Vit C Therapy in Hemodialysis: Determining the Balance of Risk and Benefit

Garry Handelman, PhD
Clinical Laboratory and Nutrition Sciences
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WHAT IS HEMODIALYSIS?

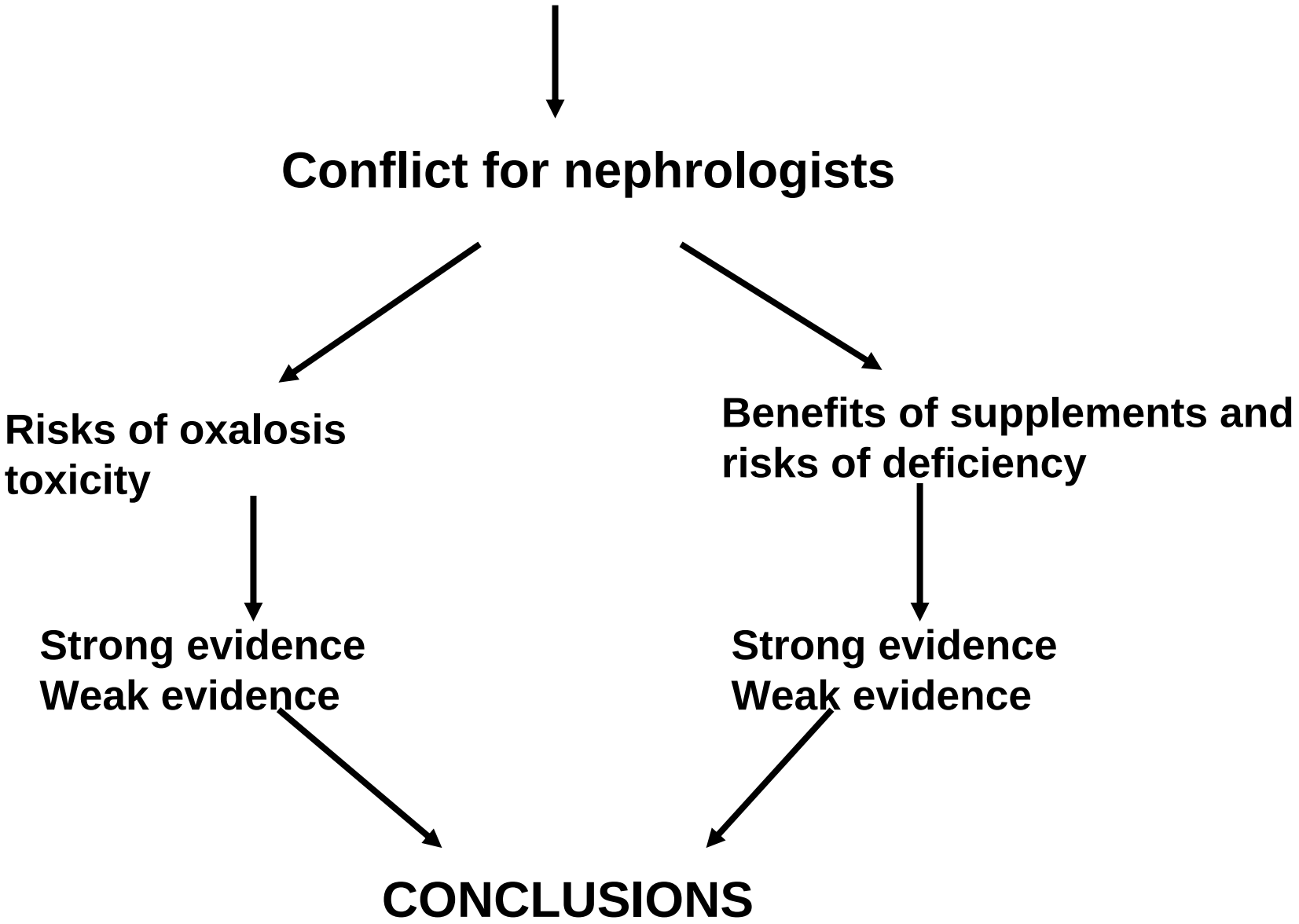
It's use of an "artificial kidney". The patients's bloodstream is circulated though this machine, using a dialyzer cartridge. The artificial kidney removes water, uream sodium, potassium and other materials that are removed by the healthy kidney.

WHAT ARE THE LIMITATIONS OF HEMODIALYSIS?

The machine does NOT perform all tasks thar are done by the healthy kidney. It does NOT make erythropoeitin (EPO), which is made by the healthy kidney. EPO is needed to stimulate new red blood cell production in the bone marrow.

Patients are often given VERY LARGE doses of EPO, that costs thousands of dollars/year. It would be useful to develop ways to minimize EPO use. Vitamin C can accomplish that.

VITAMIN C IN DIALYSIS PATIENTS



FROM THE ODYSSEY, BY HOMER

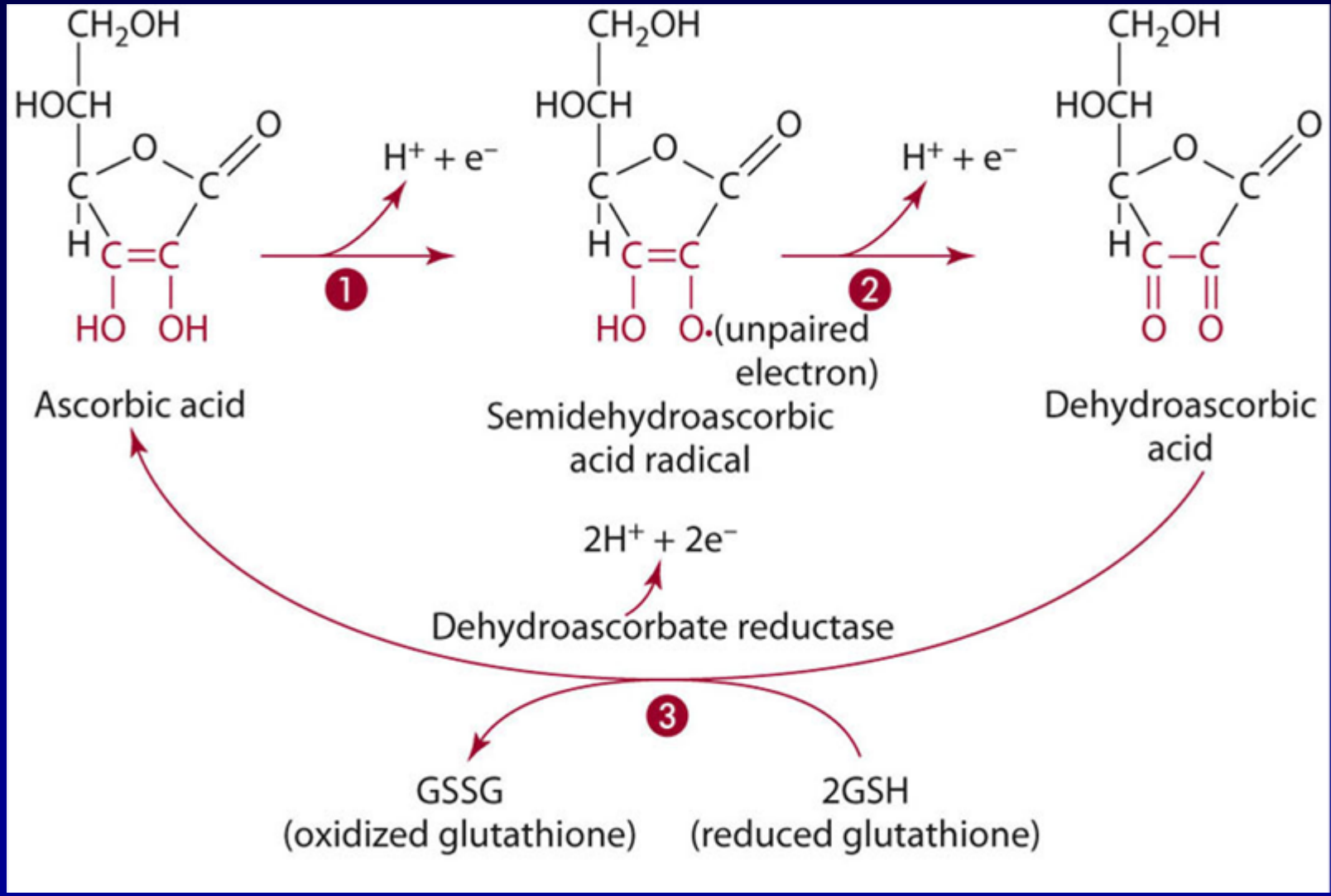
“Then we entered the Straits in great fear of mind, for on the one hand was Scylla, and on the other dread Charybdis kept sucking up the salt water…

We could see the bottom of the whirlpool all black with sand and mud, and the men were at their wit's ends for fear…While we were taken up with this, and were expecting each moment to be our last, Scylla pounced down suddenly upon us and snatched up my six best men.”

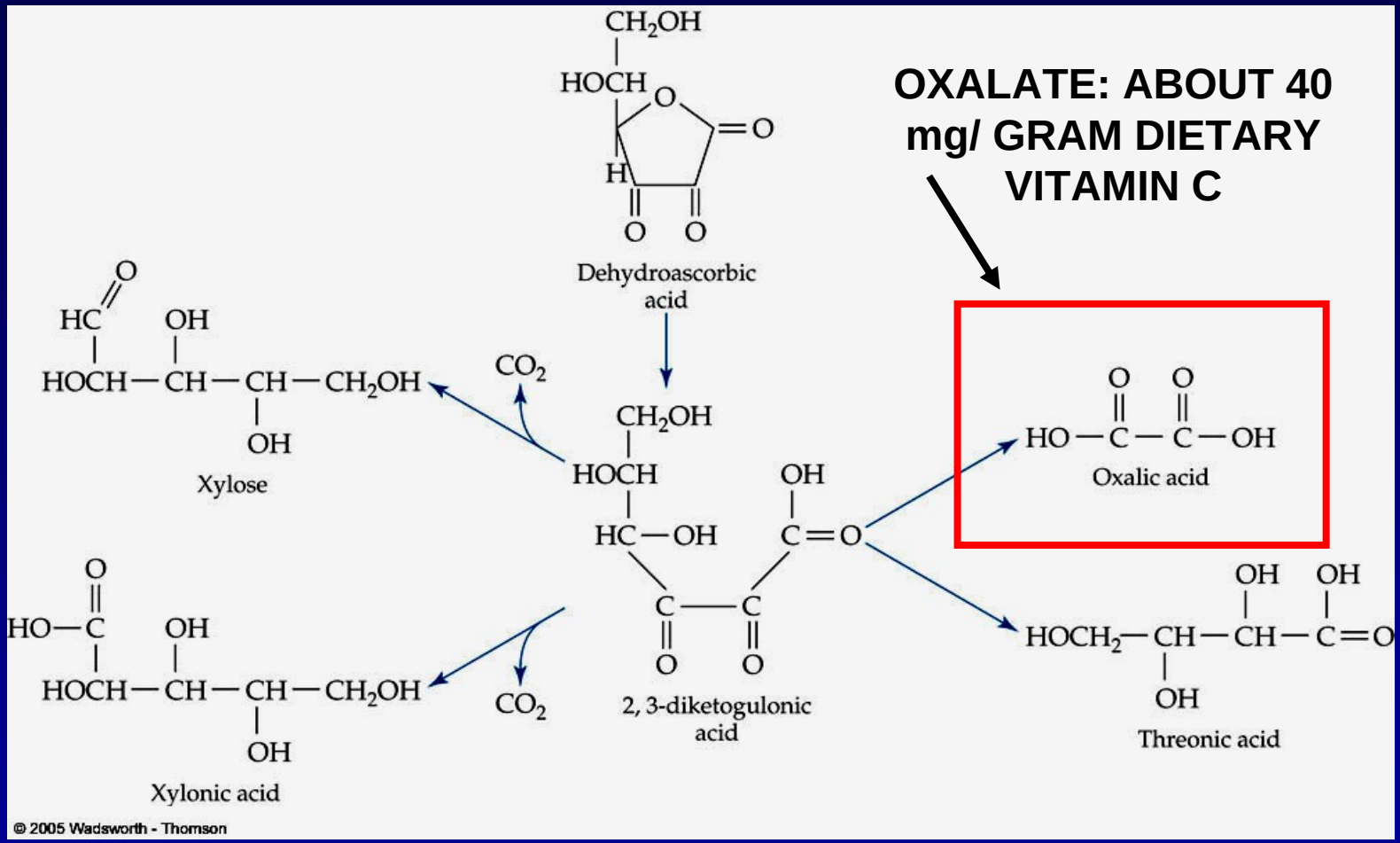
SCYLLA!

CHARYBDIS!

Nephrologists see VITAMIN C DEFICIENCY as the lesser peril, so we risk it to avoid the greater danger of OXALOSIS.



Vitamin C (ascorbic acid) is converted to dehydroascorbate when it performs its biochemical functions



The dehydroascorbate forms a set of metabolites, including some oxalate

THERE IS A DISEASE WHERE A LOT OF OXALATE IS PRODUCED, WHICH LEADS TO RETINAL INJURY.

This is a not a problem in dialysis, but doctors are still concerned, because some vitamin C is converted to oxalate.

Flecked retina in primary hyperoxaluria (PH1).

The oxalic acid production rate in PH1 has been estimated at 400-600 mg/day (Marangella, NDT, 1992).

This is NOT SEEN IN DIALYSIS PATIENTS.
But doctors avoid vitamin C, because they are concerned this will happen!

RETINAL OXALOSIS IN A 2-YEAR OLD CHILD WITH PRIMARY HYPEROXALURIA

There is evidence that vitamin C treatment for dialysis patients produces SOME oxalate: but when should we be really concerned about this?

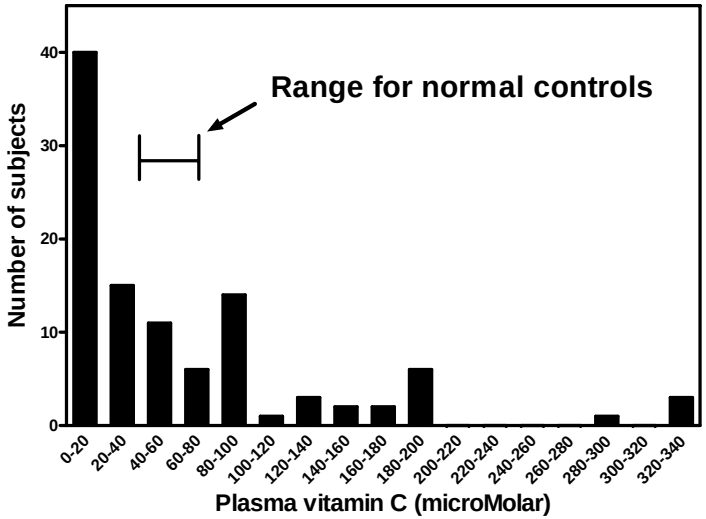
And what are the benefits that could result, vitamin C therapy?

EFFECTS OF VITAMIN C ON ANEMIA IN RENAL DISEASE

- Vitamin C supplements can efficiently increase Hb in patients with Hb<10 g/dL
- Many ESRD patients have a large accumulation of storage iron, which can be mobilized with vitamin C
- Decreased RBC lifespan in ESRD, with elevated RBC production rate, creates the need for high rates of iron mobilization, for which vitamin C can be effective

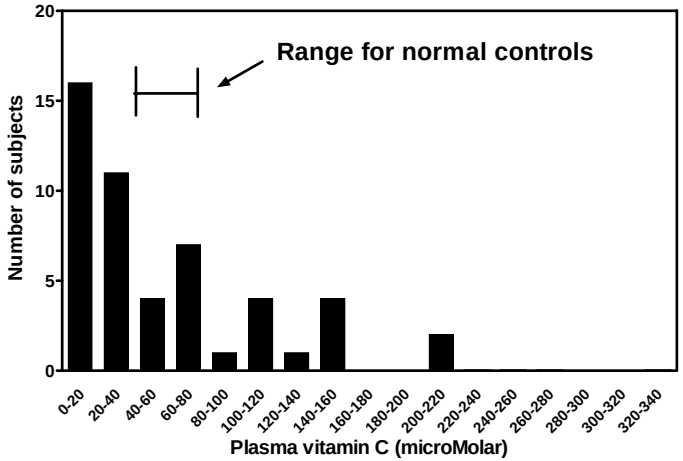
Dialysis patients show a remarkably broad range of plasma vit C, from 1-400 μM (30-80 μM is normal).

Handelman, Levin, and coworkers, NDT, 2008
Hemodialysis patients (n=119): Vitamin C measured using sensitive HPLC analysis



Hemodialysis patients (n=119)

Lim et al, 2001
Peritoneal dialysis patients (n=54)



Peritoneal dialysis patients (n=54)

SIMILAR RESULTS HAVE BEEN SEEN BY OTHER INVESTIGATORS

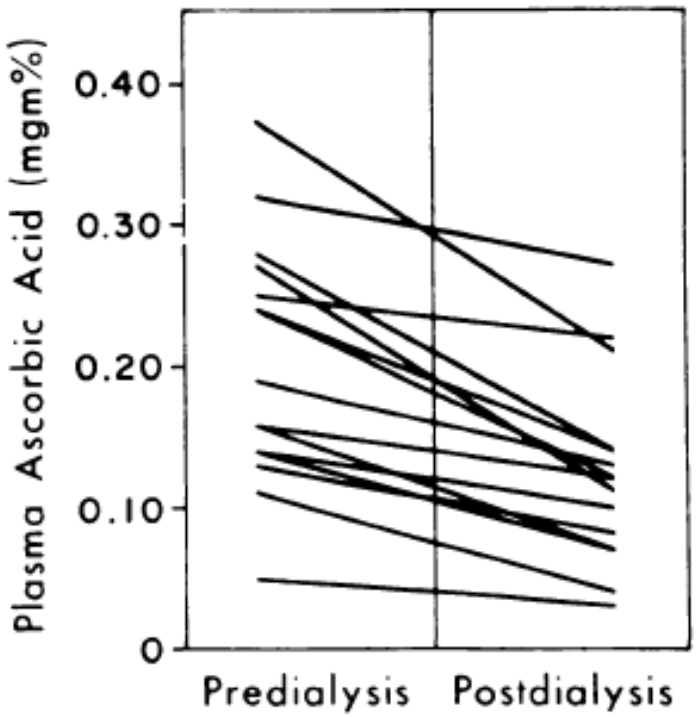
Plasma vitamin C is often low pre-dialysis, and decreases further after each dialysis.

Has been noted in some patients since the beginning of dialysis therapy, for example, Sullivan and Eisenstein (AJCN), 1970

Ultra-Flow twin-coil dialyzer 6-8 hours/treatment, 2x/week

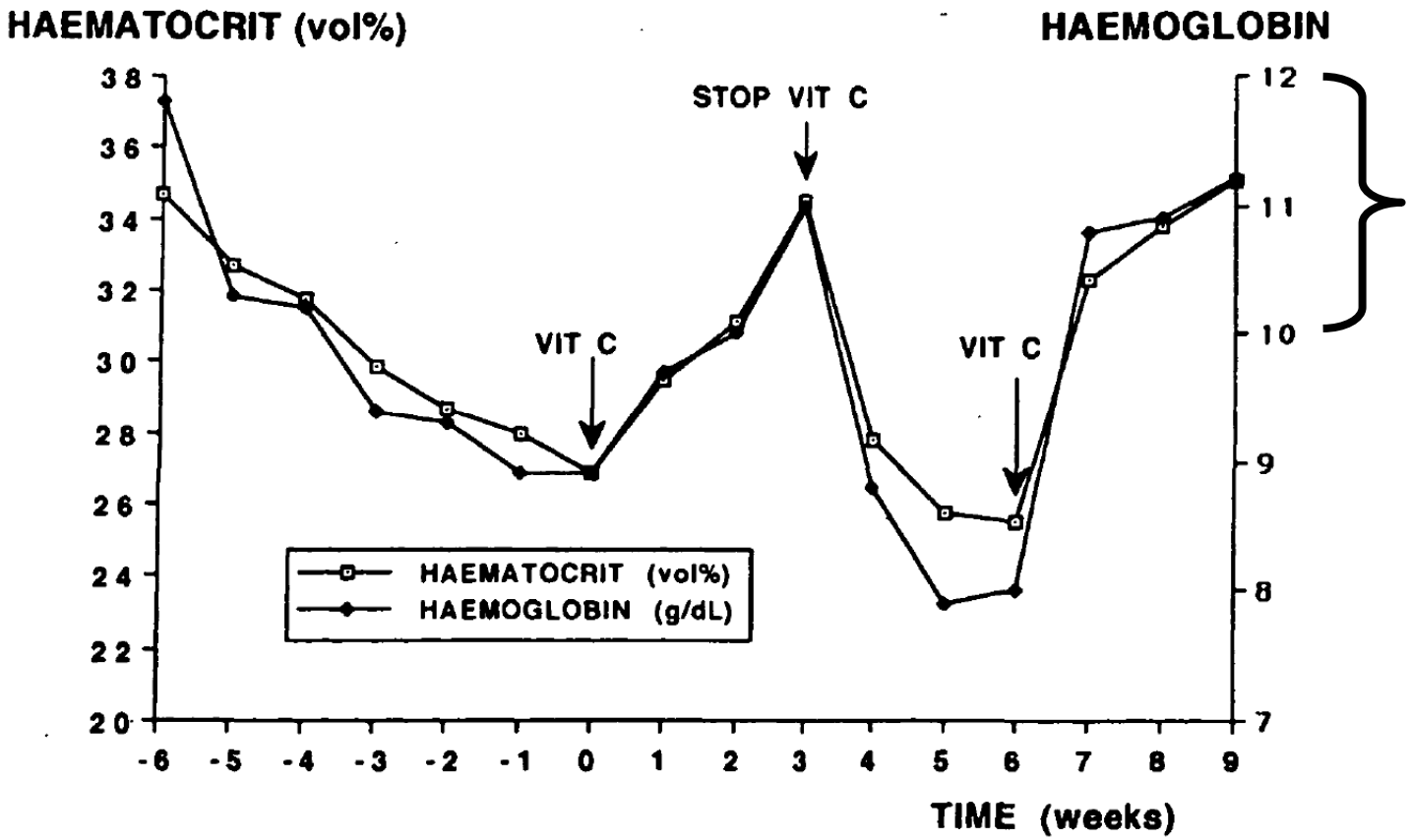
Plasma vitamin C (pre-dialysis) ranged from 2-20 µM, compared with normal, 30-80 µM.

2-20 µM



These same investigators also reported that an oral supplement of 1 gram/day of vitamin C led to plasma levels as high as 750 µM.

Vitamin C status may influence the anemia seen in hemodialysis patients



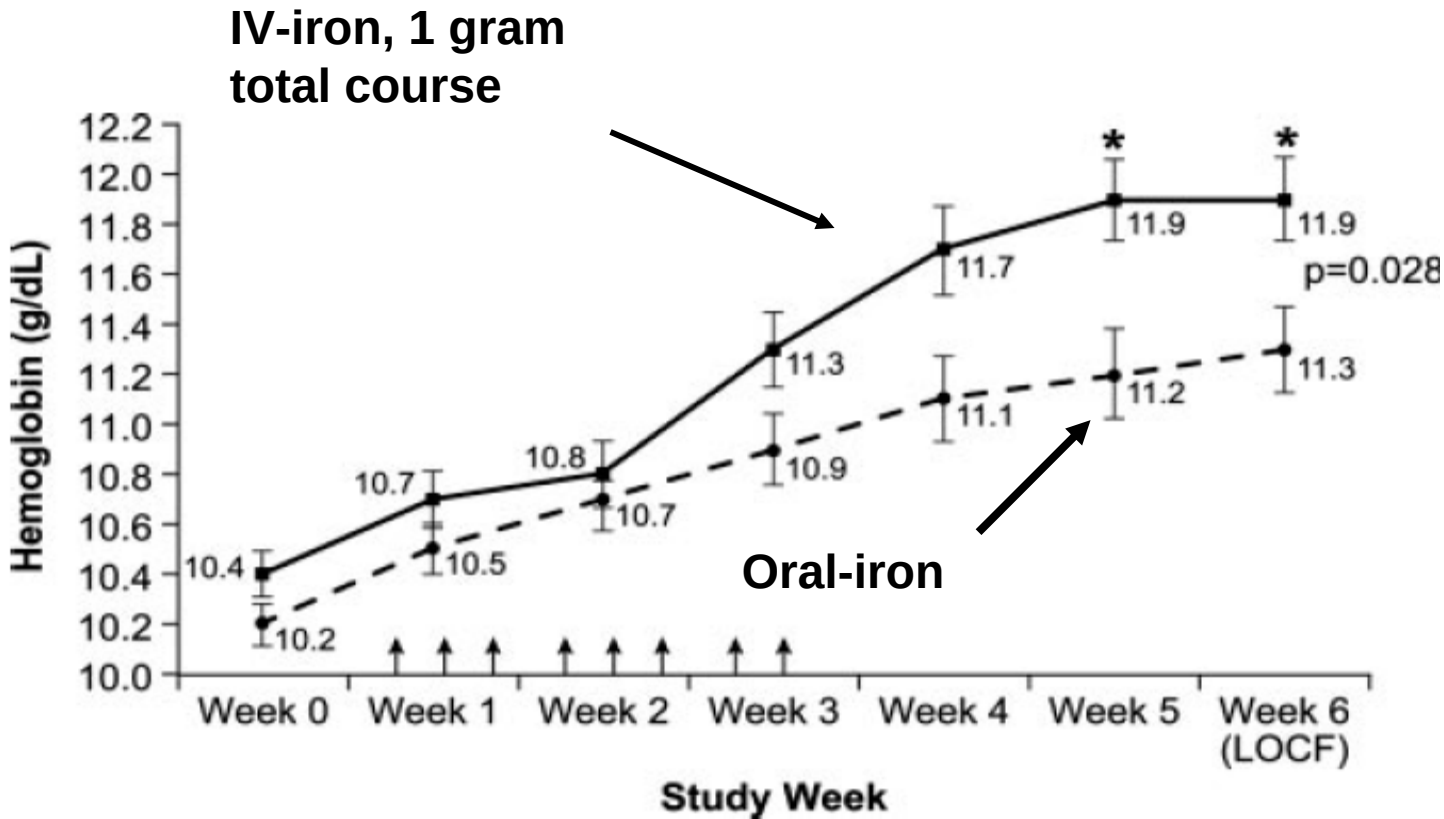
Clinical target, current anemia management

The graph shows the effect of IV vitamin C administration in 1 patient with anemia and iron overload from repeat transfusions. Clinical trial by Gastadello et al (1996).

Inspired by work of Bothwell and coworkers, who earlier showed that vitamin C could mobilize iron from nutritional tissue iron overload.

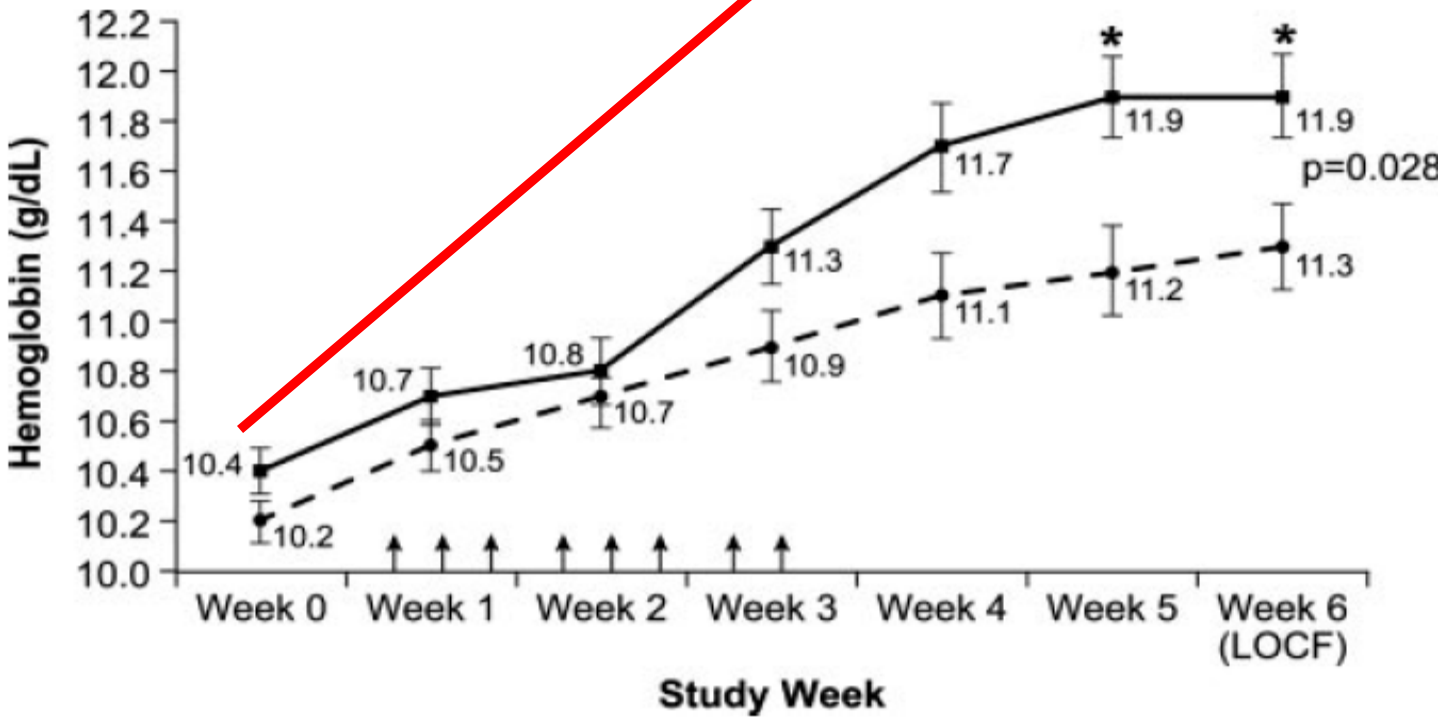
Utilization of IV-iron administered to HD patients. Representative study, showing response to 1 gram of IV-iron, with Hb increase of 1.5 g/dL (upper trace).

Coyne, et al, 2007



MAXIMUM THEORETICAL Hb INCREASE, FOLLOWING ADMINISTRATION OF 1 gram IV-iron: 5 g/dL.

X



KEY FINDINGS: IRON UTILIZATION

- The same factors that limit utilization of iron from transfusions also limit the efficiency of intravenous iron. Extensive iron accumulation is common in renal patients, after long-term treatment with IV-iron.

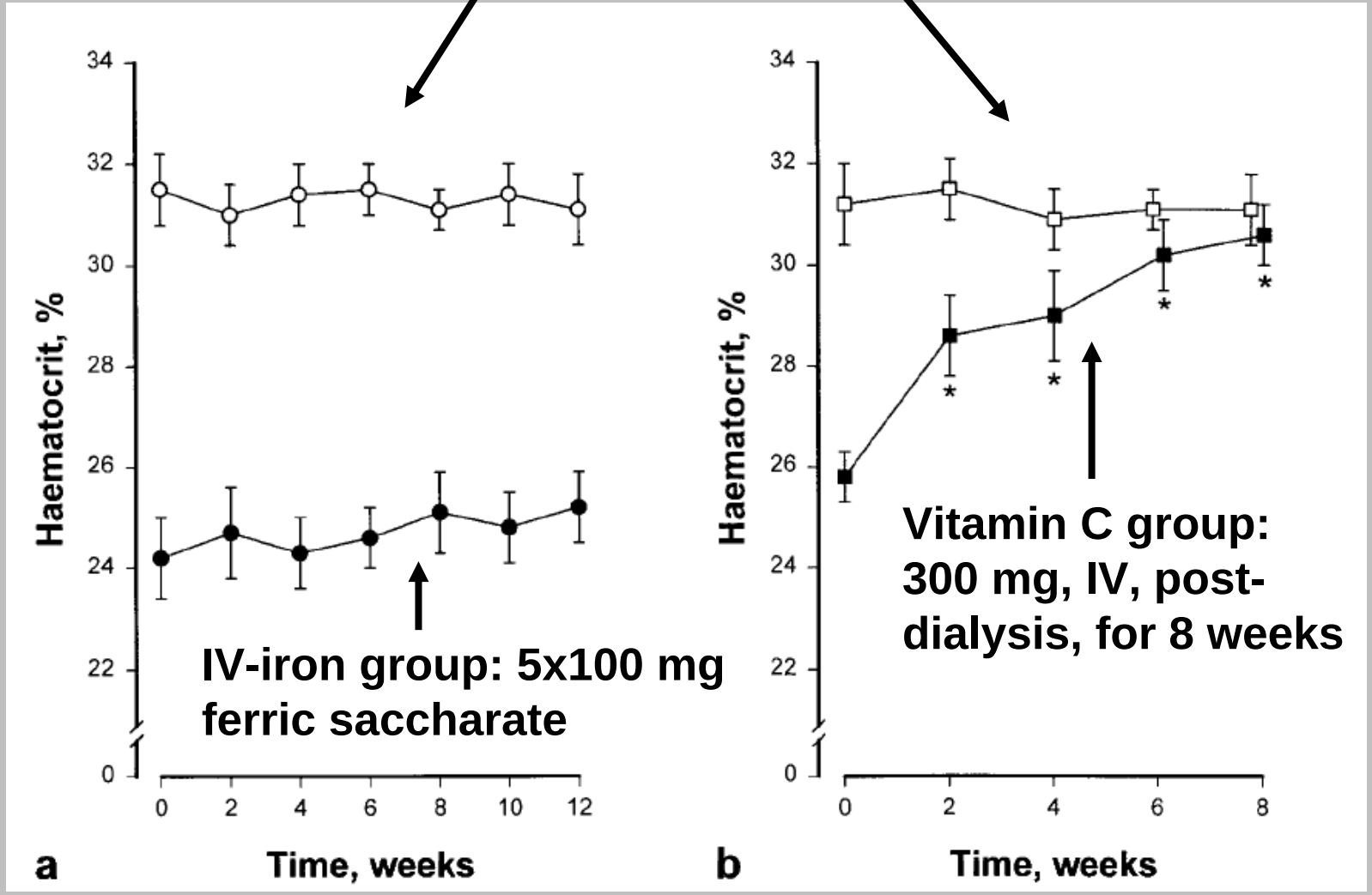
- Intravenous iron, as reported in many studies, only gets partially utilized: 10-25% is usually found in newly-synthesized Hb

- Most HD patients, and some CKD patients, may have extra iron stores that could be effectively mobilized for erythropoeisis and other iron-dependent functions.

VITAMIN C INCREASED Hb, IN EPO-RESISTANT ANEMIC HD PATIENTS

Tarng et al, NDT, 1998

CONTROLS: Patients with normal response to EPO

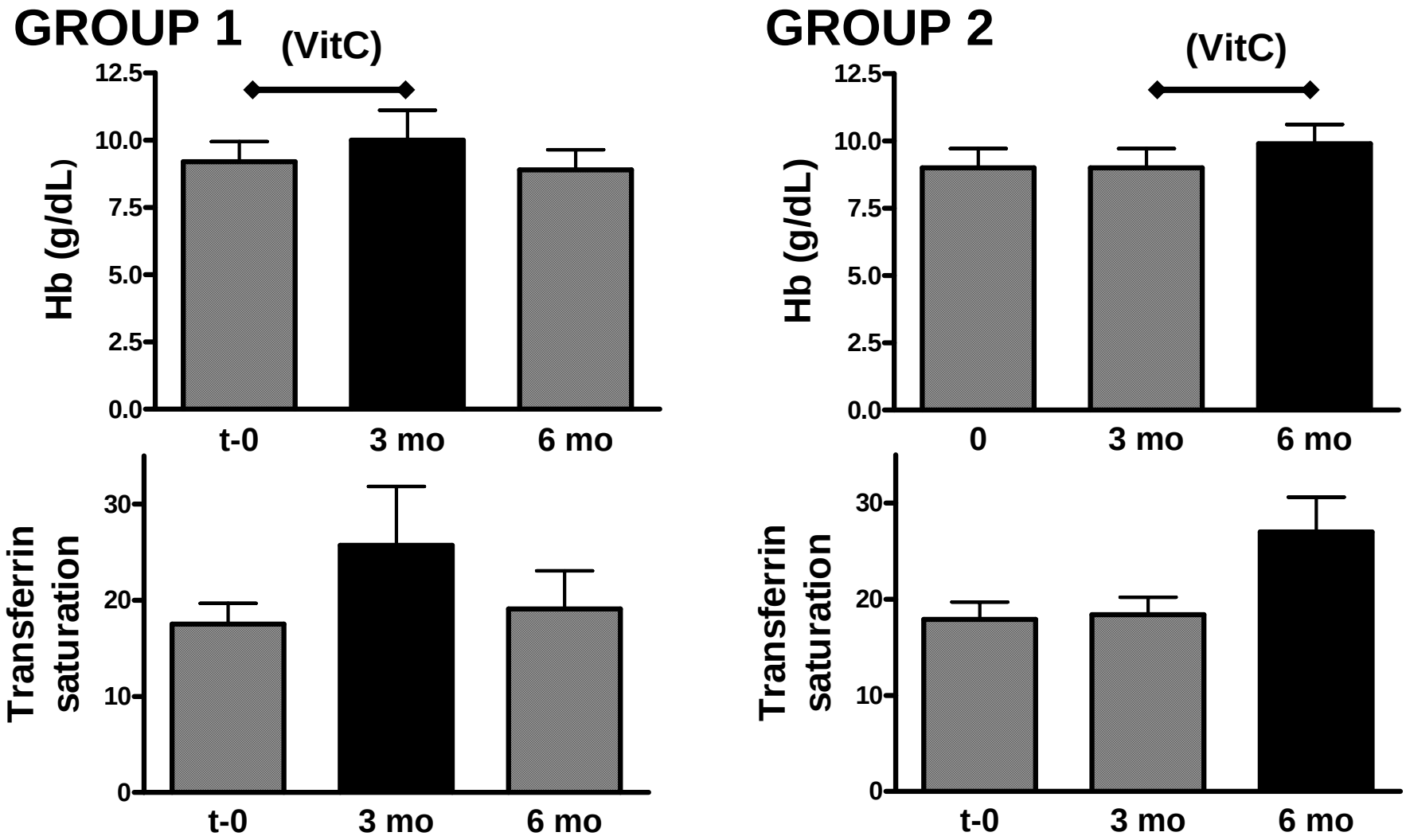


Vitamin C must be maintained or benefits lapse.

Petrarulo et al, NDT, 2000: randomized cross-over design.

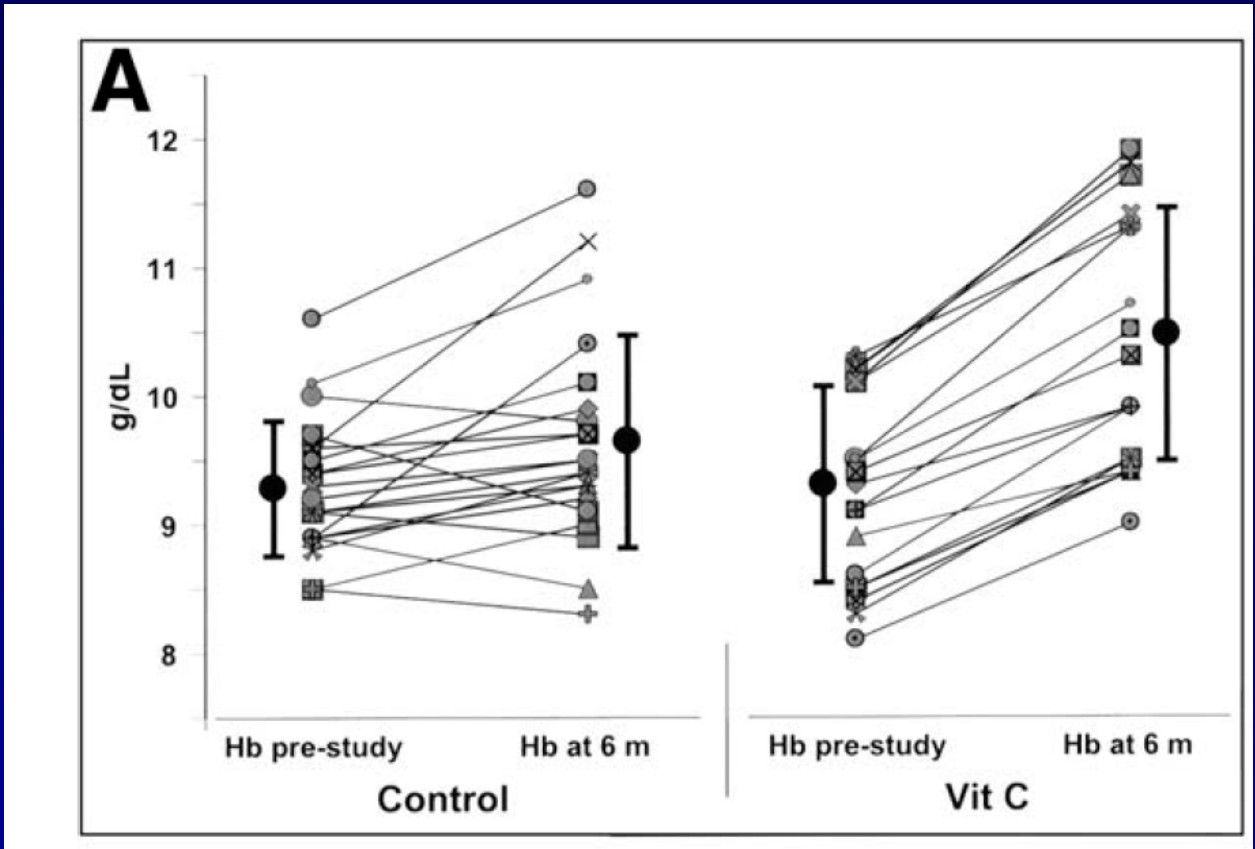
Hb and Tsat increased when vitamin C was provided.

In group 1, these indices DECLINED when vitamin C was stopped



VITAMIN C, 300 mg IV at each dialysis treatment, given for 6 months to patients with low Hb: increased Hb was seen in most subjects

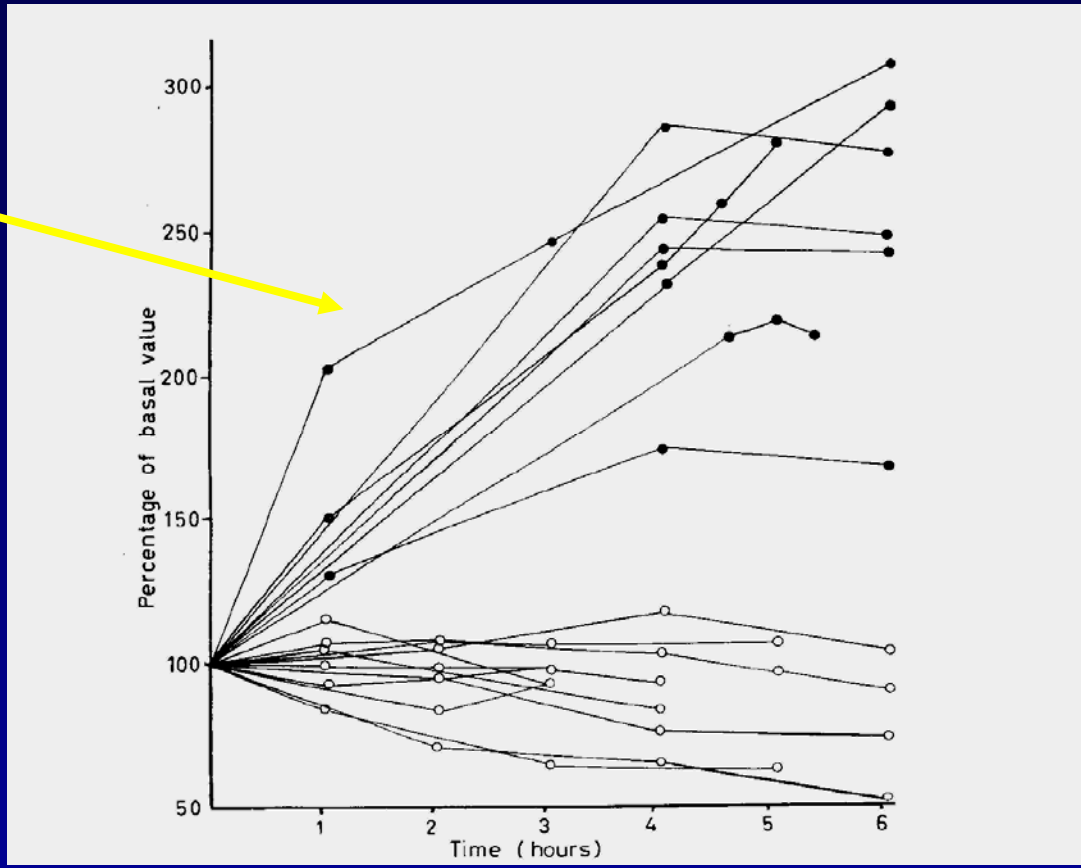
Atallah et al, AJKD, 2006



Hypothesis: If Hb continued to increase at 1 yr or longer, EPO dose, and IV-iron dose, could be adjusted substantially downward.

Vitamin C can aid the mobilization of storage iron.

Plasma iron;
Vitamin C
group



Bothwell et al (Br J Haem, 1964) injected 500 mg of vitamin C into subjects iron overload and resultant scurvy: plasma iron increased in a few hours.

Might this be harmful, from excessive free iron? Tsat should be monitored during vitamin C treatment to mobilize iron.

HOW DOES VITAMIN C WORK?

- Iron is stored in tissues as either FERRITIN or HEMOSIDERIN. Both storage forms are ferric (Fe^{3+}).

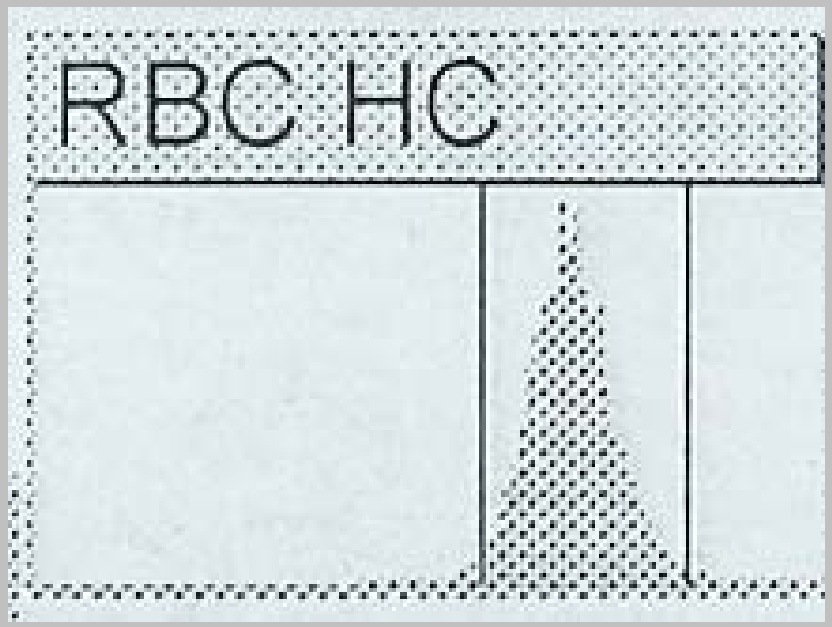
- For iron to be mobilized to the cytosol and released from storage cells, it needs to be converted to ferrous (Fe^{2+}).

- Vitamin C supplements could increase cellular levels of vitamin C, which would promote conversion:

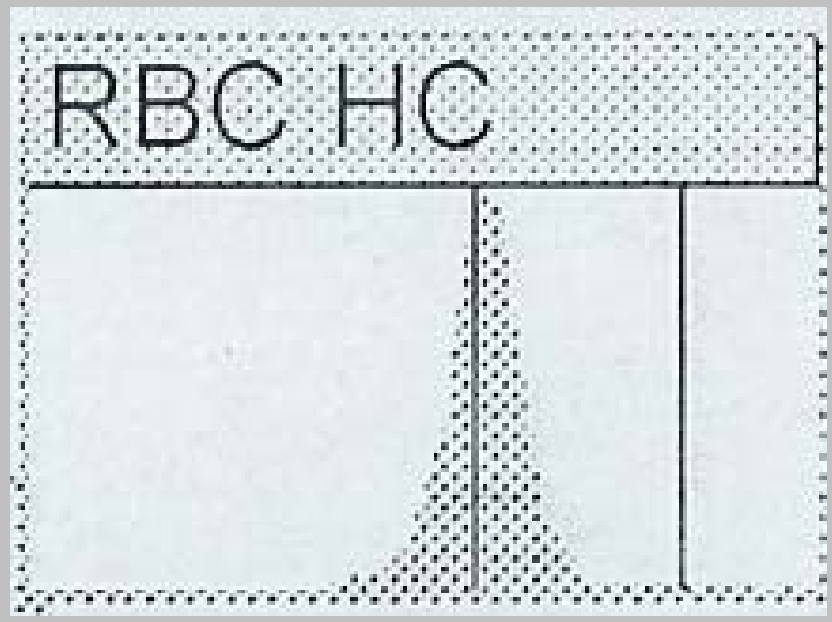
Fe^{3+} and vitamin C $\longrightarrow$ Fe^{2+} and oxidized vitamin C

This mechanism has been documented in vitamin C deficient guinea pigs and during release of iron from IV-iron complexes.

FUNCTIONAL IRON DEFICIENCY: Abundance of hypochromic RBC (right panel) despite treatment with substantial doses of IV-iron



RBC Hb PROFILE IN PATIENT WITH NORMAL Hb CONTENT/CELL

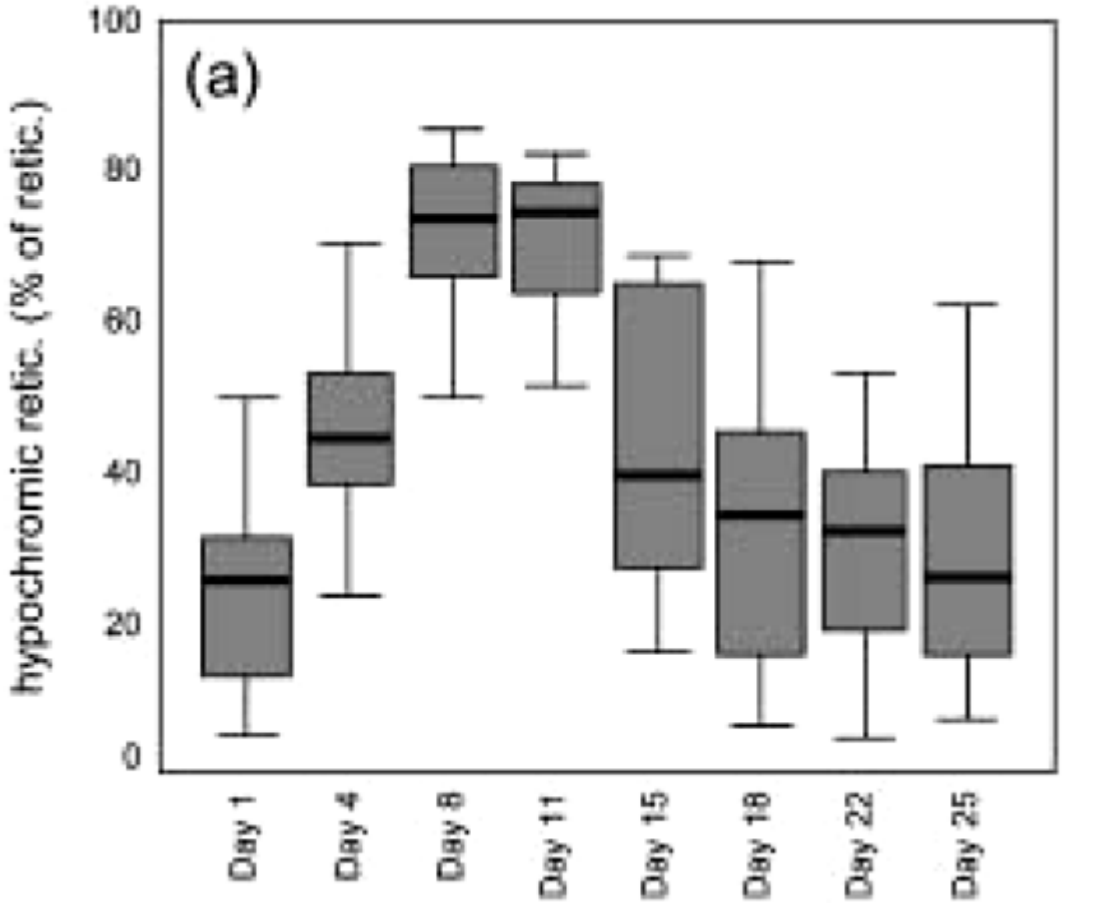


RBC Hb PROFILE IN PATIENT WITH 40% HYPOCHROMIC RBC

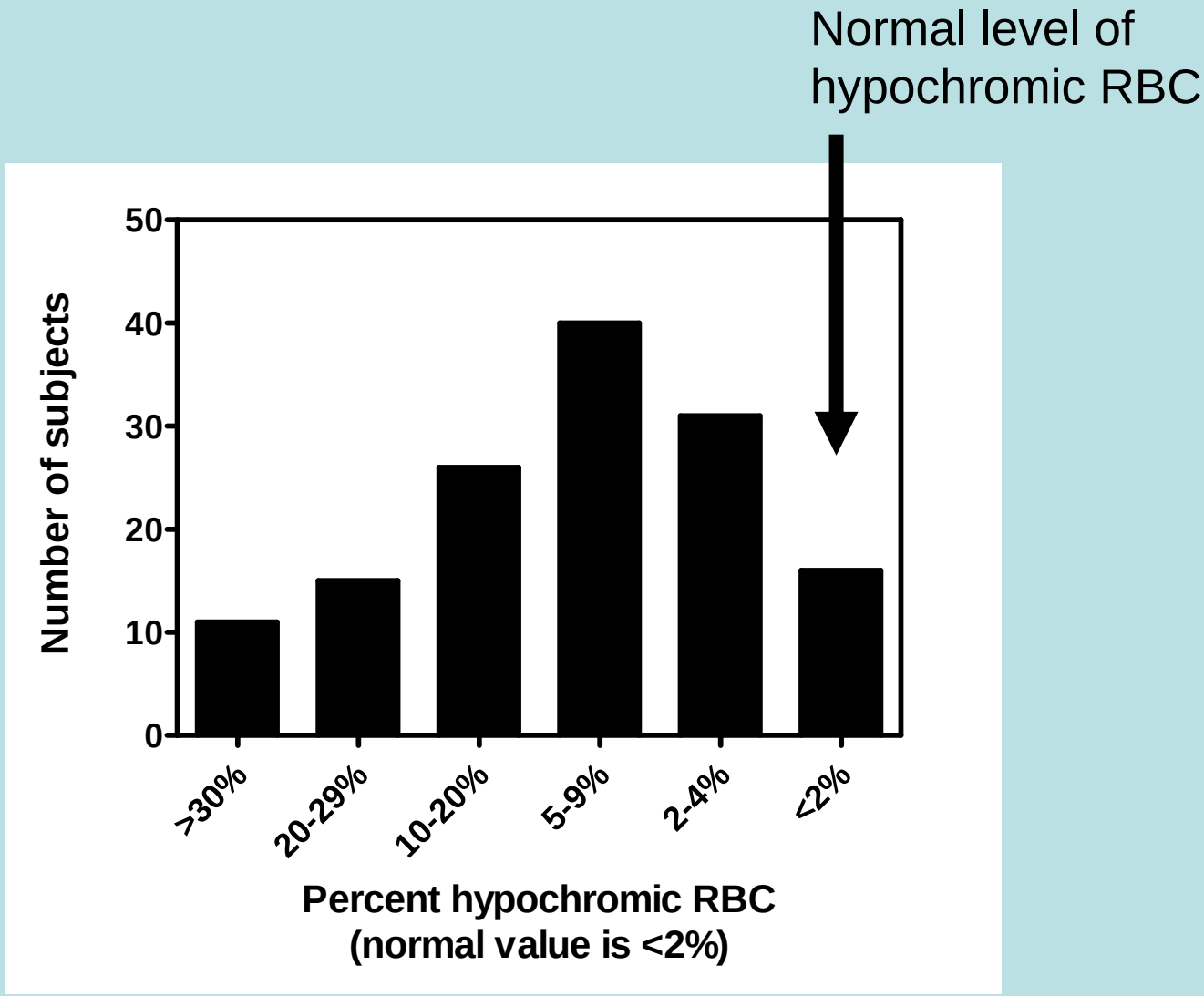
The Bayer Advia hematology analyzer counts large number of RBC and reticulocytes, and shows the Hb content and size of each cell.

ADMINISTRATION OF EPO CAN GREATLY INCREASE HYPOCHROMIC RBC AND RETICULOCYTES, BECAUSE OF LARGE IRON DEMAND

Starklint et al, 2004

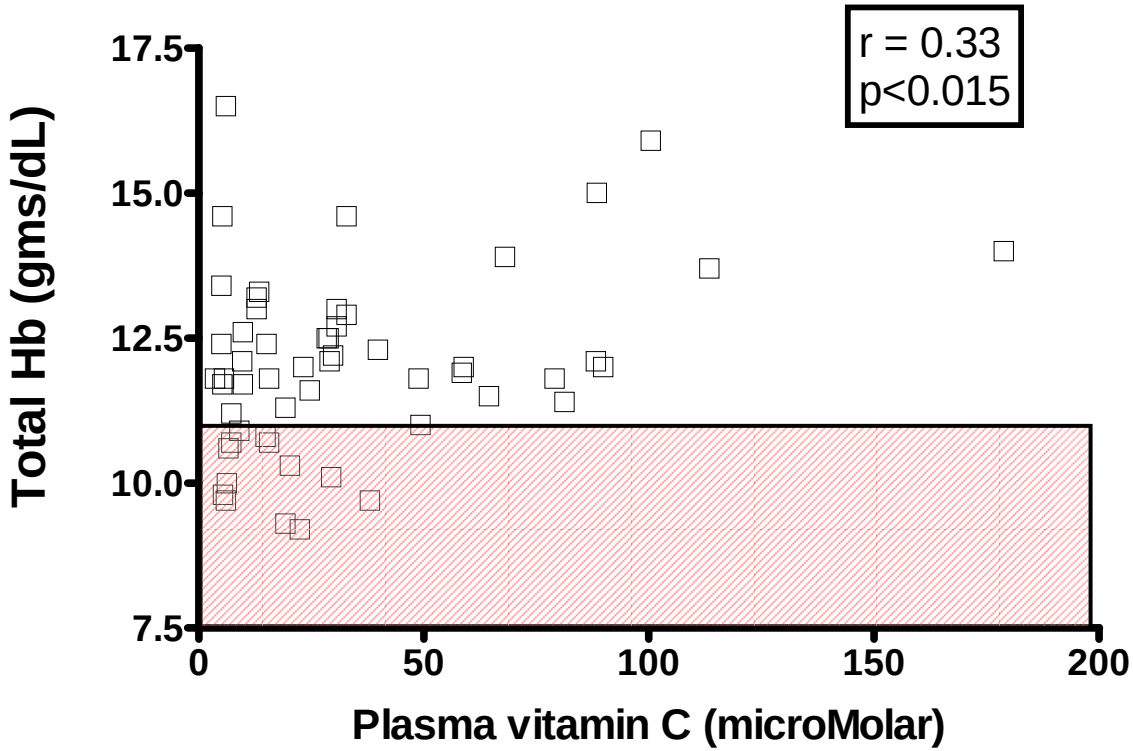


APPEARANCE OF HYPOCHROMIC RETICULOCYTES AFTER EPO TREATMENT (at day 1) IN HEMODIALYSIS PATIENTS



The relative frequency of hypochromic RBC in EPO-treated ESRD patients suggests that iron delivery is not meeting the demands of the bone marrow

(Handelman, Levin and coworkers, RRI, in preparation)



Patients with Hb below target

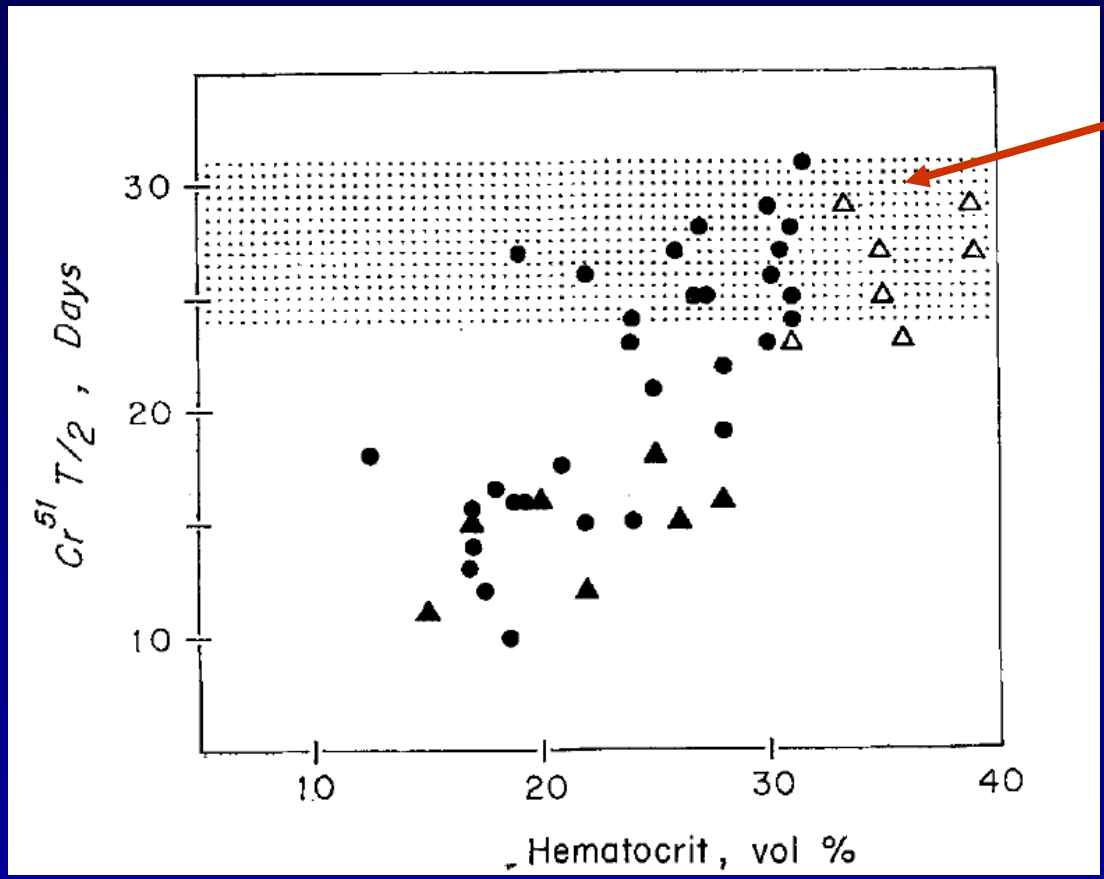
Relationship between plasma Vitamin C and Hb, Peritoneal Dialysis patients, New Haven, CT

Handelman, Finkelstein, Levin and coworkers, in press

RED-CELL SURVIVAL NORMALIZES WITH CORRECTION OF IRON-DEFICIENCY ANEMIA

McDougal, A, et al, J Pediatrics, 1970

Red-cell survival



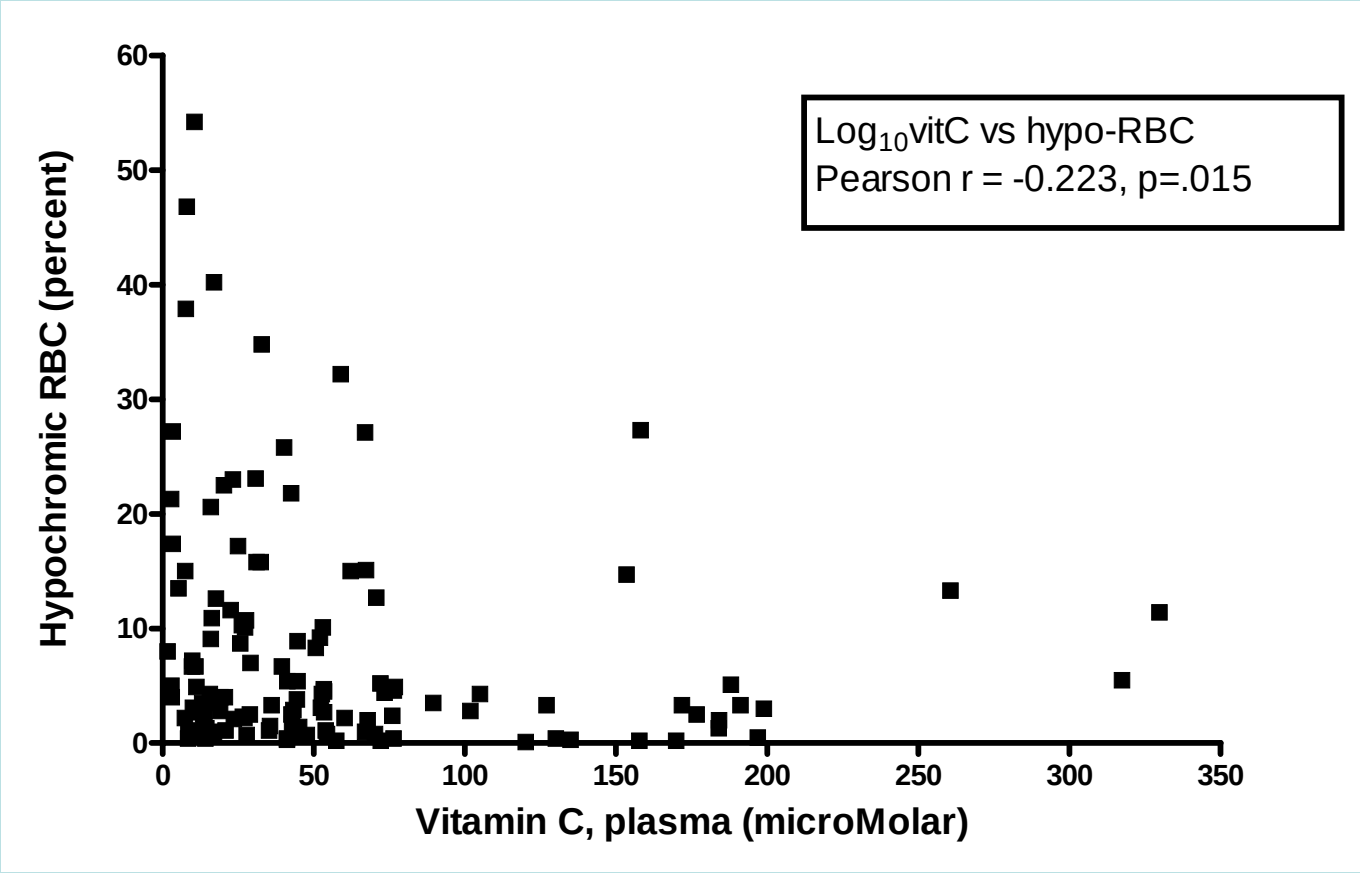
Values after anemia correction

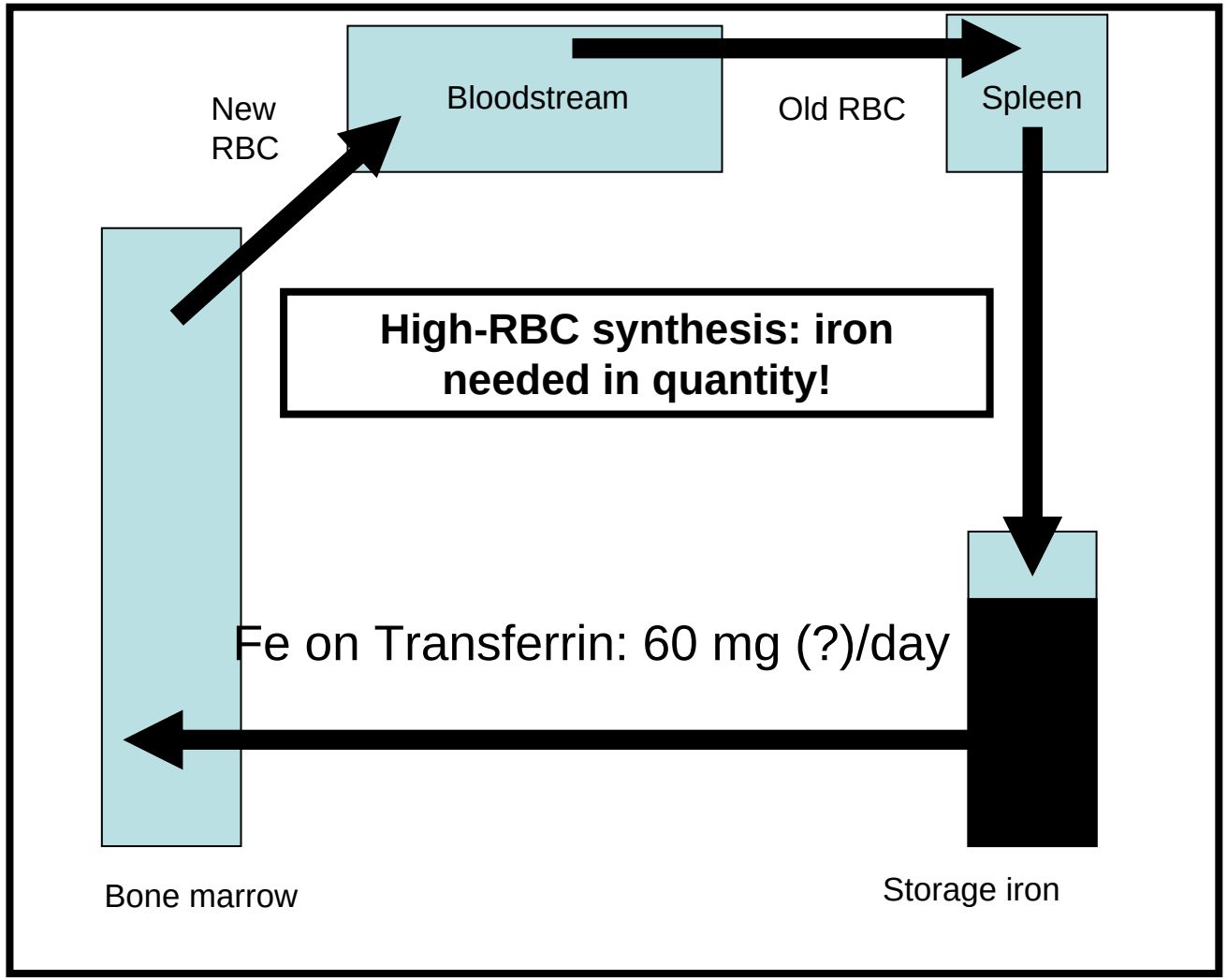
RBC in iron-deficiency anemia are characteristically hypochromic: mean Hb, 23-26 pg/cell, which is linked to short-survival.

Hypochromic RBC in ESRD patients would also show rapid turnover.

VITAMIN C MAY PREVENT HYPOCHROMIC RBC IN ESRD PATIENTS: PATIENTS WITH NORMAL OR ELEVATED PLASMA VITAMIN C SHOW FEWER HYPOCHROMIC RBC

(Handelman, Levin and coworkers, in preparation)

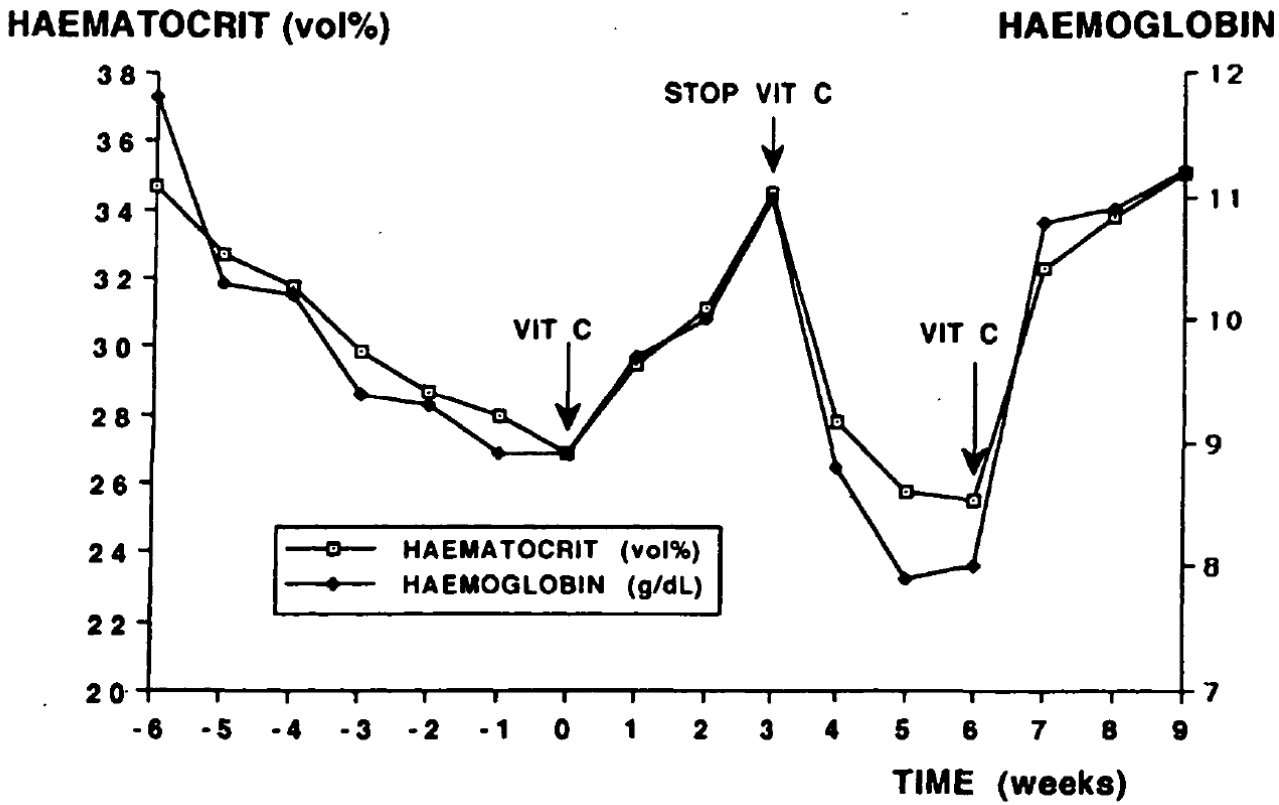




IRON CYCLING BETWEEN COMPARTMENTS: EFFECTS OF SHORTENED RBC LIFETIME. HIGH RATE OF IRON DELIVERY (AS MUCH AS 60 MG/DAY) NEEDED TO BONE MARROW.

IN A NORMAL PERSON, THE “IRON FLOW” IS ~20 MG/DAY.

EFFECTS OF VITAMIN C: ARE THERE OTHER MECHANISMS IN ADDITION TO PROMOTING IRON UTILIZATION?



Very rapid drop in Hb, after withdrawal of Vitamin C, suggests other actions of vitamin C on the red cell population, in addition to promoting Hb synthesis. RBC survival may be directly influenced by vitamin C status (Gastradello et al, NDT, 1996).

This therapy has been BLOCKED because of concerns about oxalic acid. Is that concern warranted?

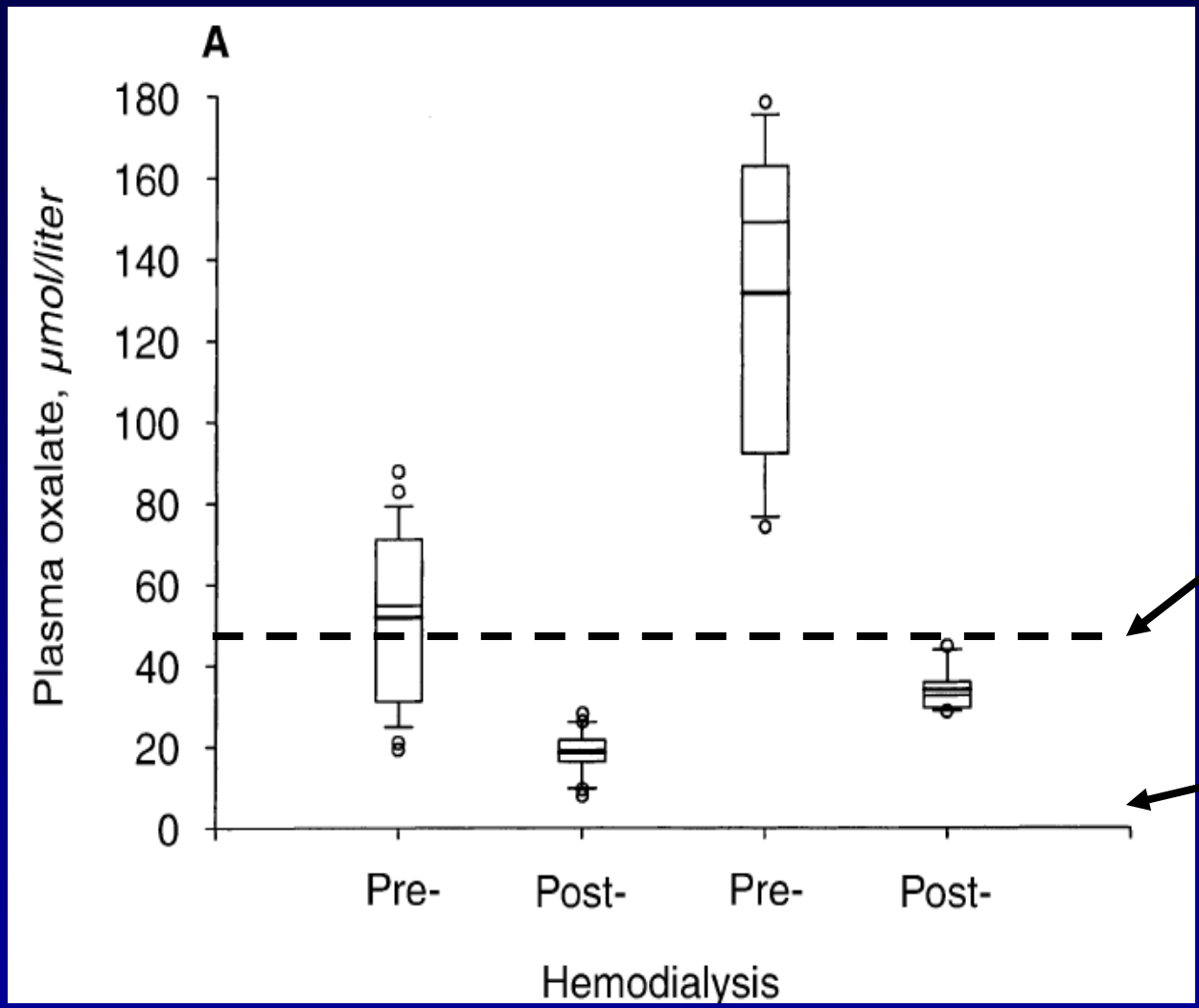
“Because of potential complications of oxalosis, vitamin C supplements should be limited to 60 mg/day for patients on dialysis.”

Brenner and Rector, The Kidney, 2004

It's true that SUSTAINED oxalate above 30 uM in plasma can lead to deposits of oxalate in tissues.

But hemodialysis treatment leads to oxalate <30 uM, after treatment is completed.

HD patients PH-1

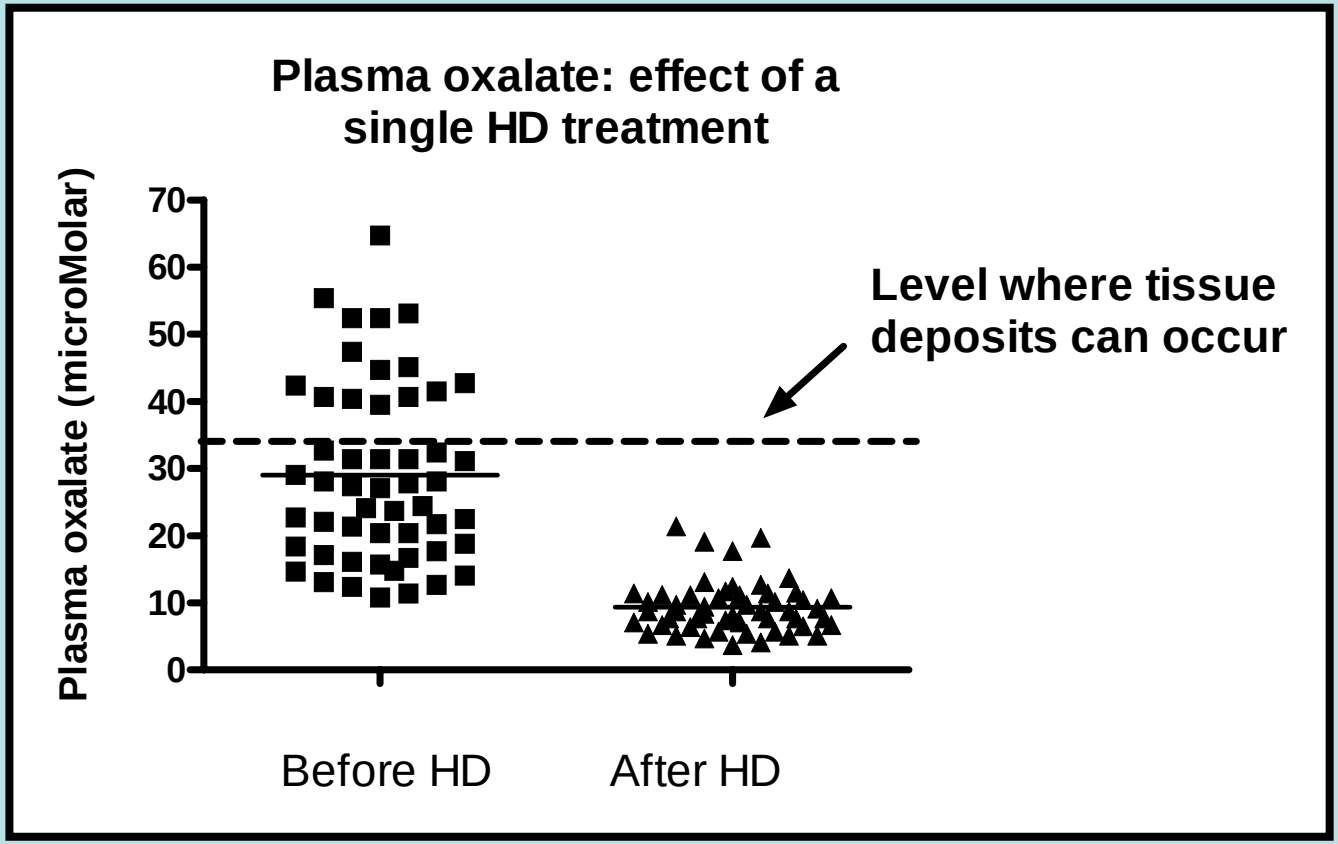


Langman et al, 1999

Supersaturation threshold

Normal level, about 2 μM.

Plasma oxalate in HD patients fluctuates above and below threshold for supersaturation, but dialysis removes a LOT of oxalate/treatment.



In our current study, the plasm oxalate of all 52 patients studied was decreased to <35 uM, after each hemodialysis treatment

- **Hoppe et al report (1996) that hemodialysis readily clears 250 mg of oxalate per session, or about 750 mg/week.**

- **Normal human oxalate production is about 50 mg/day, increasing in healthy subjects to 70 mg/day on a daily vitamin C supplement of 500 mg.**

- **THEREFORE: modern hemodialysis should remove the extra oxalate from supplemental vitamin C, with a 500 mg daily supplement.**

IS OXALOSIS OCCURRING IN DIALYSIS PATIENTS IN CURRENT PRACTICE?

Systemic oxalosis (retinal, cardiac and other complications) was reported in renal disease patients in the period 1970-1985.

It may have been aggravated by high-dose vitamin C (several grams/day).

IN OUR SAMPLE OF 119 ESRD PATIENTS IN NY, WE FOUND 10 PATIENTS TAKING 500-1000 MG OF VITAMIN C/DAY, BECAUSE OF HEALTH BENEFITS THEY WERE SEEKING.

This practice may be rather common, but no cases of RETINAL OXALOSIS have been reported in the last several years in adult HD patients. Current dialysis therapy is likey to prevent this problem.

There have been 16 studies of vitamin C supplements to improve Hb since 1995.

In 13 studies, Hb increased, and in 5 studies EPO dose also decreased.

CONCLUSIONS:

- **Vitamin C is often at very low levels in ESRD**
- **Vitamin C administration can improve anemia management, and has other potential benefits**
- **Modern dialysis therapy should remove any extra oxalate: WE ARE INVESTIGATING THIS QUESTION !**