Case Study in Chronic Renal Failure

Development of Knowledge Base: There were over 14,500 articles dealing with chronic renal failure entered into PubMed during 2000 – 2004. A current concept in this array of ideas is renoprotect and there were 204 ideas involving this term in the 2000-2004 knowledge bases. The term first appeared in the 1998 literature. Figure 1 shows these renoprotect ideas classified into five categories. Each term linked with renoprotect is shown together with a number denoting the frequency of occurrence of each idea. Only those ideas occurring 2 or more times are shown.

Figure 1. Ideas Associated with Renoprotection.

The treatment factors linked with renoprotect included losartan, transplant, ACE, angiotensin and irbesartan. The disease factors included hypertension, diabetes, and renal disease. Renal factors included protein, filtration, calcium and uria conditions. A literature review in 2003 suggested that the angiotensin II blocker, Irbesartan, showed blood pressure reduction plus an important reduction in albuminuria suggesting that the angiotensin II blocker offered significant reduction in deterioration of the kidneys. [Lewis 2003]

Renoprotect and Complications? A funded grant application describing kidney failure from the CRISP database [CRISP 2005] suggested that there might be significant complications associated with the administration of the angiotensin II blockade. The
principal adverse effects were hypothesized to be androgen deficiency leading to a drop in serum levels of testosterone together with diminution of erythropoietin production with resulting anemia.

**Exploration of the Creative Act:** This report explores the paths possible in leading to this creative act. The sentences provided by the author of the grant were analyzed and the ideas presented were compared with those in the 2000-2004 knowledge base.

**Figure 2. Ideas Expressed in CRISP Grant – Sentence 1 -- 1R21DK070165.**

Figure 2 shows the terms and ideas from the first sentence in the abstract. The sentence, provided by the author, is shown in the upper right hand corner of the figure. The informative terms are highlighted. The graph shows the ideas used by the author and included in the knowledge base (shown with thin grey lines). The ideas presented by the author and not included in the knowledge base are shown with heavy grey lines. Some of these missing ideas might be considered more important than others. The important ones are shown with a heavy black line. These missing ideas are — *androgen* with *kidney*, *androgen* with *depression*, and *anemia* with *depression*. The other ideas expressed by the author were present in the knowledge base.

Figure 3 shows the terms and ideas from the author’s eighth sentence. This sentence is key to the author’s hypothesis of adverse effects associated with *angiotensin II blockade*. The graph shows the ideas (black connecting lines) that have been previously reported and included in the knowledge base. The grey connecting lines represent those ideas not in the knowledge base. The author linked *testosterone* with *renin, angiotensin, blockade, erythropoietin*, and *anemia*. These ideas were not included in the knowledge base for
Similarly, renin with blockade, erythropoietin, testosterone, deficiency and anemia were not in the knowledge base. These missing ideas illustrate the difference between the author’s emphasis and that provided by the world’s literature. The ideas in the knowledge base connect renin with angiotensin, angiotensin with blockade, erythropoietin, deficiency, and anemia. In contrast, the ideas in the knowledge base connect testosterone with deficiency and anemia. If the intent of new research is to identify and fill missing ideas, Figure 3 illustrates the contribution made by this author.

Figure 3. Ideas Expressed in CRISP Grant – Sentence 8 -- 1R21DK070165.

Figure 4 summarizes the important terms from the author’s grant application together with the lines linking these terms. The thin black lines denote the ideas present in the knowledge base and the thicker grey lines denote those suggested by the author not in the idea resource. As seen, this author’s contribution (i.e., grey line connectors) to the body of knowledge is associated with providing missing information. Those were testosterone with erythropoietin, angiotensin and anemia. The heavier black lines show ideas that would continue to be missing after completion of the author’s research. Renin with, respectively, testosterone, androgen, and anemia would be missing. In addition, a direct connection between angiotensin and androgen would be missing.
**The Role of Androgens:** Recklehoff and Grainger [Recklehoff 1999] hypothesized that androgens increased arterial pressure by causing a hypertensive shift in the pressure-natriuresis relationship, either by having a direct effect by increasing proximal tubular reabsorption or by activation of the renin-angiotensin system. They also hypothesized that the enhanced proximal tubular reabsorption led to a tubuloglomerular feedback-mediated afferent vasodilation, which, in combination with the increase in arterial pressure, resulted in glomerular hypertension and renal injury. Gandolfo et al [Gandolfo 2004] suggested that androgens contributed to continuous loss of kidney cells though the stimulation of apoptotic pathways. They reported that *in vitro* studies indicated that androgens primed a Fas/FasL dependent apoptotic pathway in kidney tubule cells. They suggested that androgens had a role in promoting chronic renal injury in men.

**The Role of Testosterone:** Silberger [Silberger 2003] considered the hypothesis that testosterone explained a worse course of chronic renal disease in men than experienced by women. They indicated that the gender difference in renal disease existed in animals as well as humans. Lavoie et al [Lavoie 2004] evaluated the physiologic significance of a tissue renin-angiotensin system in the kidney tubule. These investigators produced mice that expressed human renin and human angiotensinogen. They reported that female mice with these transgenes showed an increase in mean arterial pressure when testosterone was administered. DeLong et al [DeLong 2005] reported that the renin-angiotensin system blockade was associated with lower levels of serum testosterone in men treated with hemodialysis. These investigators also reported that serum testosterone was negatively correlated with erythropoietin dose.
**Angiotensin-Renin Blockade:** Gronroos et al [Gronroos 1997] explored the effects of ramipril, an angiotensin-converting enzyme (ACE) inhibitor, on a series of hormones. They indicated that ramipril decreased free thyroxine. The other endocrinologic tests, including serum testosterone, were not affected by this ACE inhibitor. Chiurchiu et al [Chiurchiu 2005] reported that clinical studies showed a significant correlation between urinary protein excretion and rate of GFR decline in chronic renal disease. They indicated that randomized trials, in particular, the Ramipril Efficacy In Nephropathy (REIN) study, showed that treatments designed to reduce proteinuria were renoprotective and limited progression to ESRD. Meta-analyses of randomized clinical trials confirmed the predictive value of proteinuria and the renoprotective effect of proteinuria reduction by ACE inhibition therapy.

**Creativity in Identifying Missing Ideas:** As seen in Figure 3, the creative act suggested by the author of the grant involved supplying missing ideas. The author’s hypothesis, when viewed in terms of ideas, could be considered as a simple completion process. Missing ideas were identified and the proposal offered to provide the information. This example may represent a distinction between unimportant and not studied. The many clinical trials and meta-analyses dealing with the study of angiotensin-renin blockade did not emphasize the angiotensin-testosterone-anemia effects. This could be due to the lack of adverse effects or to lack of focus on hormonal relationships in chronic renal disease. The author’s grant proposal and the article by DeLong [DeLong 2005] seek to provide missing information. The study group in the DeLong report involved patients receiving hemodialysis. Anemia is not an uncommon event in such patients and numerous causes can be identified. The triad involving angiotensin-testosterone-anemia is not the only one that may be operative in this patient group. However, the peer-review process recognized that the question dealing with renoprotective therapy and anemia was an important one. The analysis of the ideas involved showed that those provided by the author were missing both from the knowledge base considered (2000-2004) and from the general medical literature.

**Investigator’s Insights:** The recognition of the missing ideas by the investigator and colleagues was somewhat mystical as none of the authors of the 2005 article [DeLong 2005] had a publication history linking testosterone, androgen deficiency, renin-angiotensin blockade, and anemia. While there were over 250 articles in PubMed linking testosterone with renal function, 13 articles dealt with the specific triad of testosterone, renal function and angiotensin. Of those, the DeLong et al article [DeLong 2005] was the only one suggesting an adverse effect of angiotensin. Accordingly, the decision to study testosterone and renin-angiotensin blockade isn’t apparent on the basis of personal experience characterized by publication history or general publication knowledge dealing with the pertinent combination of variables. When queried regarding the possible path leading to the creative act, the investigator suggested that the result was the consequence of an extensive review of the literature. No further insights were offered.[Logan 2005]