The discovery of erythropoietin and then its provision as a drug were rightly hailed as landmarks in nephrology. However, in efforts to define its use, four large randomized trials over the last 12 years have found few of the hypothesized benefits and some unexpected harm. Physicians are now told to give every patient for whom an erythropoiesis-stimulating agent (ESA) is prescribed a five-page warning that begins with this question and answer “What is the most important information I should know about Epogen? Using Epo-gen can lead to death or other serious side effects.” What went wrong?

The opinion piece in this issue of CJASN by Rajiv Agarwal attempts to provide some clinical common sense in this very muddled area (1). Although we have reservations about some of his notions, we appreciate his approach. However, we are also concerned that the area of anemia treatment continues to absorb such a large amount of the discussion and most importantly the investigation in chronic kidney disease (CKD) and ESRD. Almost all of the effort, and there has been lots, has focused on the finer and finer tuning of therapy with ESAs and to a certain extent intravenous iron. The intense interest in this area rests heavily on the fact that these are expensive drugs, so that relatively small dose adjustments can mean very big differences in expenses and profits. This economic interest has allowed industry and their payers to narrow our research in ESRD. There are problems in addition to anemia for these patients even if the solutions do not yield patents and profits.

There are other important, unsolved, and largely unaddressed problems even within uremic anemia. For example, red blood cell (RBC) lifespan is reduced by approximately 50% in uremia. This phenomenon was recognized more than 50 years ago and confirmed in 2004 during the ESA era. Indeed, the most recent study noted that “… RBC lifespan was not different from that reported half a century ago” (2). This disappointing result was in the face not only of ESA, but also of intensive hemodialysis (daily or nocturnal). As shown in the 1950s, the shortened RBC life is due to some element(s) of the uremic milieu because cells transfused from normal subjects are rapidly destroyed in the uremic subject, and contrariwise cells from people with uremia enjoy normal survival when transfused into normal subjects. Equally disappointing, we have no better idea of why RBCs have briefer lives than we did half a century ago. This seems a tractable problem and one that could yield potentially important results. If we knew the factor(s) responsible, and then learned to remove them or reduce their production, ESA and iron use would decline with savings in money and toxicity. Perhaps yet other benefits would accrue. The lack of industry interest in reducing ESA use seems obvious, but their lack of interest should not so dominate our research.

Beyond anemia, multiple areas in ESRD of high relevance to patients languish largely unexplored. Blood pressure control in ESRD is a persistent mystery. The value of oral nutritional supplementation has received little attention. Many ideas exist for prevention of infection of chronic catheters, but studies compelling enough to change practice are lacking. The value of aspirin as a preventive agent is unknown in ESRD. Even an area that has received considerable attention—bone and mineral metabolism—has many large clinical gaps. For example, we still do not know whether material differences are obtained between calcium and non-calcium phosphate binders. Understanding acid-base balance is very incomplete, and solid targets for treatment are nonexistent. The lists could be extended. Why are we expending so much effort in ever finer tuning of the hemoglobin target as if it were the Holy Grail of patient survival and well being when we have done so little to determine bicarbonate or blood pressure targets?

Dr. Agarwal’s current article calls for an individualized approach to anemia therapy. Although we agree that guidelines may have been influenced by profit seeking and were insufficiently grounded in data, some targets for hemoglobin level and maximum ESA dose are needed. He espouses the reasonable and current ones. The value of raising hemoglobin above 12 g/dl even in special circumstances is more dubious. Surely one must discount statements by industry spokespeople such as Alonzo Mourning. One desires evidence better than pharmaceutical company advocacy for the value of hemoglobin levels above 12 g/dl in very active patients. Such a study would be exceedingly difficult to perform if only because such subjects are rare. ESAs have dramatically reduced transfusions, but the argument that the lower limit for hemoglobin should be 10 g/dl because that limits doctors from ordering transfusions is not entirely convincing. As Dr. Agarwal notes, the need for transfusions in other settings is uncertain unless the level is below 6.
Such a level was common before ESAs but seems too low. However, 10 g/dl may not be the optimal lower limit.

We began by asking why the attitude toward ESA use has gone from miracle cure to muddle. We can only hazard some opinions. First, the expectations were too great. Uremia is complex. Even what Depner has termed “the residual syndrome” of dialysis-treated uremia is complex, and if we persist in viewing dialysis only as urea removal, progress seems unlikely (3,4). Better and better urea removal has not changed RBC survival and did not improve patient survival in the Hemodialysis Study Group Trial (HEMO). Likewise, simply fixing hemoglobin to a normal level was unlikely to and did not resolve the residual syndrome. Make no mistake—urea-based dialysis prescriptions and ESA therapy have been advances, but incremental ones. However, simply doing more and more of these and expecting different and quantum improvements is irrational. Uremia may be complex, but complex does not mean insoluble.

An additional reason for our current state of unease is that nephrologists understandably assumed that if the natural set point for hemoglobin were 13 to 15 g/dl, shooting for that range would be beneficial. Indeed, observational studies had found better outcomes in ESRD patients with normal or near normal hemoglobin levels. We remain uncertain as to why aiming for normal levels was wrong, but it was: maybe an independent toxicity of ESA or a consequence of raising hemoglobin or a combination. However, more and more efforts to determine exactly why targets above 12 g/dl are risky would seem likely to yield diminishing returns. This may be an unsatisfying position for some.

The high profitability of ESA for pharmaceutical companies and dialysis providers coupled with very incomplete knowledge on best usage almost certainly drove increased prescribing to targets now considered excessive. The higher use of ESA derived in part from profit motives, but one must acknowledge that the risks have unfolded haltingly and remain counterintuitive. Nevertheless, the taint of profits having influenced care, care that now seems to have been occasionally injurious, contributes to the current malaise. It is disquieting that similar situations may still exist with iron therapy, vitamin D analogues and cinacalcet.

The current targets for ESA usage seem reasonable. Accumulated evidence supports them. Small areas of uncertainty will always persist. Consideration of patient needs and discussions with individual patients certainly are preferable to the well meaning but ultimately misguided and terrifying warnings physicians are being asked to provide patients. Now it is past time to move on to other pressing issues in ESRD, even if they are not patentable profit centers.

Disclosures
None.

References