Erythropoietin: Beyond a Prescription for Renal Patients

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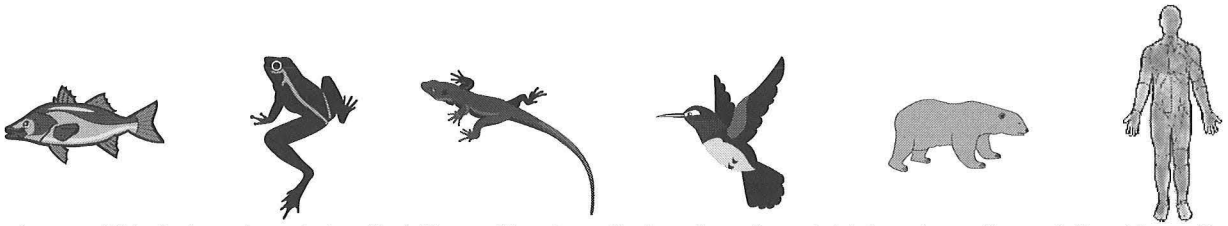

Disclosure: This is to acknowledge that Orson Moe has disclosed no financial interest or other relationships with commercial concerns related directly or indirectly to this program. Dr. Moe will be discussing off-label uses in his presentation.

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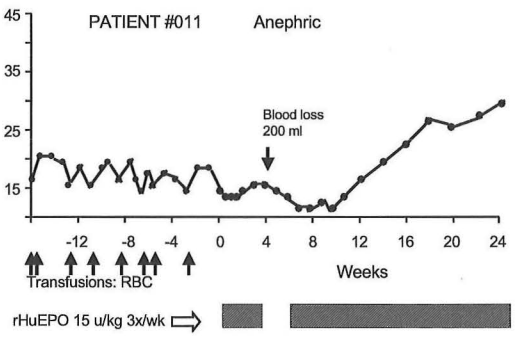
INTRODUCTION

A case from a bygone era...

G.L. was a 39 year old caucasian who had renal failure from congenital reflux nephropathy. Because of chronic suppurative pyelonepritis, he had undergone bilateral nephrectomies. He had been on hemodialysis for 14 years and failed three allografts over about a ten year period. He reacted to 100% of the antigen panel and could never get a negative cross match. Because of his anephric status, he was extremely anemic and was transfusion-dependent. His high level of sensitization was probably from the rejected allografts but the multiple transfusions probably contributed as well. In addition to sensitization, he was inflicted with fairly severe Fe overload despite repeated chelation therapy. Because of this complication, blood transfusions were restricted only to the point when he had angina at rest or minimal exertion. He had coronary artery disease that was not considered amenable to bypass or angioplasty. He had a significant family history of coronary disease. Socially, he was of Italian descent, a non-smoker, and a father of one biologic and two adopted children.

One Sunday afternoon, Mr. L experienced angina at rest and his wife strongly adviced him to go to the hospital for a transfusion. He declined and resorted to complete bed rest and increased his nitroglycerin which left him angina-free for the rest of the day. That same evening during his sleep, he expired at the age of forty with a massive myocardial infraction. This happened in 1987.

In that same year, data appeared in the *New England Journal of Medicine* showing the results of combined phase I and II trial of the use of erythropoietin in patients with end stage renal disease. The figure on the right shows a nephrectomized patient not unlike the one described above. The response of the hematocrit to erythropoietin was nothing short of sensational. This dramatic response in 1987 will be consider completely routine today in any dialysis unit.



N Engl J Med 1987

The clinical use of erythropoietin

To most nephrologists today, anemia of chronic renal failure is a disease of transient existence. A low hemoglobin is encountered when a patient presents with end-stage renal disease without prior medical attention. After initiation of erythropoietin therapy, the anemia disappears. The hematocrit in a dialysis patient used to be an entity that nephrologists struggled with as in the above patient. In 2001, the hematocrit is a number that the doctor dials in as he or she pleases with the upper limit defined mostly by Medicare reimbursement policies.

There have been a number of momentous advances in clinical nephrology in the past 15 years. The expansion of choice for anti-hypertensive agents have improved the ease in blood pressure control. Pharmacologic interruption of the renin-angiotensin system has successfully

retarded progression of renal disease. The use of calcineurin inhibitors has significantly improved long term graft survival. Many more examples can be quoted. However, none of these advances come close to the vicinity of a cure. For the practicing physician, erythropoietin is practically a cure for anemia of chronic renal disease. There are ongoing debates about the prescription of erythropoietin but the overall consensus of how to use this drug is fairly well developed. One can summarize the salient features of erythropoietin prescription in patients with chronic renal failure in the accompanying Table. For those who seek more details and discussion, an abundance of clinical review articles permeate the literature.

Management of Anemia of Chronic Renal Disease

- Give Erythropoietin
- Fe replete
- Erythropoietin resistance
  - Fe, Folate, B_{12} deficiency
  - Occult bleed
  - Underlying infection
  - Hyperparathyroidism
  - Aluminum toxicity
  - Inadequate dialysis
  - "Functional" Fe deficiency
- Adjust dose of Erythropoietin
- Parenteral Fe

One can safely claim that we have secured an efficacious replacement therapy with great clinical utility. However, is that all a physician should care about in terms of the biology of erythropoietin? Another patient is presented in this Grand Rounds that should spark the clinician to quest for more information on this most interesting hormone.

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United States Renal Data System. www.usrds.org

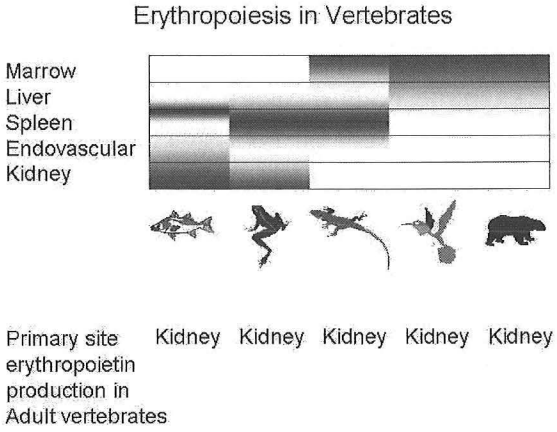
EVOLUTION OF ERYTHROPOIESIS IN VERTEBRATES

Oxygen carrying pigments

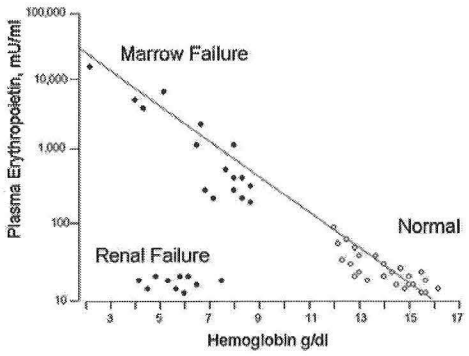
Life on this planet has been estimated to be about 4 billion years old following the birth of the moon with stabilized conditions on earth about 4.5 billion years ago. At the dawn of life, all life forms were anaerobic because there was very little molecular oxygen on the planet. Free molecular oxygen is a product of life. The first photosynthetic organism was the cyanobacteria which utilizes CO_2 and H_2O to build more complex carbon compounds. As they harness photo energy to strip the hydrogen off water, molecular oxygen emerged as a by-product. O_2 appeared in the atmosphere 3 billion years ago and accumulated to a new steady state about 1.5 billion years ago. Since the origin

of aerobic existence, O_2-carrying pigments have been vital to animal life. They have been classified into five types based on their color and sedimentation coefficients by Svedberg and Hedenius in 1934 (hemoglobin, erythrocruocin, hemocyanin, chlorocruocin, and hemerythrin) and is still valid today. Vertebrates have been in existence probably for about 500 million years. Oxygen carrying pigments in vertebrates are characterized by two features: 1. They utilize almost exclusively hemoglobin. 2. The pigment is sequestered within lipid bilayer-delimited erythrocytes. Hemoglobin has been found in the most primitive unicellular organisms. The current theory is that all four pigments probably co-evolved. The packaging of hemoglobin into red corpuscles is likely an recent event in vertebrates. The intracellular restriction of hemoglobin is requisite to ensure high concentrations of the vital respiratory pigment in the vicinity of critical enzymes required for both the O_2 and CO_2 transport functions of hemoglobin.

Erythropoiesis in vertebrates: From paracrine to endocrine



In all vertebrates, embryonic erythropoiesis is in the yolk sac or its equivalent. After birth, the site of erythropoiesis shifts to other organs. In fish, erythropoiesis after birth is in the kidney with some contribution from the spleen depending on the species. In amphibians, the kidney remains the major site of erythropoiesis after birth during the larval stage. It is replaced later by the liver transiently in some species and finally in the adult by the spleen. In higher vertebrates, some variable contribution to erythropoiesis comes from the liver and spleen but the predominant site of erythropoiesis in birds and mammals is in the bone marrow. Although erythropoiesis has migrated from the kidney to other organs, the site of erythropoietin production has remained in the kidney. Organ ablation experiments have shown that the kidney is responsible for >90% of the circulating erythropoietin in mammals. The human data equivalent to the ablation experiments come from patients with renal disease. Erythropoietin has a log-linear relationship with hemoglobin concentration in a variety of anemias except in renal disease where erythropoietin remains low despite extremely low hemoglobin concentrations.



Throughout the evolution of vertebrates over some 500 million years, erythropoietin has transformed from a paracrine to an endocrine hormone. This finding beckons two questions. 1. Why did the erythropoietic factory migrate from the kidney to the spleen and then the bone marrow? 2. With the migration of erythropoiesis, why did the erythropoietin production stayed in the kidney. The first question will be addressed briefly and the second one will receive more elaborate consideration in a later section.

Migration away from the kidney

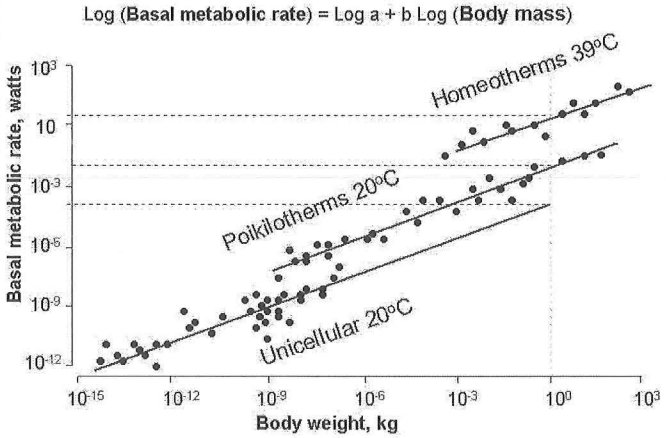
Although no one knows the definitive answer as to why the migration occurred, a straight forward speculation can be offered. The departure from the kidney to the marrow may be simply a result of space constraints. In the most general sense, allometry is the study of size and its consequence in living organisms. It is a quantitative study of a particular physiologic or morphologic parameter as a function of the size of the organism. Empirically, the parameter of interest is always related to the body mass by the allometric equation.

$Y = a \cdot X^{b}$ where Y is the physiologic or morphologic parameter
X is body mass

a and b are empirical constants which enable biologist to make quantitative comparisons.
A double log plot of the empirical data allows allometrists to compute a and b.
$\text{Log } Y = \text{Log } a + b \cdot \text{Log } X$

For example, body surface area can be related to body mass in a positive fashion as one can logically expect. Heart rate on the other hand is related to body mass in a negative fashion, i.e. larger organisms in general has slower heart rates. Notice that the x-axis spans from a 1 mg paramecium to a 10,000 kg blue whale. The value on the y-axis when X=1 (LogX=0) yields the value of a.

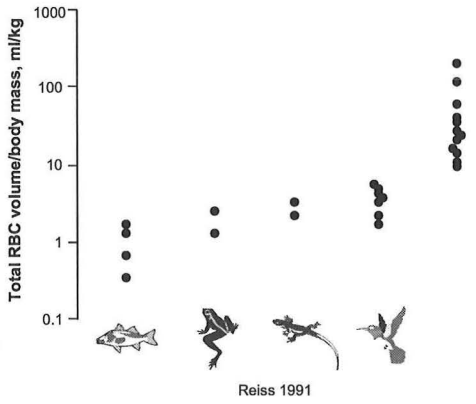
An allometric analysis of basal metabolic rate (BMR) was performed by Peters and colleagues in unicellular organisms, poikilotherms and homeotherms spanning about 90 species. The allometric plot is shown on the right relating BMR to body mass (BM). The correponding allometric equations are shown below:



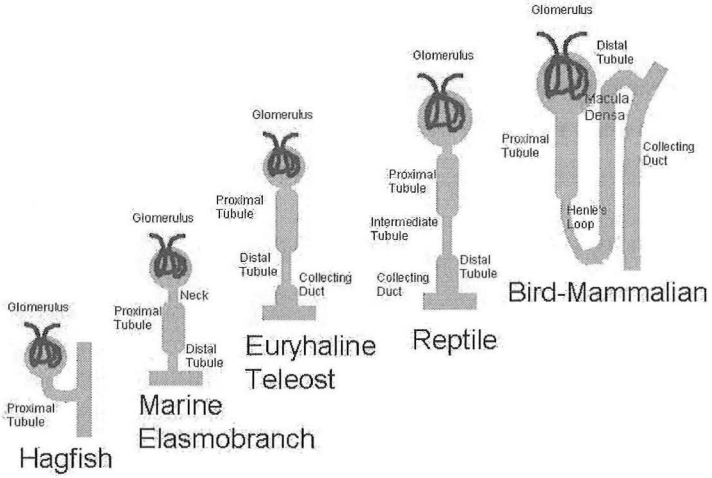
Unicellular $BMR = 0.0176 \cdot (BM)^{0.756}$
Poikilotherm $BMR = 0.144 \cdot (BM)^{0.738}$
Homeotherm $BMR = 4.10 \cdot (BM)^{0.739}$

While b remains strikingly constant, the value of a increases dramatically from unicellular organisms to homeotherms. Stated another way, for a given body mass, poikilotherms has about 8 times and homeotherms have about 230 times higher basal metabolic rate than unicellular organisms. In an aerobic world, this basal metabolic rate can be translated into O_2 consumption. This higher O_2 consumption must be attained by higher cardiac output as well as higher O_2 carrying capacity. When one compares the total red cell volume of

vertebrates as Reiss did, one finds a striking difference between lower and higher vertebrates. Note that for a given body mass, mammals have red cell volume that is 100 to 1000 times that of fish. This places an immense demand on the erythropoietic organ. While the piscine kidney may suffice to sustain 0.2-2 ml of circulating red cells per kg body mass, it will be enormously taxing to require the kidney to maintain a red cell mass of over 100 ml/kg. Contemporary with this increase in red cell volume is an increase in the complexity of the kidney as an organ of homeostatic defense of the *milieu interne*.



The evolution and migration of vertebrates started from seawater to fresh water and eventually to land. The demand on water and Na^+ conservation became increasing more challenging. The nephrons in the cyclostomes are just glomeruli. While bathing in hypertonic saline, Na conservation is not a major concern and being an osmoconformers, cyclostomes have no need for urinary concentration or dilution. In the shark, the proximal tubule appeared and there is a short segment of distal tubule. In the fresh water fish and amphibians, one needs to add a diluting segment to deal with the massive electrolyte-free water load as well elaborate Na^+ conservation mechanisms. Finally on land, one needs sophisticated concentrating mechanisms as well as powerful Na^+ reabsorptive mechanisms to deal with virtually salt-free terrestrial subsistence. In addition to water and electrolyte homeostasis, the increasing metabolic rate and the feast-and-famine physiology associated with terrestrial life obligate high capacity and highly regulated nitrogenous excretory mechanisms. Thus the mammalian kidney is faced with highly demanding tasks. When coupled with an ever increasing need to scale up erythropoiesis, it is not difficult to fathom why red cell production has to leave the kidney. This provides a reasonable answer to the first question of why erythropoiesis left. The second question is more complex.



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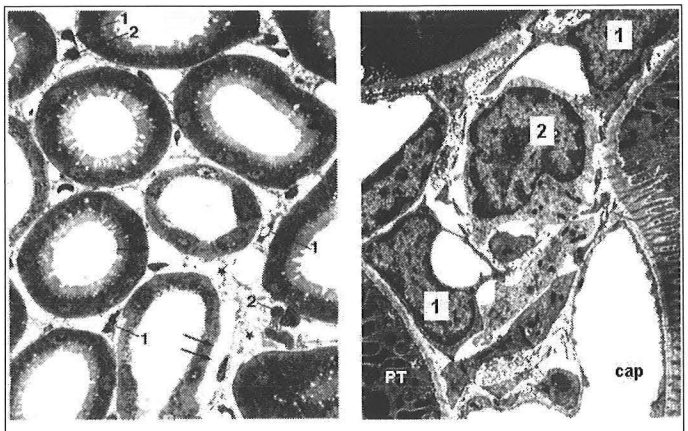
ERYTHROPOIETIN PRODUCTION IN THE KIDNEY

When erythropoiesis migrated and erythropoietin production stayed, erythropoietin became an endocrine hormone. Why did the erythropoietin-producing cell stay in the kidney? To address this issue, one needs to pose three questions:

1. What is and where is this cell?
2. What is being sensed by this cell?
3. Why do these cells have to be in the kidney?

What is and where is this cell?

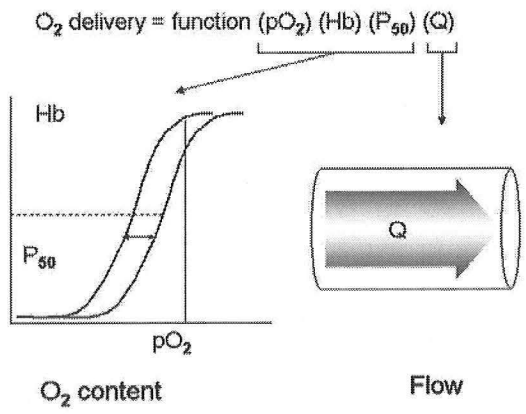


Type 1: Fibroblast
Type 2: Round cells

PT: Proximal tubule
Cap: Peritubular capillary

In the first few years after the reagents became available, there were some controversy about whether this cell is in the glomerulus, tubule, vasculature or the interstitium. Some of the variation may reflect species differences but technical problems accounted for most of the discrepancies. Today, controversy still exist as to whether the renal tubule produces erythropoietin. However, most will agree that in mammals, at least rodents or higher, the erythropoietin-producing cell resides in the renal interstitium. Scattered among the interstitial matrix are two morphologic distinct cell types. The type 1 cell is stellate in appearance and is called the interstitial fibroblast. Type 2 cells are rounded and are lymphocyte-like. They express class II MHC molecules and are important in antigen presentation. The type 1 fibroblast can be further sub-classified but we will not get into the details. The type 1 fibroblasts are full of microfilaments which support an extensive array of processes that interdigitate between and abut on both the tubular epithelium and the capillary. They are also full of rough endoplasmic reticulum indicating they are synthetically active.

What is being sensed by this cell?



A physiologic sensor is supposed to signal error. Errors that alert homeostatic mechanisms to effect rectification . In this case, the error should be inadequate O_2 delivery. Erythropoietin then signals for increase in O_2-carrying capacity of the blood. How should one sense O_2 delivery? O_2 delivery is a function of O_2 content and flow. O_2 content is determined by the O_2 tension of the blood, the hemoglobin concentration and the affinity of O_2 (or P_{50} of hemoglobin). One can consider the various parameters that one can sense, decide whether they should be sensed and then examine the experimental and clinical data to see if the model is compatible with the facts.

What parameter can we sense?	Should we?	Do we? Experimental	Do we? Clinical
		↑ Increased EPO/HCT	
pO_2	yes	↑ hypoxic hypoxia	↑COPD ↑cyanotic heart disease
Hb	yes	↑anemia ↑carbon monoxide	↑anemia ↑carbon monoxide
P_{50} Large Right shift	yes	↑ Acute severe acidosis	

It appears that hematocrit increases in response to either a fall in pO_2, a fall in hemoglobin, or a large right shift of P_{50} (which reduces the affinity of hemoglobin for O_2). To achieve all these goals, a simple single parameter sensor can be O_2 delivery. A further perusal of the data reveals that the situation is not so simplistic.

If O_2 delivery is all that matters, one would expect a physiologic increase in hematocrit in response to decreased blood flow and a decrease in hematocrit in response to increased blood flow to the kidney. In reality, none of the above happens. Neither plasma erythropoietin nor hematocrit changes with alterations in blood flow. A left shift in P_{50} which does not impair loading but in fact facilitates loading, should not affect O_2 delivery and hence not activate the sensing mechanism. In fact a left shift in P_{50} is associated with high erythropoietin levels and polycythemia. Finally, in compensated anemia where the decreased O_2 carrying capacity is offset by increased flow, delivery is normalized. Yet, erythropoietin levels are high. In sum, the data does not support a paradigm of sensing O_2 delivery as the error message to trigger erythropoietin production.

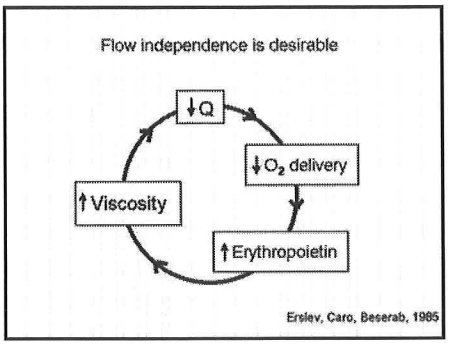
Desirable

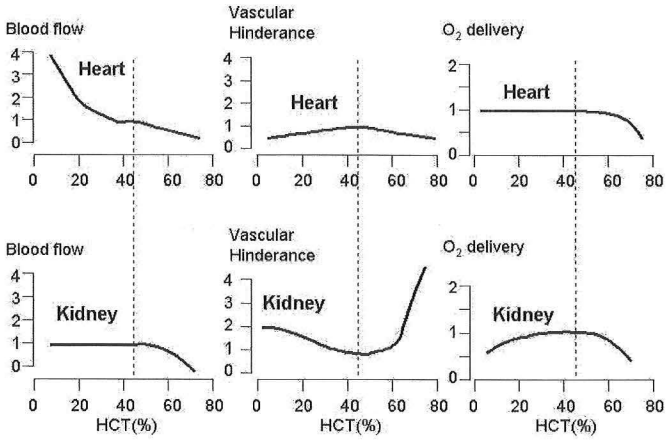
- Dissociation from flow
  - Oblivious to short term variations
  - Minimal compensatory flow
- Delivery and consumption
  - Integration of supply and demand
  - Means to sense it

The task of assessing total body supply and demand of O_2 is delegated to the kidney. Theoretical considerations will predict certain features to be desirable for this sensor to be efficient and effective. First, blood flow is a highly variable parameter and it is wise to dissociate it from the O_2 carrying capacity of the blood. In addition, anemia is associated with compensatory increase in cardiac output. This compensatory response if not nullified in the kidney would prevent an adaptive increase in erythropoietin. Second, it is desirable to integrate the sensing of supply to that of demand. Finally, one needs to consider the mechanisms available in biology to perform these tasks. Evolution has taught us that this is accomplished reasonably successfully in the kidney for millions of years in thousands of species. We will examine flow independence and integration of supply and demand.

Can the kidney fulfill these functions?

Flow independence. Recall that blood flow which no doubt alters O_2 delivery is not sensed by the kidney as an error signal. This is evident by the lack of change in erythropoietin levels and hematocrit in response to changes in flow. Due to the linear relationship between resistence and viscosity, Erslev, Caro and Besarab have pointed out that if decreased blood flow to the kidney stimulates erythropoietin and secondary erythrocytosis, the feedback would further decrease renal blood flow and thus begets a vicious cycle. How does one take renal blood flow out of the O_2 delivery term?

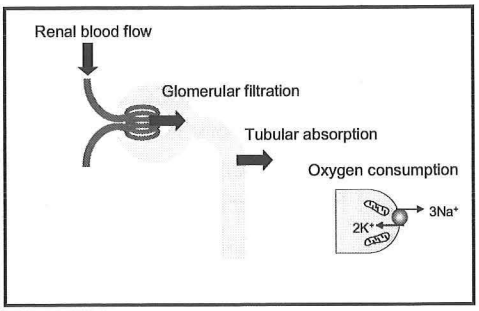


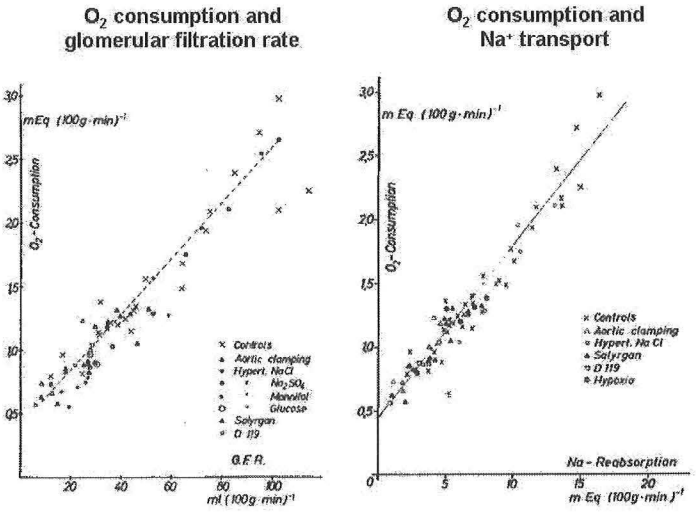


Fan et al. 1980

First, the renal circulation is highly autoregulated due to a combination of intrinsic myogenic reflexes in the renal arterioles and more importantly, a build-in autoregulatory paracrine system called tubuloglomerular feedback unique for terrestrial mammals. Renal blood flow remains well maintained down to a perfusion pressure of 80 mm Hg. The relative constancy of renal blood flow was elegantly demonstrated by Grupp and coworkers who showed that when cardiac output increases in response to anemia, the fractional delivery to the kidneys decreases and that the absolute increase of blood flow to the kidney is minimized. Fan and Chien elegantly demonstrated the unique nature of the renal circulation. A number of vascular beds were studied but the Figure below shows only the heart and the kidney. Although blood flow to the heart increases in response to anemia, blood flow to the kidney remains relatively unchanged due to vasoconstriction that offsets the effect of lower viscosity. This results in decreased O_2 content in the blood in the presence of constant flow. Therefore erythropoietin increases appropriately. In erythrocytosis, renal blood flow dramatically decreases due to a combination of increased viscosity and vasoconstriction. This results in significant fall in renal blood flow and O_2 delivery. Erythrocytosis is the most potent inhibitor of erythropoietin production. How can erythropoietin be suppressed in this instance? Additional mechanisms must exist.

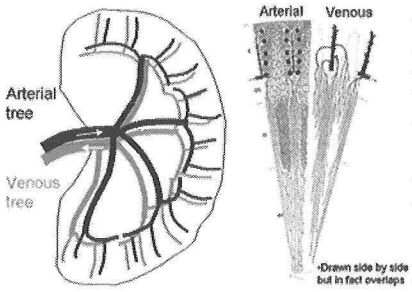
Coupling between supply and demand. Dr. Van Slyke has shown nearly sixty years ago that under spontaneously variations in renal blood flow, there is a linear relationship between O_2 consumption and renal blood flow. Since then, numerous studies have been done to address the coupling between blood flow and O_2 consumption. The data from Kramer and Deetjen will be used to illustrate the point. O_2 consumption in the kidney is primarily devoted to Na^+ transport. In order to maintain ion and water homeostasis, tubular ion absorption has to be adjusted according to glomerular filtration. For example, if a protein load (nice steak dinner) increases glomerular filtration by 20% over 4 hrs, the net increase in filtrate will be about 5 L's of extracellular fluid. If tubular absorption does not increase accordingly, then the price of the steak will be massive loss of extracellular fluid volume. Because of this phenomenon of glomerular-tubular balance, renal blood flow is tightly coupled to glomerular filtration rate, which in turn is coupled to Na^+ transport and O_2 consumption.

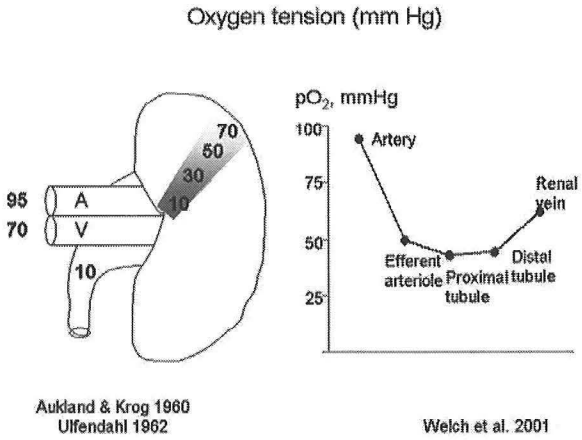




Kramer and Deetjen 1963

Now one has to consider how to sense O_2 delivery in the context of O_2 consumption. At first glance this seems like the most improbable place. Traditionally, the kidney has been perceived as a luxuriously perfused organ. This view is based on the following data. Being less than 2% of the body mass, the kidney is endowed with 25% of the cardiac output. As a result, the renal venous O_2 tension is highest in the body and the A-V O_2 difference is the smallest. At this level. it really seems counterproductive to place the sensor in the kidney. The high O_2 tension in the renal vein in reality does not reflect a luxuriously perfused organ. There are features of the renal circulation that is unique. First is that it is the most extensive arrays of arteriovenous countercurrent circuits. Just about every arterial branch is in juxtaposition with a venous counterpart flowing in the opposite direction. Second unique feature is that the kidney is the only portal circulation where two capillaries are in series; the glomerular tuft and the peritubular capillaries. The efferent "arteriole" is anatomically a "venule" from the glomerulus.



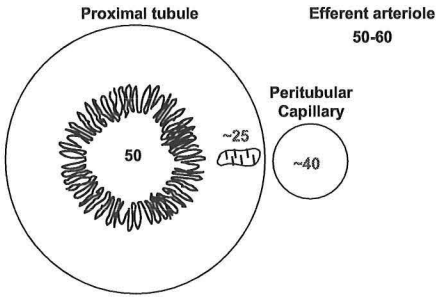


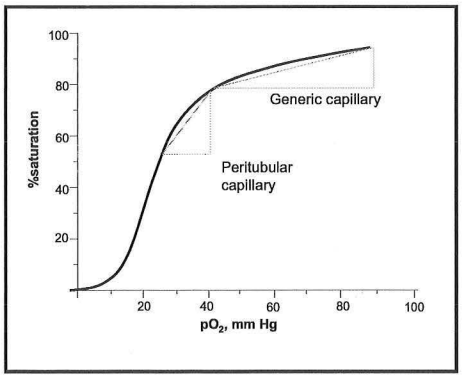
Examination of renal tissue O_2 tension shows that >85% of the renal parenchymal is below that of the renal vein. The highest tissue pO_2 is right at the superficial cortex and is barely that of the renal vein. Towards the medulla, tissue pO_2 falls to as low as 10 mm Hg. Urinary pO_2 simply reflects tissue pO_2 in the deep medulla. These findings support the notion of physiologic A-V O_2 shunting at both the pre-glomerular and post-glomerular levels. Therefore the highest renal venous pO_2 is not a consequence of underutilization but rather a reflection of extensive shunting of O_2 from renal tissue.

Metabolism in the renal tubular cell is varied with the cortex having the highest dependence on the tricarboxylic acid cycle and the inner medulla having the highest glycolytic activity

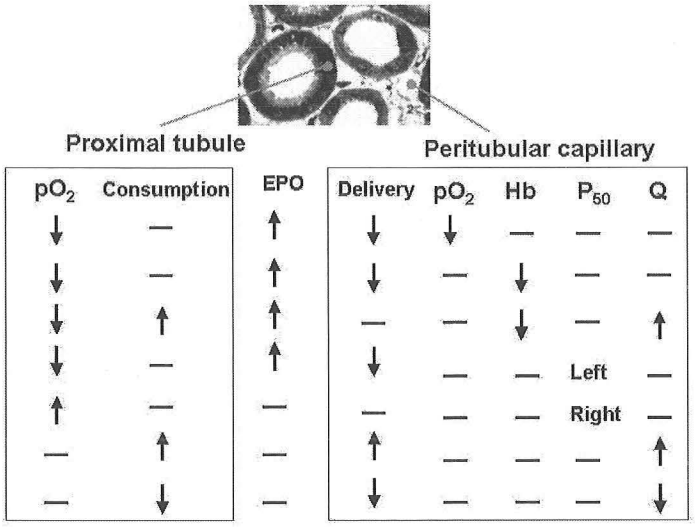
	Oxidative	Glycolytic
Cortex	>97%	>3%
Outer medulla	50%	50%
Inner medulla	30%	70%

In the deep cortex where tissue pO_2 falls towards about 40-50 mm Hg, the cells in that vicinity are still primarily utilizing aerobic metabolism. In this region, supply and demand are very closely approximated with relatively limited reserve. A sensor in the deep cortex would be very sensitive to small imbalances in O_2 delivery and consumption. This is exactly where the erythropoietin-producing type 1 fibroblast resides. A more careful scrutiny of this region reviews that the tubular luminal pO_2 likely does not reflect the pO_2 near the basolateral membrane of the tubule where O_2 consumption is the highest. A more realistic (although not actually measured) model of pO_2 is shown in the Figure above. In essence what the renal tubule has done is to shift the unloading of O_2 from the flat part of the O_2-Hb

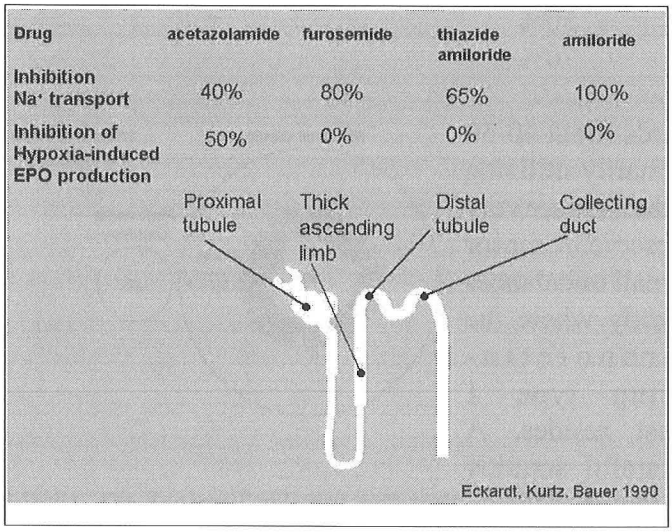




dissociation curve to the steep part. Since the actual biologic entity sensed is more likely to be O_2 tension rather than O_2 content (there is little evidence of ability to sense O_2 content), it crucial to have a linear relationship between O_2 content and pressure. The placement of the sensing cell at this renal locale achieves that purpose. One can summarize the facts and attempt to create a model to explain all the clinical and experimental findings. The most logical sensing mechanism will be proximal tubule pO_2 as erythropoietin secretion is increased in all conditions that decrease the theoretical proximal tubule pO_2.



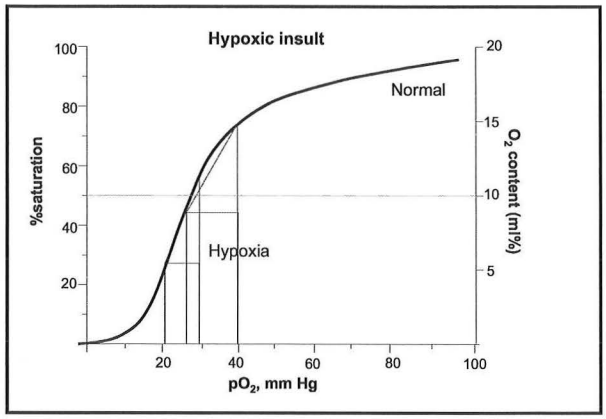
Additional evidence are available to support the notion of sensing the balance between supply and demand. When proximal tubule O_2 consumption is diminished by inhibition of transport without any change in O_2 supply, erythropoietin levels are reduced. A reptilian example in support of this theory has also be described. The newt kidney responds to anoxia, carbon monoxide, or hemolysis by increasing erythropoietin production. In these conditions, local lactate levels are elevated and a distinctive cell hypertrophies in the cortex. This cell has been termed the lactate-sensitive cell. This phenomenon can be mimicked by infusion of Na lactate which does not represent an acid load nor is it a hypoxic condition. It is likely that the erythropoietin-producing cell in the newt responds to lactate as a surrogate for imbalance of O_2 delivery and consumption.

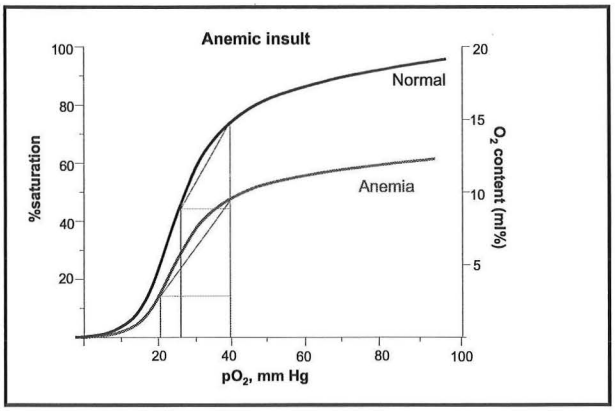


Reduced erythropoietin in patients with renal disease has been attributed to physical destruction of the renal parenchyma including the interstitial type 1 fibroblast. However, there are instances where low erythropoietin is associated with only moderately reduced GFR. It is highly likely that we encounter clinical examples of "functional" erythropoietin deficiency caused by the low renal tubule transport rates and low O_2 consumption.

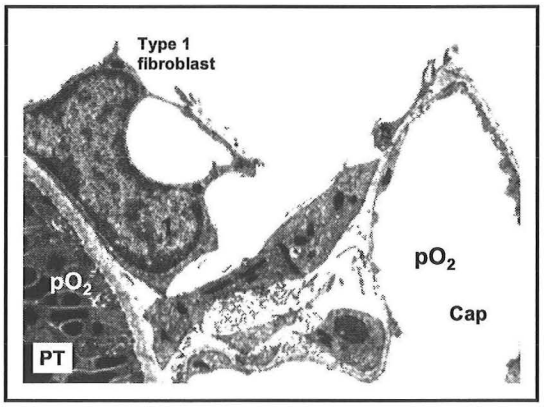
One possible sensing parameter that can explain all the findings is the proximal tubule pO_2. Could this be the ultimate regulated variable? Again, careful consideration reveals more complex mechanisms. Induction of both hypoxia and anemia causes significant increase of erythropoietin. However, when one tries to calculate the reduction in O_2 delivery (with provision for confounding

factors such as hyperventilation and left shift in P50 in acute hypoxia, and compensatory increase in cardiac output in anemia) in the conditions of hypoxia vs. anemia (or carbon monoxide), anemia and carbon monoxide always seem to provoke a much higher erythropoietin response. Why is that?





Despite a less severe drop in proximal tubule pO_2, anemia seems to have a stronger impact on erythropoietin secretion. A possible answer lies in the fact that anemia drops the proximal tubule pO_2 with minimal effect of the capillary pO_2 whereas both proximal tubule and capillary pO_2 are reduced in hypoxia. If a error sensing system can register both pO_2's, this kind of physiologic response becomes possible. The type I fibroblast is poised in juxtaposition to the proximal tubule and the capillary- a perfect candidate for the proposed sensor.



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EXTRA-ERYTHROPOIETIC EFFECTS OF ERYTHROPOIETIN

There are very few if any hormone that has single function. Likewise, very few physilogy effects are reliant on single hormones. Erythropoiesis is dependent on multiple cytokines and erythropoietin most likely has multiple effects other than stimulating erythropoiesis. Erythropoietin receptors are distributed widely in mammals. The extra-erythropoietic actions of erythropoietin is beginning to surface. A complete review of this topic is beyond this discussion. The most promising action will be as protective agents against ischemia-reperfusion injury.

Putative Functions of Erythropoietin

CNS	Development
	Neuroprotection during ischemia
Endothelium	Growth and development
	Vasoconstriction
Heart	Development
Kidney	Tubular protection during ischemia
Uterus	Vascular regeneration

Selected Literature

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SUMMARY

1. Erythropoietin as a replacement hormone has literally rendered anemia of end stage renal failure a transient disease in renal patients.
2. The highly unusual patient presented in this Grand Round with extramedullary hematopoiesis in the kidney represents a curious speculative example of activation of distant evolutionary roots of renal hematopoiesis.
3. The kidney was an erythroipoietic organ in lower vertebrates such as marine and fresh water fish and amphibian larvae. In higher vertebrates, erythropoisis migrated to the spleen and eventually the bone marrow. While erythropoiesis has relocated, erythropoietin production has remained basically unchanged throughout vertebrate history.
4. The migration of erythropoiesis to the bone marrow may be due to the space constraints in the kidney in the face of increasing demands for erythrocyte production and metabolic and excretory functions.
5. In mammals, erythropoietin is produced at least in the type 1 interstitial cell in the kidney intercalated between the proximal tubule and the peritubular capillary. The location is critical because, the unique renal countercurrent circulation provides generous physiologic AV shunting placing the relationship between O_2 content and O_2 tension is in the linear range of the O_2-Hb dissociation curve.
6. The renal site is critical also for the facts that renal blood flow is less influenced by systemic blood flow and renal O_2 consumption is dictated by supply hence establishing a relatively constant coupling between supply and demand. An imbalance of O_2 supply and demand leads to alterations in pO_2 in the proximal tubule.
7. A hypothetical sensing mechanism is proposed where both proximal tubule and capillary pO_2 are sensed as error signals and are integrated to trigger the rectifying response of erythropoietin production.

8. Erythropoietin has actions other than erythropoiesis. Therapeutic possibilities exist as an interventional agent against ischemic-reperfusion injury.

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