and direct assays. Currently, the main assay is isoelectric focusing combined with immunoblot that relies on the difference in sugar moieties between the administered and the endogenous erythropoietin.

This will continue to be a challenge as there are many generic biosimilar products flooding the market which creates a huge number of targets for the testing laboratories. Some erythropoietin produced in human cell lines may have glycans very similar to endogenous erythropoietin. Many newer methods are being developed to handle these new changes.

Current methods to detect exogenous erythropoietin

Method	Features
Indirect methods	
Soluble transferrin receptor assay	
Combination of hematocrit, serum Epo, soluble transferrin receptor concentrations, reticulocyte hematocrit, and % macrocytes	Useful as a first screening Can be improved when comparing an athlete's individual hematologic values against his or her own historical baseline
Combination of hematocrit, reticulocyte count, soluble transferrin receptor, and beta-globine mRN	Not very sensitive
Direct methods	
IEF/immunoblots	Standard method used by WADA accreditated labs
Lectin-based IEF	Experimental
2D electrophoresis	May be used as a confirmatory test to rule out nonspecific reactions
Microscale sample purification combined with MALDI-TOF and IT/RTOF mass spectrometry	Experimental



Legal misuse

There is no doubt that erythropoietin has been a life-saving drug. The title of this section does not mean to imply that practitioners intentionally misused the drug in any way. However, there is evidence to indicate that physicians really are not really as familiar with this drug as they should be considering that approximately two decades have elapsed since this drug was being given to patients.

There have been many clinical trials on erythropoietin both in the oncology and nephrology fields. There is no doubt that anemia is relieved and quality of life is improved. However, there are disturbing trends emerging on two fronts.

1. As researchers tried to look for the universally expected beneficial effect on cardiovascular outcomes, the results are either neutral or showing a tendency towards a harmful effect.
2. In patients with underlying malignancies, erythropoietin may be a two-edge sword while improving hemoglobin on one hand but promoting tumor growth on the other.

Three major trials in CKD patients have yielded disappointing results in terms of cardiovascular outcomes (Beserab 98, Singh 06, Drueke 06, Pfeffer 09).

Four major trials in CKD patients

Acronym	Trial	[Hb] (g/dl)	Dose	
NHCT	Normal Hematocrit	9-11 13-15	160 U kg^{-1} wk^{-1} 460 U kg^{-1} wk^{-1} Epoetin-α	Higher rate of death and myocardial infarction
CREATE	Cardiovascular Risk reduction by Early Anemia Treatment with Epoetin-β	10.5-11.5 13-15	2000 U wk^{-1} 5000 U wk^{-1} Epoetin-β	Higher rate of 1st CV event Higher risk of needing dialysis
CHOIR	Correction of Hemoglobin and Outcomes in Renal Insufficiency	11.3 13.5	5506 U wk^{-1} 10952 U wk^{-1} Epoetin-α	Higher composite events Death CHF hospitalization
TREAT	Trial to Reduce Cardiovascular Events with Aranesp Therapy	9 13	0 μg/mon 176 μg/mon Darbopoietin	Composite outcome neutral Higher strokes and thromboembolism Cancer-related deaths

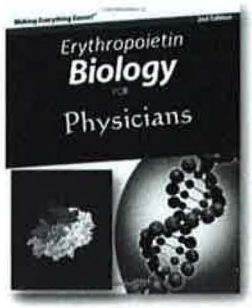
At this point in time, these concerns have not halted the use of the drug but it should at least call attention to the fact that there is more meets the eye. There are some fundamental foundations of the clinical use of erythropoietin that are likely not true.

Foundations for clinical applications

Myth	*Scientific fact*
There is one optimal [Hb] for all	Concept of optimal Hb
EPO dose is gauged by [Hb] so the level of EPO is irrelevant	EPOR is ubiquitous and there are extra-erythroid effects
EPO resistance is real but as long as we can get the [Hb] up, we are fine	EPO resistance in CKD is real
There will always be new and improved versions of ESA's to do trials and to write prescriptions with	What products are available or in the pipeline

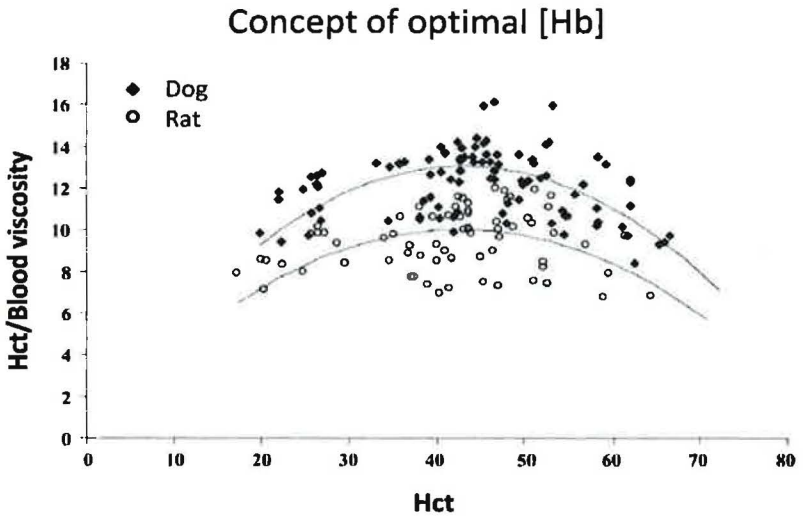
To try and settle each one of these, one needs to look beyond randomized control trials and seek more knowledge on the basic biology of erythropoietin. We will address each of the four questions with data.

Erythropoietin Biology



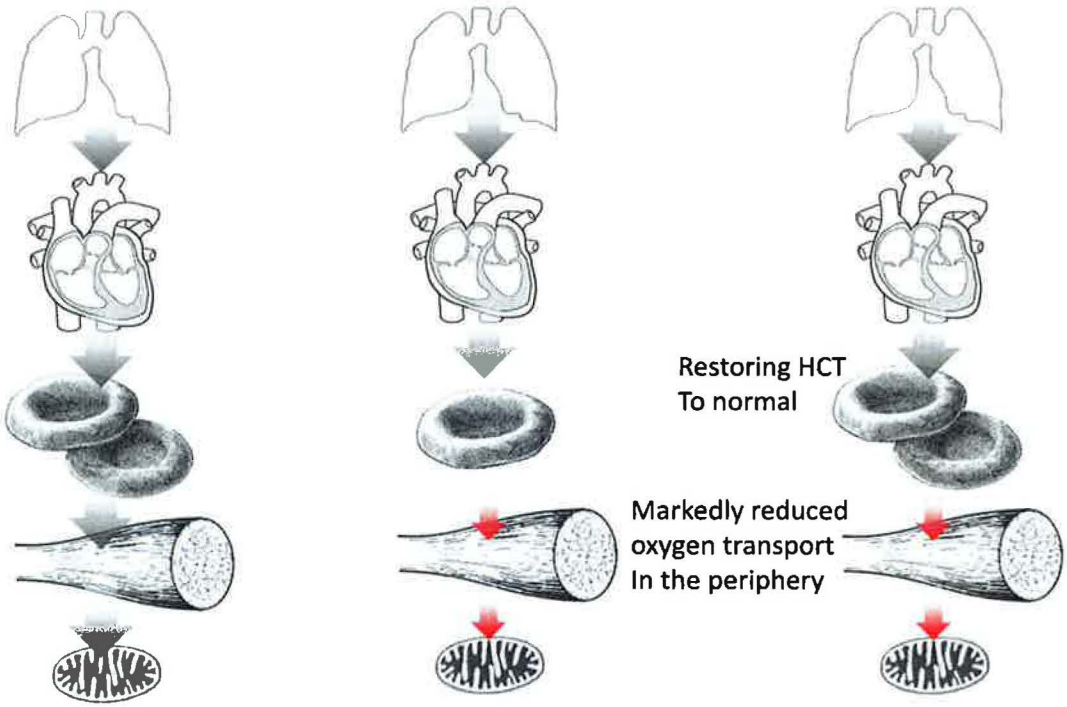
•There is one optimal [Hb] or HCT for all

Unfortunately, some practitioners have come to the belief that one should search for one hematocrit and the way to seek for that magic number is by a randomized controlled trial. The concept of optimal hematocrit has been in the literature for more than half a century. Epidemiologic studies from the Framingham database showed a U curve relationship between hemoglobin concentration and mortality suggesting the existence of an optimal [Hb] (Gagnon 94). While higher HCT increases oxygen carrying capacity, it also increases viscosity which is counterproductive to oxygen transport. The "oxygen transport potential" is represented by HCT divided by viscosity. From a hemorreological perspective, this is the theoretical ability to deliver oxygen to the microcirculation (Crowell 67). The optimal Hct physiologically is defined by the value that yields the highest Hct/viscosity (Bogar 05).



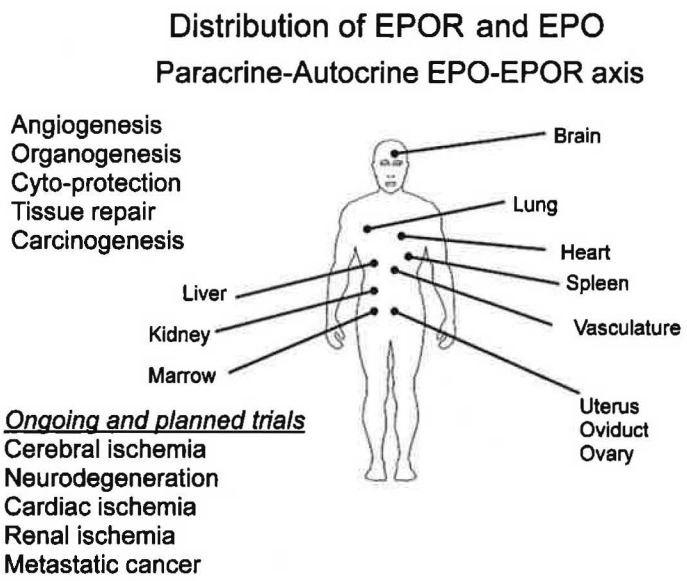
The plot of Hct/viscosity against Hct is an "inverted U" with the optimal HCT defined by the peak of the U. The maximal Hct/blood viscosity and optimal HCT varies from species to species and both parameters can change with exercise and blood flow.

This relationship has never been determined in the setting of CKD. Clinicians make the assumption that the Hct determined by the norm derived from healthy individual also applies to patients with CKD. This reasoning is in fact flawed. There is good evidence that oxygen transport in the peripheral is severely impaired in patients with CKD (Moore 93, Marrades 96) and improvement in HCT with erythropoietin led to limited improvement in oxygen transport (Marrades 96).



•EPO dose is gauged by [Hb] so the level of EPO is irrelevant

It is clear that EpoR is ubiquitously expressed (D'Andrea 90) and erythropoietin has many actions in addition to its hematopoitic effects (Jelkman 07, Cariou 08). Erythropoietin promotes proliferation and migration of endothelial cells, stimulates production of modulators of vascular tone, favours a pro-angiogenic phenotype and induces neovascularisation. In vascular smooth muscle cells, erythropoietin causes contraction. Erythropoietin exerts cardioprotective effects. In the central nervous system, EpoR is expressed in neurons, astrocytes and brain capillary endothelial cells. Erythropoietin exerts neuroprotective and neurotrophic effects. In kidney, there is mounting evidence that, erythropoietin is renoprotective in the setting of ischemia reperfusion.



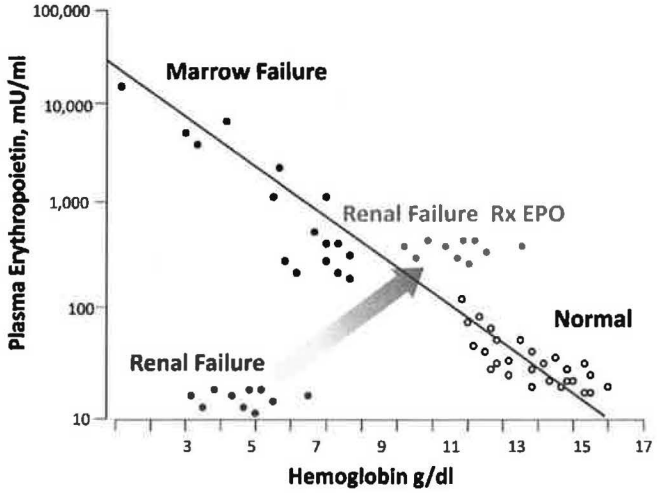
There is very little chance that the administered erythropoietin will have no effects other than erythropoiesis. The potential mechanisms of adverse effects have been summarized by Fishbane and Beserab (Fishbane 07) and Singh (Singh 10).

Possible mechanisms of worsened cardiovascular or cancer outcome

1. Increased viscosity- impaired microcirculation
2. Thromboembolism- procoagulant action
3. Vasoconstriction
4. Concomitant iron therapy and iron toxicity
5. Activation of low affinity heterodimeric Epo-R and the generic β-receptor for interleukins

•EPO resistance is real but as long as we get the [Hb] up, it should be fine.

Erythropoietin resistance exists by definition in uremia. When [Hb] is restored by recombinant erythropoietin, the level of plasma erythropoietin is higher than that of a normal individual. This is simply due to the fact that the anemia of CKD is a multifactorial disease where erythropoietin deficiency is only one culprit. There is a whole host of other factors including blood loss, reduced erythrocyte survival, and marrow resistance to not just erythropoietin but many molecules that promote erythropoiesis.



One of the best evidence that supports this notion is the fact that increasing dosage of dialysis improves the Hct without change or even a reduction in dosage of erythropoietin. Erythropoietin resistance can be due to a chronic inflammatory state and from inadequate clearance of uremic toxins. In general, the approach to dialysis is usually targeted to adequate rather than optimal clearance.

Instead of searching for possible underlying causes of erythropoietin resistance, practitioners often opt for increasing the dosage of erythropoietin and couple this with generous doses of parenteral iron.

Hematinic deficiency
  Iron or folate deficiency
Aluminum toxicity
Hyperparathyroid

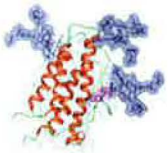
Excess proinflammatory cytokines
  IL-6, TNF-α,
Suppressed pro-erythropoietic factors
  IGF-1
Uremic toxins
  Inadequate dialysis

•There will always be new and improved versions of ESA's to do trials and to write prescriptions with

This happens to be true. However, clinicians should be better informed about what is currently available and what is in the pipeline. With increasing complexity of therapy, only thorough understanding of these products can equip the physician with the ability to prescribe these agents. All these compounds bear the name *epoetin*. Alterations in primary amino acid sequence lead to a prefix such as *Darbe*. The Greek letter postfix indicates differences in post-translational modifications.

Erythropoietin
165 aa backbone
2 disulfide (C7-C161; C29-C33)
3 N-linked (N24, 38, 83) 1 O-linked (S126) glycan

Generic	Trade name	Host	Comments
Epoetin-α	Epogen, Procrit Eprex, Erypo, Espo	CHO (Chinese Hamster Ovary) cells	O-acetylated sialic acid increased. Contains Neu5Gc which is not human
Epoetin-β	Recormon, Epogin, NeoRecorman	CHO cells	Higherdegree of basic isoforms
Epoetin-ω	Epomax	BHK (Baby Hamster Kidney) cells	N-chains sulfated Smaller amounts of O-bound sugars, higher basic
Darbopoietin-α	Aranesp NESP		5 aa "mutein" 2 additional N-linked glycans 22 sialic acids, 51% sugar 3-4 times longer T1/2
Epoetin-δ	Dynepo	HT1080 (Human fibrosarcoma) cell	Upstream activator of native EPO. Glycans closest to human. No Neu5Gc
CERA	Mircera	CHO cells	Methoxy-PEG polymer added via amide bonds. Longest T1/2
Other Biosimilars	>80 products as of end of 2009 Growing yearly	Wide range	Wide variety of compounds: Abseamed. Hexl, Binocrit, Silapo, Retacrit, Vintor, Wepox, Eposino, Shanpoietin, Hemax, Repotin, Eposino, NingHongXin, Zyrop, Alphaepoetina...



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EPO-fusion proteins	CNTO528: Antibody fusion protein with hematopoietic peptide	Long T1/2
Peptide EPO	Hematide. Two peptide chains linked to a pegylation chain	Effective again pure red cell aplasia from anti-EPO Ab. Cardiovascular risk
Small molecules	Very limited success	
Epo gene	Ex-vivo delivery Autologous dermal cores hypoxia-driven PGK promoter	Constitutive promoter leads to fatal polycythema
Prolyl hydroxylase inhibitor	Activates endogenous EPO gene FG2216	Phase I
GATA antagonists	Activates endogenous EPO gene	Animal studies
Phosphatase inhibtor	Amplifies and prolong receptor activation	Animal studies
Expansion of precursors	Pre-EPO sensitive phase – CFU-E	Animal studies
Non-erythropoietic tissue protective peptides	Eliminate erythropoietic activity CEPO (Carbamyolation of N-term and lysine resideus)	Tissue protection

Summary

The short history of recombinant erythropoietin reflects biomedical triumph of rapid bench to bedside translation that revolutionized the treatment of chronic kidney disease. At the same time, this history is paralleled by one of the most contradictory and controversial sequence of events in the biotech and pharmaceutical industry and public policy. As the patent expires, one witnesses a colossal avalanche of generic look-alikes all over the world. The success in clinical application was also accompanied by a large insurgence of illegitimate use of the drug driven by blind or misguided ambition to excel in high performance sports regardless of means to reach the goals of victory and glory. This has created unprecedented challenges in reinforcing and detection of the prohibited use of this drug in sports. Despite the importance of detection and the almost unlimited technologies available, this is not resolved yet. On the legal approved use of the drug, there has been certain degree of ignorance and indifference on the part of the medical community resulting in the unexpected emergence of undesirable outcomes from erythropoietin therapy. The EPO-EpoR axis has an enormously broad myriad of functions. Despite the complexity it poses, there exist many opportunities to manipulate this system therapeutically with new agents in the horizon. We are in dire need of more biomedical research so we can fully realize and capitalize on the potential gains and prevent the potential fallbacks in the future. We also need to close the gap between the cutting edge research and the database and comprehension of EPO biology secured by the practitioner.

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