

Carl M. Kjellstrand, MD, PhD, FACP, FRCP(C)

Clinical Professor of Medicine, Loyola University Chicago
Adjunct Professor, University of Alberta, Canada
Adjunct Professor, SUNY at Brooklyn, New York
Docent, Karolinska Institute, Stockholm, Sweden.

Synopsis from the article: [Kjellstrand CM, Evans RL, Petersen RJ, Shideman JR, von Hartitzsch B, Buselmeier TJ. The “unphysiology” of dialysis: A major cause of dialysis side effects? Kidney Int 1975; Suppl 2:30-4](#)

In dialysis, it is more important that body chemistries are normal (“physiologic”) than that an arbitrary Kt/V is achieved.

THE UN-PHYSIOLOGY HYPOTHESIS

THEME:

*“We hold this truth to be self-evident in dialysis:
Normal chemistries and physiology are better than abnormal...a lot better”*

In the mid 1970's, my coworkers at the University of Minnesota and I did a series of studies and analyses of why dialysis patients do so poorly. We did two studies, one on short-term effects, where we studied patients at every dialysis, and one long-term study where patient were followed for several months.

These studies led us to formulate the “Un-physiology Hypothesis” which stated that side effects seemed particularly common in patients who experience great swings in body weight, urea (osmolality), and potassium, and who had—as a consequence of their large fluid load—severe hypertension.

In the **short-term study**, we asked patients if they developed headaches, cramps, or if their blood pressure "crashed" during dialysis. We studied the influence of the fluid removal rate (ultrafiltration rate) and how fast the osmolality in the blood declined, mainly due to the fall in urea. Not surprisingly, the faster and more violent the changes, the sicker the patients became. No patients whose ultrafiltration was less than 1 kg or osmolality dropped less than 5 mosm/kg, developed any symptoms, while 50% of the dialyses with an ultrafiltration over 2 kg and an osmolality drop over 15 mosm/kg had symptoms.

In the **long-term study**, we followed 30 patients after their kidneys had been removed in preparation for renal transplantation. They were observed for more than 5 months of dialysis. Five of the 30 patients developed evidence of damage to their nervous systems.

Four factors were studied, to see if they influenced the occurrence of damage to the nervous system:

1. **Demographics** (age, gender, diagnosis, time elapsed since dialysis was begun)
2. **Very bad “uremia”** — very high levels of blood urea nitrogen and serum creatinine before the first dialysis. We called this the “neglect factor.”
3. **How well dialysis controlled the levels of both small and “middle” molecules**
4. **How well “physiology” was controlled.** We assessed the level of "unphysiology" by looking at: (a) the serum potassium concentration before each dialysis, (b) the extent by which blood urea nitrogen and serum osmolality fell, (c) how much fluid needed to be removed during each dialysis, and (d) how well blood pressure was controlled.

Finally, we analyzed various combinations of these factors to determine if these combinations were associated with ill-effects.

We found that neglect and "un-physiology" were the two major factors that correlated with damage to the nervous system. If patients came early to be dialyzed and "physiology" was well-maintained (as 23 patients in the study fitted into that category), none of these patients evidenced damage. However, 5/7 (71%) of patients who had both factors present became worse. In this study, neither demographic factors nor factors of uremia or middle molecule levels had any influence on nervous system damage.

We then reasoned that once patients came to dialysis, neglect could not be influenced--but "physiology" could be, and this reasoning led to a number of analyses and considerations. First, **the more "unphysiologic" dialysis is, and the more abnormal chemistries and fluid levels are before dialysis, the more violently they will change during dialysis and the more ill-effects that patients will experience.** This is the “Un-physiology Hypothesis.” The best way, we contemplated, to get rid of "un-physiology" is to **dialyze often – i.e., dialyze daily.** There is no possibility of keeping body chemistries within normal limits with three dialyses per week. The serum potassium level is above normal; the patient is acidotic and fluid-overloaded before each dialysis.

Secondly, when dialysis is over, the patient's serum potassium level is below normal and the patient is alkalotic and short of fluid in the vascular space. The patient's body is never in a normal state; it is in an abnormal state, both before *and* after dialysis.

This unsatisfactory state of affairs rears its head in many ways: In dialysis patients, the death rate from acute cardiovascular problems is twice as high on Mondays and Tuesdays when patients come in after two days without dialysis and with major “un-physiology,” when compared to the death rate of the other days of the week. A simple look at the waiting rooms of dialysis units, where there are often post-dialysis patients lying on stretchers, sometimes for hours, receiving intravenous fluids or chicken broth to treat their low blood pressures after too fast, too infrequent, and too violent dialyses have been carried out, will illustrate this point well.

FROM THE THEME:
NORMAL IS BETTER THAN ABNORMAL.

"UNPHYSIOLOGY" IS BAD.

**DAILY HEMODIALYSIS IS MUCH BETTER THAN THREE TIMES
PER WEEK DIALYSES.**

This observation has been described in more than 500 scientific studies and articles. [A list of these publications is available:](#)

(<http://www.homedialysis.org/v1/resources/#ClinicalOutcomes>) Bibliography of literature on daily hemodialysis and selected home hemodialysis (included with permission from Dr. Carl M. Kjellstrand) (40 pages; 497 kb)

References:

- Kjellstrand CM. Reflections on dialysis side effects. Rein et Foie, *Maladies de la Nutrition* 1974; 16B:327-35.
- Kjellstrand CM, Shideman JR, Bosl R, Buselmeier TJ. Theoretical aspects and complications of frequent or ultra-efficient short dialysis. Rein et Foie, *Maladies de la Nutrition* 1974; 16B:375-81.
- Kjellstrand C, Evans R. Considerations of new dialysis schedules: Theoretical evaluation and review of literature. *Opuscula Medico-Technica Lundensia* 1975; XVI:26-37.
- Kjellstrand CM, Rosa AA, Shideman JR, Rodrigo F, Davin TD, Lynch RE. Optimal dialysis frequency and duration: The "unphysiology hypothesis". *Kidney Int* 1978; 13:S120-4.

Comments by Christopher R. Blagg, MD, FRCP:

This article, published in 1975, is an example of an important common sense article that soon became forgotten as the late 1970s and the 1980s saw rapid expansion of dialysis facilities, the introduction of more efficient dialyzers and shorter dialysis times, and eventually the somewhat misguided, large reliance on Kt/V as a measure of adequacy of dialysis.

The fact that three times a week hemodialysis began as a treatment for patients who dialyzed 6 to 8 hours overnight and that these patients did very well was soon forgotten except in a few places such as Seattle in the USA and Tassin in France. As a result, dialysis became an ordeal for many patients because of episodes of low blood pressure during dialysis and the fatigue that they experienced following a short dialysis.

When more frequent hemodialysis, both daily and nightly, began to be used again in the mid-1990s, the "un-physiology" hypothesis was rediscovered as the lucky patients who had access to these treatments found that the side effects of dialysis, both during and between treatments, were very greatly reduced. The hypothesis has in effect been proved by more frequent dialysis and it is only to be hoped that many more patients will be able to benefit from these treatments in the future.