

Fruitful Collaboration of Physician/Physiologist and Engineer in the Treatment of Renal Disease

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I first met Frank Gotch in the Fall of 1967 when I was employed at Dow Chemical in Walnut Creek, California and he was the director of the University of California Renal Center at San Francisco General Hospital. My responsibilities at Dow were to run the pilot plant that produced prototype hollow-fiber dialyzers for testing by his pioneering dialysis program. In addition, I was responsible for making production improvements to assure the future supply of these new dialyzers. I did not realize it at the time but we were embarking on a collaboration that has lasted for over 30 years.

As the major production hurdles were progressively addressed, we found what appeared to be a thrombogenicity problem with this type of dialyzer. Once that problem was resolved we started to deal with the dialyzer as a predictable element of the treatment and to deal with questions regarding how it should be used to deliver optimal therapy to the ESRD patient. Working on these problems started with a traditional supplier-user relationship but evolved into a close collaboration to answer fundamental questions of physiology which has resulted in not just a rewarding professional career but a long personal friendship.

I believe that one of the most profound results of this collaboration has been a unique way of looking at the fundamental problems in the dialysis field by coupling Frank's observations and curiosity with the application of basic physical laws and a structured problem-solving approach which is common in the engineering field. In addition, the creative atmosphere that has existed during the years of our collaboration has yielded, I believe, some very innovative approaches to experimental and study design.

The collaboration between myself and Frank Gotch can be illustrated by discussing several practical problems we addressed: 1) Resolution of the hollow-fiber dialyzer thrombogenicity problem; 2) studies of the transport of CO₂ and the transport of bicarbonate in both acetate and bicarbonate dialysate; 3) protein nutrition in a wide variety of subjects; and 4) the use of mass balance principles in kinetic analyses.

Hollow-Fiber Dialyzer Thrombogenicity Problem

The technique we developed for sequential testing of dialyzers to measure thrombogenicity illustrates the way in which our collaboration led to unique approaches to experimental design and analysis.

Our initial collaboration at the University of California Renal Center at San Francisco General Hospital involved determining transport characteristics and the suitability of the new hollow-fiber dialyzers for long-term chronic dialysis. During the initial phases of that program, we encountered episodes of severe clotting of the dialyzer that were sufficient to terminate the use of the clotted dialyzer and require a second to be used during the remainder of the same treatment. This was a worrisome finding because there had always been a concern that dialyzers with a small blood flow path, represented by hollow fibers with an inside diameter of 200 μ , might not be usable in the general dialysis population. We attempted to measure a wide variety of clotting parameters on the study patient in order to determine if there were restrictions on the utility of this new dialyzer, with the possibility that some individuals might not be candidates for its use.

After a number of these two-dialyzer treatments, using what were presumed to be identical dialyzers, we made the observation that the second dialyzer always clotted less than the initial one and concluded that the first dialyzer had in some way reacted with the patient's clotting mechanism and reduced the thrombogenicity of the patient. From this observation we formulated an experimental design that used an "experimental" kidney (i.e., one where manufacturing changes were made) and used it first for a fixed period of time, at which point the dialyzer was retired and a "control" dialyzer (i.e., one that was made using normal manufacturing procedures) was used for the remainder of the session. Using this approach with the patient as his own control, if the second dialyzer clotted more than the first, we concluded that the initial one was less thrombogenic, and the processes used to manufacture it were preferable.

From this experimental design, it was possible to determine the importance of absolutely sterile manufacturing techniques to avoid clotting of dialyzers, and while this finding in retrospect may appear obvious, in the late 1960s these techniques were still being developed (Cuprophane sheets used in Kiil dialyzers were routinely soaked in tap water).

Discovery of the sensitivity to nonsterile solutions has led to manufacturing processes that currently result in dialyzers that not only clot very little but are frequently sufficiently thromboresistant to be used numerous times.

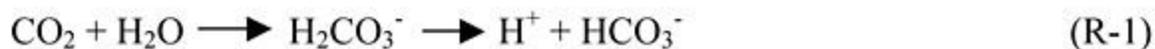
CO₂ and Bicarbonate Transport

Our efforts at modeling acid-base during dialysis involved measuring transport of CO₂ and bicarbonate and illustrate the importance of defining systems in the modeling process. They also illustrate the use of structured problem solving, novel experimental design, and data analysis techniques.

Definition of the system

Clear definition of a problem is one of the fundamentals of a structured analysis. In order to study acid-base problems and therapeutic responses it was important to model both CO₂ and bicarbonate. This required an unequivocal

definition of the CO₂ system that reflected the relationships involved between this gas and its products in the blood (see Reaction R-1 below). Such a model would allow analysis of the transport of carbon dioxide during dialysis (1, 2) as well as evaluation of the popular misconception that acetate, the nearly universally used dialysate anion for countering metabolic acid production at that time, was stoichiometrically transformed into bicarbonate in the body. In addition, there was concern about hypoxia during dialysis for which there were several theories (3—5). Finally, we wished to analyze the transport of CO₂ as a part of the overall acid-base correction problem in dialysis.



It had been traditional to consider “total CO₂” (i.e., dissolved CO₂ as well as bicarbonate) as the CO₂ content of the body. We decided that this was potentially confusing because the third step shown in Reaction R-1 had acid-base consequences and should be considered separately. We concluded that to study CO₂ transport, only dissolved CO₂ and its hydrated form, H₂CO₃ would be considered part of the CO₂ system. That is, HCO₃⁻ should be considered a separate solute and not part of the CO₂ system.

In a normal individual virtually all of the CO₂ excreted is via the lungs. In the dialysis patient a very small amount (less than 2% of normal production) is cleared by the dialyzer. But a significant amount (more than 20% of normal production) is removed via the reaction R-1 when carried fully to the right. That is, as HCO₃⁻ is dialyzed out of the patient during acetate dialysis, the reaction moves to the right and CO₂ disappears from the system—not by dialysis of the dissolved gas, but because of the chemical reactions shown. Importantly, this process also acidifies the patient because equal amounts of H⁺ are being generated, and much of this additional acid is being neutralized by other buffers or supplying the H⁺ that is consumed when acetate is metabolized to CO₂ and H₂O.

This approach yielding an unequivocal definition of the CO₂ system helped to explain quantitatively the observed dialysis hypoxia when acetate was used (2, 3, 5), and it contributed to the nearly universal move to bicarbonate over the past two decades.

Quantifying HCO₃ Transport

In studying the acid-base problem in the dialysis patient, it was necessary to accurately assess the HCO₃⁻ transport of the dialyzer. When conducting transport studies one commonly will evaluate the flux of a material (mass transferred/min) as a function of the concentration driving force determined by the inlet concentration difference between blood and dialysate (C_{Bi} — C_{Di}), with the dialysance, D, as the proportionality constant:

$$D = \text{Flux} / (C_{\text{Bi}} - C_{\text{Di}}) \quad \text{Eq. 1}$$

The flux can be measured either as change in content of the blood ($Q_{Bi}C_{Bi} - Q_{Bo}C_{Bo}$) or by the change in content of the dialysate ($Q_{Di}C_{Di} - Q_{Do}C_{Do}$). Measurements on the blood side can be complicated because of the heterogeneous nature of blood with an aqueous phase, nonaqueous constituents, and cells. This heterogeneity can cause problems in determining in vivo transport constants from blood side measurements. Dialysate side measurements, while more straightforward because of the comparative ease of aqueous determinations, sometimes suffer from low concentrations and associated problems of analytical accuracy. To have absolute confidence in the resulting transport values, it is important to assure that a mass balance can be closed—i.e., that the same amount of material is measured leaving the blood as is measured being picked up by the dialysate.

$$\text{Flux}_B = \text{Flux}_D$$

Eq. 2a

$$(Q_{Bi}C_{Bi} - Q_{Bo}C_{Bo}) = (Q_{Di}C_{Di} - Q_{Do}C_{Do})$$

Eq. 2b

Where Q_{Bi} represents the effective blood water flow for the specific solute being measured (6). If the right and left sides of Eq. 2a match, then one can have confidence in the validity of determinations. If they don't (which in studies of this type is not uncommon), then there is a problem with methods, assumptions, or calculations that must be addressed. This problem in mass balance closure plagued our studies of HCO_3^- transport and resulted in at least a year-long delay until we determined that using two different methods (one for blood side, another for dialysate side) was the cause of these differences (7). Others looking at similar data erroneously concluded that metabolic processes in the red cell were generating large quantities of CO_2 (8—10).

Obtaining Precision at Low Levels of Transport

Obtaining a precise measure of bicarbonate transport was crucial in our studies of acid—base correction during dialysis. Bicarbonate is lost at a significant rate during acetate treatment (the nearly universal type of dialysis conducted at the time). Conversely, during bicarbonate dialysis HCO_3^- transport has a direct impact on the ability to correct the acid-base problem for these patients. As a result we set out to measure bicarbonate transport in a range of dialyzers (11). The classic method of measuring the relevant transport constant, D , from dialysate side measurements is to expand Eq. 1 above:

$$D = \text{Flux} / (C_{Bi} - C_{Di}) = (Q_{Di}C_{Di} - Q_{Do}C_{Do}) / (C_{Bi} - C_{Di})$$

Eq. 3

A major problem in these studies was that during HCO_3^- dialyses, the fluxes ($Q_{Di}C_{Di} - Q_{Do}C_{Do}$) as well as the concentration driving force ($C_{Bi} - C_{Di}$) were small numbers, so that the calculation shown in Eq. 3 resulted in wide variations and accurate transport constants for the study dialyzers could not be determined with confidence. Another problem was that the blood side is a heterogeneous fluid where HCO_3^- does not distribute evenly. Also, charged

material, such as HCO_3^- , will distribute differently in plasma and cells due to Donnan Ratio considerations. As a result, it was difficult to measure flux from the “blood side.”

A re-examination of Eq. 3 shows that:

$$\text{Flux} = D (C_{\text{Bi}} - C_{\text{Di}}) = (Q_{\text{Di}}C_{\text{Di}} - Q_{\text{Do}}C_{\text{Do}}) \quad \text{Eq. 3a}$$

If we plotted “Flux” ($Q_{\text{Di}}C_{\text{Di}} - Q_{\text{Do}}C_{\text{Do}}$), the change in content of the aqueous dialysate as a function of the concentration driving force ($C_{\text{Bi}} - C_{\text{Di}}$) over a range of these variables, we obtained a graphical representation of Eq. 3a which is a line with the slope, D (Fig. 1). This approach to our transport studies yielded very stable transport constants for the dialyzers under study and also allowed us to compute the Donnan Ratio for HCO_3^- as 0.68, comparable to a literature value of 0.69, and effectively closed a blood to dialysate mass balance.

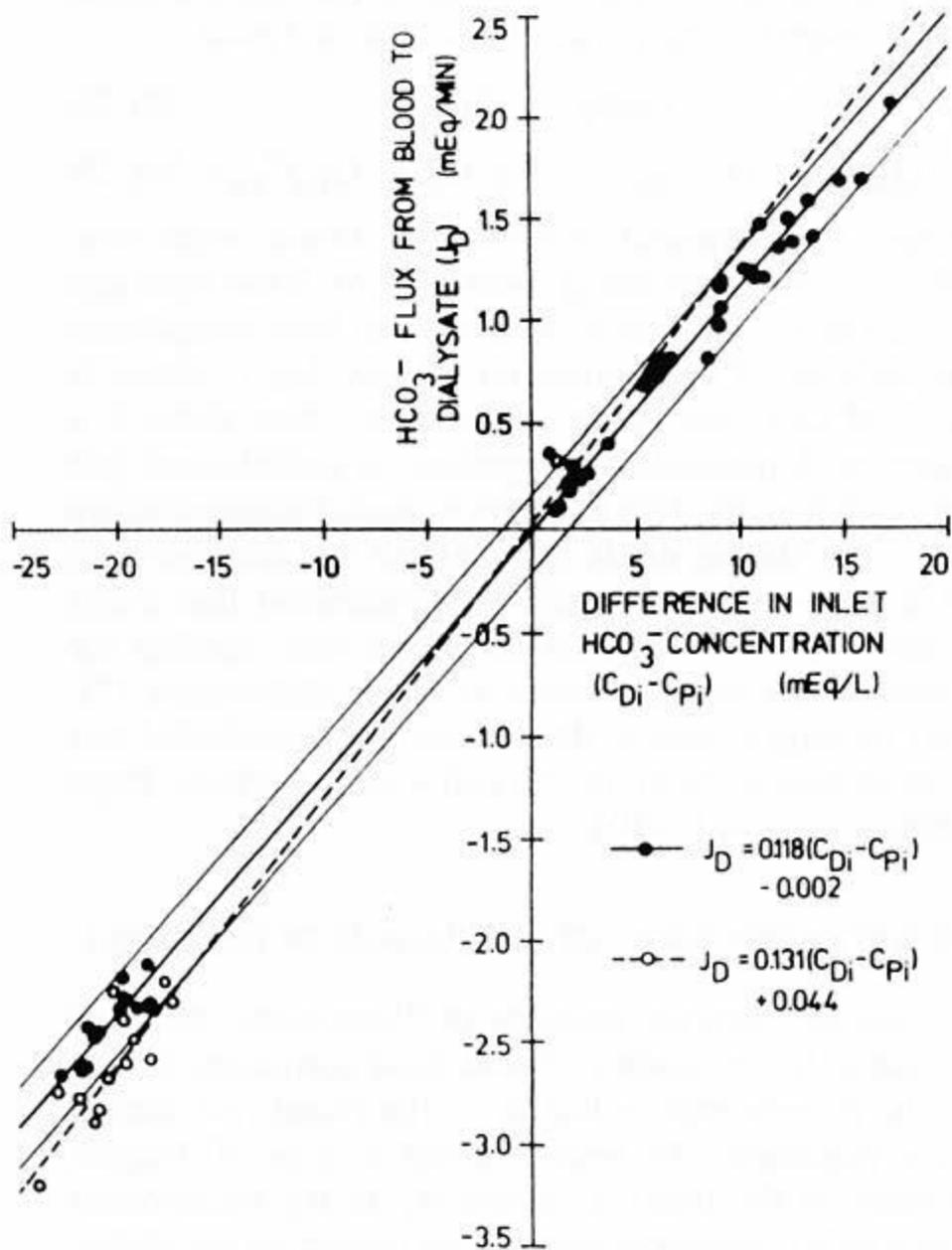


FIG. 1. Bicarbonate flux as a function of concentration driving force. Mathematical analysis of this relationship is used to determine the dialysance, and mass transfer coefficients for two dialyzers (11).

This unique analytical technique, which gave these studies considerably greater accuracy than traditional techniques would have obtained, resulted from an understanding of the relationship that we were trying to evaluate (Eq. 3a) and developing an experimental technique and analytical methods to best address the problem of low flux rates.

Protein Nutrition in a Wide Variety of Subjects

Frank and I collaborated on a number of studies and analyses to understand protein nutrition in dialyzed patients and to extend this understanding to nondialyzed individuals. These efforts, including the evaluation of other work in this field, reinforced our belief that the relationship of variables under investigation must be critically analyzed in order to reveal the underlying mechanisms being studied. Once this is done, the resulting relationship can be a powerful tool in treatment planning and monitoring the effectiveness of therapeutic tactics.

Determining Protein Intake

A widely used relationship is one introduced in the early 1970s relating protein intake to blood levels of urea (S_u) and creatinine (S_{cr}) (12). As a result of their research the investigators found an excellent linear correlation between S_u/S_{cr} as a function of protein intake (g/day) in the form of:

$$S_u/S_{cr} = 0.13 (\text{protein intake}) + 0.77 \quad (r = 0.94) \quad \text{Eq. 4}$$

This relationship (Fig. 2) is suggested by the authors as a means of estimating the protein intake from serum urea and creatinine levels, and it has been in use as a nutritional parameter ever since. However, it seems that the authors failed to try to thoroughly understand what it meant and whether it really could be used for its suggested purpose.

As we began our own studies of urea and net protein catabolism during the same period, we developed a relationship between net protein catabolism and net urea nitrogen generation (13, 14). These studies resulted in the following (see Fig. 3):

$$G_U = 0.154PCR - 1.7 \quad \text{Eq. 5}$$

/p>

where G_U is net urea nitrogen production (g/day) and PCR is the net protein catabolic rate (g/day).

Eq. 5, which was developed during metabolic balance studies, has been tested in uremics, dialysis patients, normals and a wide variety of other disease conditions, and has been found to be valid over a range of catabolism from 20—350 g/day (13—17). It describes the fundamental disposition of the major protein nitrogen catabolite, urea, in humans.

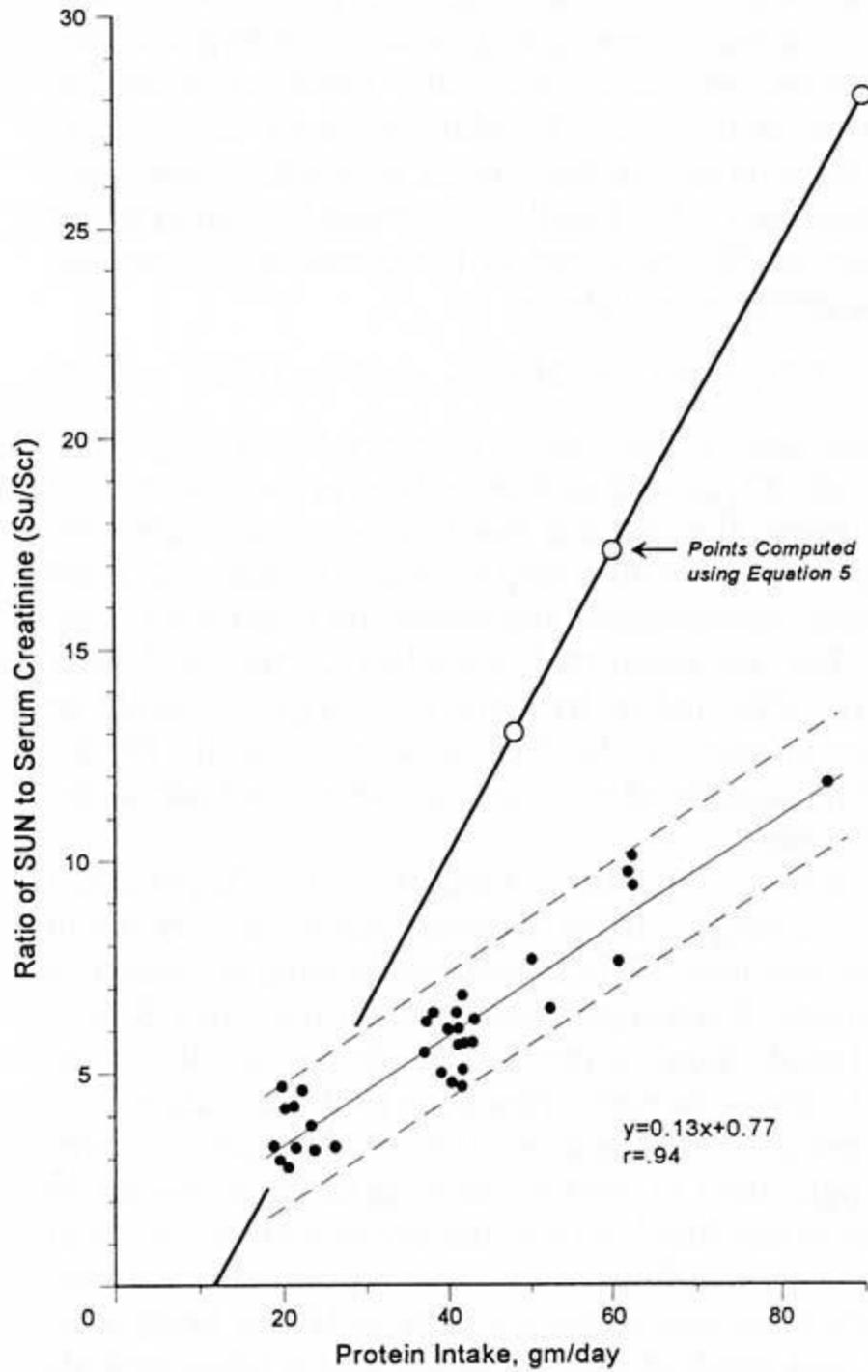


FIG. 2. Ratio of serum urea nitrogen and creatinine, Su /Scr, as a function of protein intake replotted from (12). Expected net protein catabolic rates (protein intake in nutritionally stable patient) and Su /Scr for an example patient are superimposed on the original data.

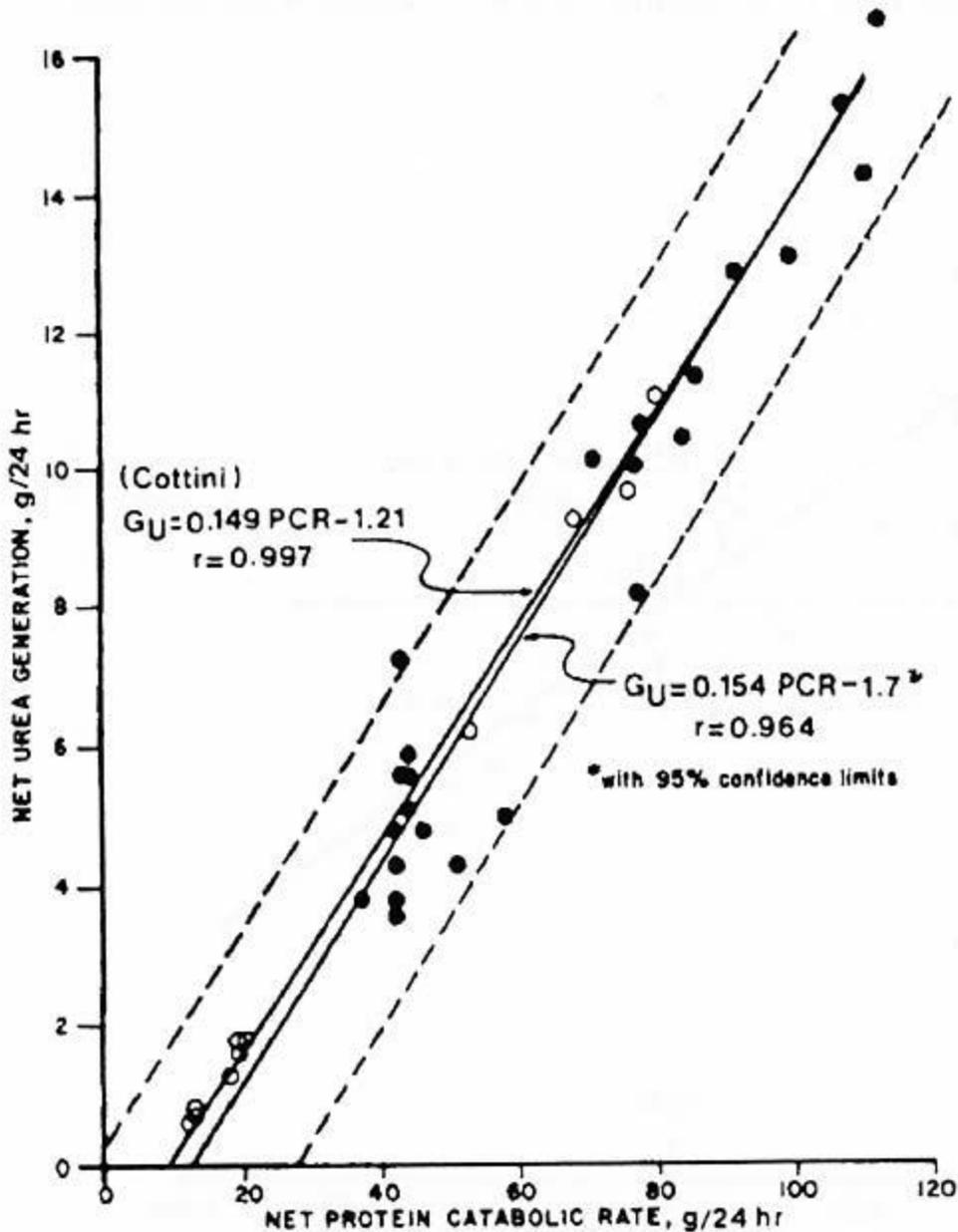


FIG. 3. Relationship of net urea generation as a function of net protein catabolic rate from References 13, 14, and 6.

The value of Fig. 3 is more than the satisfaction that there is a good linear correlation between the two variables, as an in-depth analysis of the regression equation (Eq. 5) will illustrate. Eq. 5 shows that 15.4% of protein catabolized will end up as urea nitrogen. Also, from its x-intercept (i.e., when $G_U = 0$, $\text{PCR} = 1.7/0.154$) about 11 g of protein will contribute their nitrogen to compounds and other metabolic routes as obligatory losses independent of the level of protein catabolism. Since Eq. 5 is an accurate description of nitrogen catabolites in humans, it can be used to test the validity of Eq. 4

An immediate reason to question Eq. 4 is that it indicates that if protein intake could figuratively be brought to zero, measurable levels of urea would still be expected, inferring its continued production with no protein catabolism (i.e., when $x = 0$, $y = 0.77$, and $S_u = 0.77S_{Cr}$). This is in conflict with known metabolic mechanisms of urea production. Eq. 4 (from Fig. 2) can be tested using Eq. 5. In Table 1, a hypothetical stable patient is selected whose protein intake (and rate of net protein catabolism) varies from 48 to 90 g/day. Urea production is calculated for this patient from Eq. 5, while steady-state urea and creatinine concentrations are determined from steady state urea relationships (see below). The table shows that the protein intake estimated from Eq. 4 for this simple case is in error by a factor of more than two. In addition, when the S_u/S_{Cr} and intake values from Table 1 are plotted on Fig. 2, the level of error in protein intake that would result if Eq. 4 were used in the manner the authors suggest is clear. (Also note that the regression of the computed points has an x-intercept at protein intake of 11 g/day which is consistent with Fig. 3 indicating that there is a minimum protein intake of this level that is needed for obligatory nitrogen losses). From this example, it is clear that Eq. 4, while consistent with the investigator's data, cannot be accepted as a fundamental nutritional parameter and that further examination should be made of why such a relationship exists.

TABLE 1. Analysis of protein intake and its relation to blood urea and creatinine levels

Protein intake, g/day	48 (0.8 g/kg)	60 (1.0 g/kg)	90 (1.5 g/kg)
Creat clearance K_{Cr} , ml/min-assumed	20.0	20.0	20.0
Creat production G_{Cr} , mg/min-assumed	0.625	0.625	0.625
S_{Cr} (also C_{Cr} , mg/dL)*	3.0	3.0	3.0
Urea clearance K_U , ml/min-assumed $1/2 K_{Cr}$	10.0	10.0	10.0
Urea production (net) G_U , mg/min †	3.95	5.24	8.44
S_U (urea nitrogen, also CU mg/dL) ‡	39.5	52.4	84.4
S_U/S_{Cr} calculated	13.2	17.5	28.1
Est protein intake (g/day), from Eq. 4 §	97.0	129.0	210.0
Error (est/actual)	202%	215%	233%

* $S_{Cr} = (\text{creat production})/(\text{creat clearance})$; see discussion of mass balance below.

† From Eq. 5 and transformed from g/day to mg/min.

‡ $S_U = (\text{net urea production})/(\text{urea clearance})$: see discussion of mass balance (see Eq. 7c below).

§ Substituting the " S_U/S_{Cr} calculated" value and solving for estimated protein intake.

Unfortunately, evaluation of many medical studies shows that it is not uncommon for investigators to simply graph their data in an x—y format with little attempt to understand the relation of the variables analyzed. The failure to more fully analyze data is regrettable because it curtails the level of knowledge that ultimately could come out of good experimental work. Furthermore, examining derived relationships for "reasonableness" would go a long way to avoid embarrassment, wild goose chases, and artifactual results.

Applying the Results

Equation 5 opened a wide range of possibilities in understanding protein nutrition and what can be done to influence it generally, not just in dialysis patients. Using rearrangements of this equation and quantitation using steady state relationships, it was now possible to obtain accurate ongoing estimates of net protein catabolic rate (PCR) from periodic measurements of blood urea and creatinine levels. It was also possible to make reliable estimates of changing renal function (6, 19, 23).

A further area of fruitful investigation was to examine the use of parenteral solutions for acutely ill patients and how it could be possible to take nutritional support to a level of effectiveness far beyond the common practice of using nutritional support to, in effect, “give a hospital tray to a patient through a tube.” As mentioned above, PCR can be accurately estimated from commonly measured blood values, so that this parameter can be evaluated as a dependent variable while investigating a range factors that can alter it. That is, one could now change energy and amino acid administration and measure the effect on the net catabolic status of the patient. For example, in Fig. 4 at the same amino acid infusion rate we were able to increase the rate of glucose infusion and quantify the drop in PCR (the protein sparing effect of administration of energy) (6, 13, 18—20).

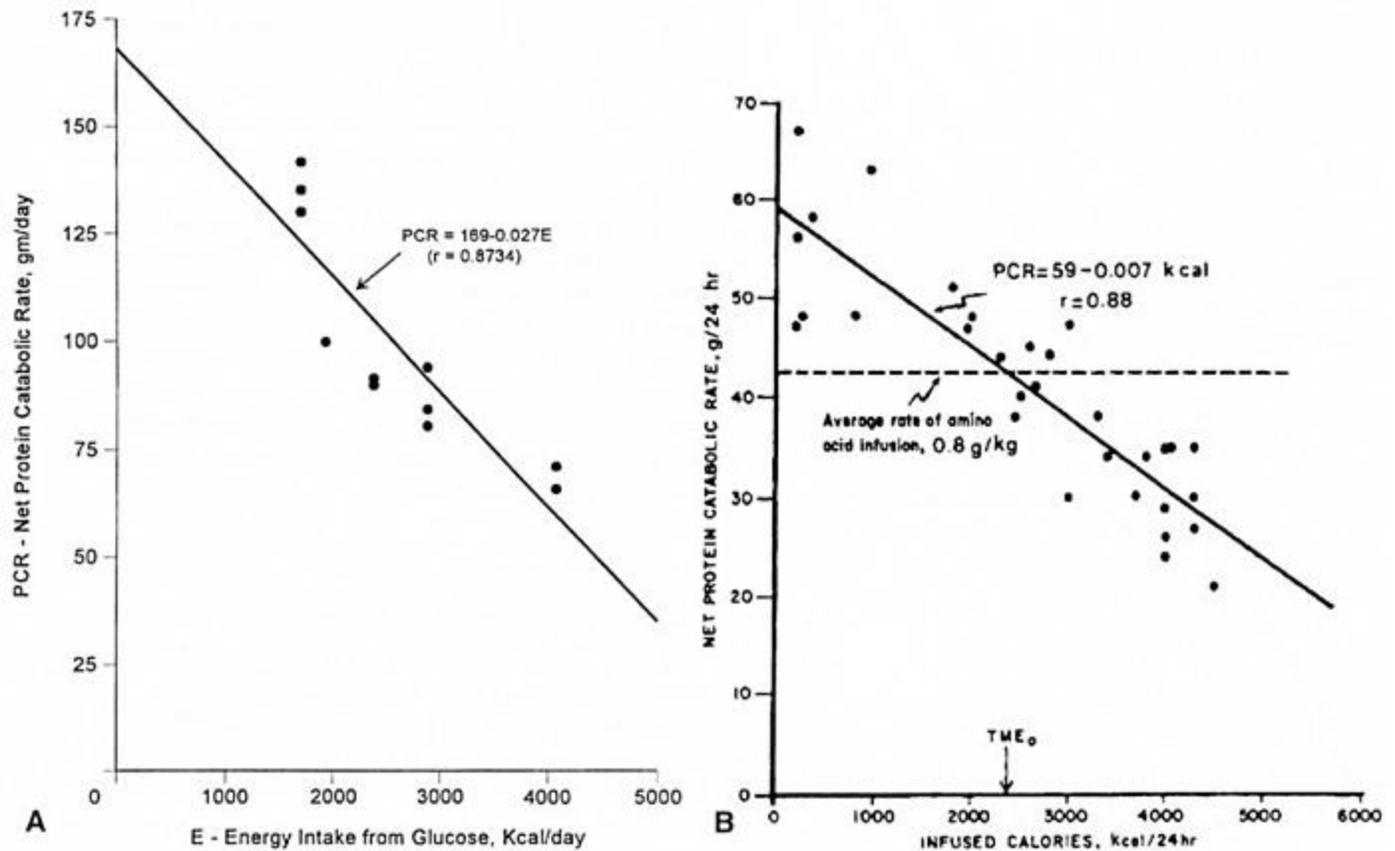


FIG. 4. Net protein catabolic rate as a function of parenterally administered energy in the form of glucose in an acutely ill patients. (a), nonuremic patient undergoing total parenteral nutrition (18); (b), patient with renal failure undergoing periodic dialysis (13, 6).

In addition, in studies funded by the National Cancer Institute, increased amino acid infusion to critically ill patients to make up for a negative protein balance, resulted in increased PCR as expected—i.e., increased amino acids will result in more being catabolized, as shown in Fig. 5 (18). It is interesting, however, to examine the slope of the PCR-amino acid infusion rate relationship (in Fig. 5 it is ~ 0.7). This slope indicates the effectiveness of this strategy; a slope of 1.0 would indicate that the added protein equivalents were simply being burned up, so one would hope for a slope < 1.0, which would indicate that some fraction of the additional amino acids were being used to produce needed protein by the patient.

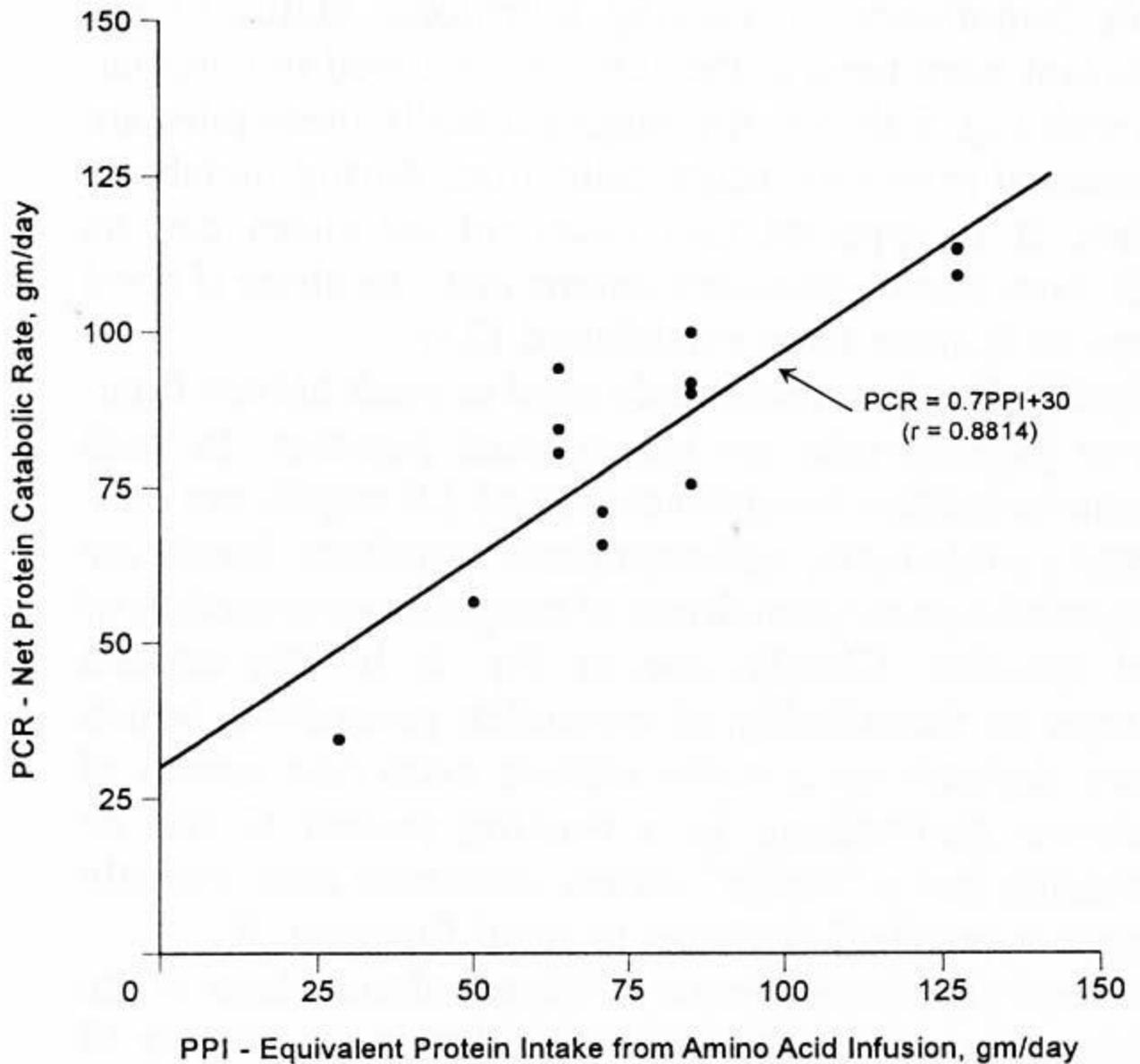


FIG. 5. Net protein catabolic rate as a function of parenterally administered protein equivalents in the form of amino acids in an acutely ill patients. Patient was nonuremic patient undergoing total parenteral nutrition (18).

The Use of Mass Balance Principles in Kinetic Analyses

Perhaps the best-known aspect of our collaboration is in the area of modeling various systems, with the urea kinetic model illustrating the power of applying the principle of mass balance to a solute system (6, 21, 22). The concept of conservation of mass, or mass balance—the idea that matter cannot be created or destroyed— may seem obvious. It is, however, a fundamental physical principle and a very powerful one in analyzing various physiologic systems. It underlies much of engineering and has been fundamental in the collaborative work that Frank and I have pursued. Applications of the work have included development of methods for assessing the adequacy of dialysis and monitoring nutritional status of patients as discussed above.

Defining the System

The use of mass balance to describe a system starts by formulation of a model. The formulation of the model is not a perfunctory task and is actually the most difficult step because it requires an in-depth understanding of the overall system and the precise manner in which the system acts as a whole. It is best approached by constructing a diagram, such as that for urea and creatinine in Fig. 6. It should be stressed that the best person to construct diagrams such as that shown in Fig. 6 is not a mathematician but someone who thoroughly understands the system being modeled. That is, the difficulty in creating such a diagram lies in the need to fully understand and quantitatively isolate all of the specific elements of the system being modeled—how the modeled substance is distributed and how it appears and disappears. In short, someone who fully understands the physiology of the system and can put this understanding into quantitative terms represented by Fig. 6. It turned out that in my collaboration with Frank, that “person” was frequently a combination of the two of us.

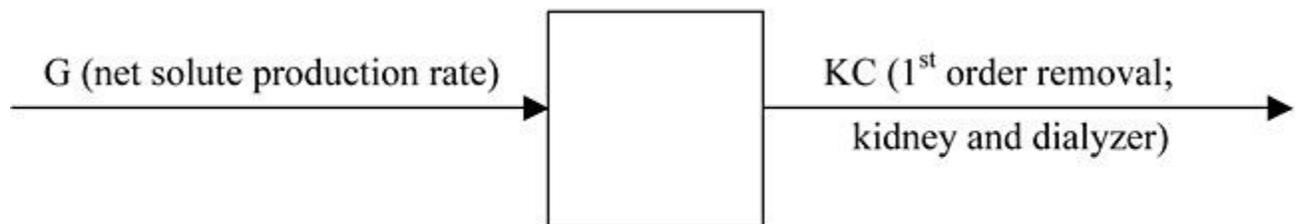


FIG. 6. Diagram of single pool model for the study of catabolites in the dialysis patient

The use of such a diagram is extremely helpful because it establishes the relative relationship of various aspects of the system. In these diagrams, the box represents the system content; in the case of urea and creatinine, this is considered to be total body water. The quantitative description of the inputs and outputs must be consistent with the

description of system content— generally either constants, such as net creatinine production, or first order terms, which depend on the system content for their magnitude such as the removal of solute by clearance mechanisms. In the case of clearance mechanisms, the rate of removal will be the product of clearance (K, mL/min) and the concentration of the volume being cleared each minute (C, mass/mL). Time dependence is also possible, such as a substance generated from periodic meals, although this may be difficult to quantitate. For urea the generation rate is generally assumed to be a constant (zero order).

Characterizing the Model

The quantitative expression of mass balance takes the form:

$$\text{Accumulation (increase in system content)} = \text{input to system} - \text{output from system} \quad \text{Eq. 6}$$

Once the system has been defined and a diagram drawn, Eq. 6 can be applied to it. This is a mechanical step of substituting terms from the diagram into Eq. 6, and illustrates the importance of accurately and deliberately constructing the diagram before this step is started. With reference to Fig. 6, the following substitutions would be made:

$$\begin{aligned} \text{Accumulation (increase in system content): } & d(VC)/dt \\ \text{Input to system: } & G \\ \text{Output from system: } & KC \end{aligned}$$

The system content in this case is the product of its volume and concentration, expressed mathematically as $d(VC)/dt$. Substituting these terms into Eq. 6 yields:

$$d(VC)/dt = G - KC \quad \text{Eq. 7}$$

Where the change in system content, expressed as the product of body water (mL) and urea concentration (mg/ mL), is equal to net urea production G (mg/min) minus the rate of removal KC. This expression can then be integrated to yield a relationship describing urea concentration as a function of time. In the absence of volume changes this expression is:

$$C = C_0 e^{-Kt/V} + G/K(1 - e^{-Kt/V}) \quad \text{Eq. 8}$$

Where C_0 is the initial value of C, the urea concentration. Solution of Eq. 7 with volume changes is the underlying expression used in urea kinetic modeling for guiding dialysis therapy. Its solution appears elsewhere (6).

The derivation of Eq. 7 and Eq. 8 assumes that the contents of the system are well mixed so that the material added or removed is immediately reflected in the system content (the assumption of a single pool). Most systems are manifestly multipool. However, in this case the rates of input and output are normally small enough relative to the overall content and the assumption of single pool gives a reasonably accurate approximation of actual system behavior.

Applications Derived from Examining Steady State

While the mathematical solution of the mass balance equation (Eq. 7) is apparent, considerable insights can be gained from examining steady state—Eq. 6 and Eq. 7 when there is no accumulation. This in fact is the case in most of normal physiology when there are limited changes in body chemistry, and is the situation before a patient requires dialysis. Nonetheless, once the mass balance equation has been formulated, there is a great temptation to immediately solve it to yield expressions such as Eq. 8. It is worthwhile, however, to first consider the system when it is at steady state.

Steady state is when there is no accumulation and the left side of Eq. 6 is zero (i.e., in Fig. 6 and Eq. 7, where neither body water, urea or creatinine concentration, nor their product change): $d(VC)$ in Eq. 7 is zero. In this case Eq. 6 becomes:

$$0 = \text{Input} - \text{output} \quad \text{Eq. 6a}$$

$$\text{Input} = \text{Output} \quad \text{Eq. 6b}$$

And for Eq. 7:

$$0 = G - KC \quad \text{Eq.7a}$$

$$G = KC \quad \text{Eq.7b}$$

One can rearrange Eq. 7b to yield

$$C = G/K \quad \text{Eq.7c}$$

$$K = G/C \quad \text{Eq.7d}$$

Eq. 7d is used clinically to evaluate creatinine clearance where a 24—hour urine collection is used to estimate the creatinine production rate, G , and the serum creatinine level is used as the system concentration, C . Eq. 7c was used to estimate values for steady state urea and creatinine concentrations in Table 1 in the process of assessing the validity of Eq. 4. It is also part of the second term in Eq. 8 and projects the concentration when the dialyzed patient's

urea level will come into steady state (i.e., when $-Kt/V$ becomes large enough that $e^{-Kt/V}$ becomes very small) and indicates the lowest concentration that is possible, G/K .

As mentioned, Eq. 7d is commonly used to determine both creatinine and urea clearance rates. It is also clear from Eq. 7b that the net generation rate of both of these solutes can be computed from the clearance and their steady state concentrations. These values are of considerable importance in tracking nutritional status of patients and were used in the studies discussed in conjunction with Fig. 5 above. Although generally these rates are determined from total urine collections during metabolic studies, it is apparent that excellent estimates can be made from blood chemistry determinations alone if good values of K have been established (23).

Finally, Eq. 7c is commonly used to track kidney function in patients who are losing renal function. In such patients creatinine levels in excess of 2.0 mg/dL are considered problematic, and stabilized creatinine levels are considered a successful arrest of progressive reduction of renal function. Clearly, use of Eq. 7c in this context depends on the stability of creatinine generation, which in turn depends on a stable muscle mass (the source of creatinine production). In a wasting patient G can be decreasing and a “stable” serum creatinine may actually indicate a matched decrease in renal function, K .

Several studies of the use of these relationships in the tracking of renal function and nutrition in the acutely ill patient as well as the nondialyzed patient appear elsewhere (18—20, 23).

Understanding Dialysis from Interdisciplinary Collaboration

The more than three decades that I have known Frank, and our collaborations over a large percentage of that interval, have been professionally and personally fruitful. I would like to think that our collaboration has had an impact on the way that both of us view problems, experimental design, analysis of results, and a number of other aspects of looking at the physiology of patients in general. Multidisciplinary collaboration involves more than just putting people with different specialties on the same team. Each team member must start to think differently, and learn enough about the other specialties to anticipate elements of the other’s contribution and to question assumptions and approaches. Each team member then has an expanded intellectual framework to work with. If all members of the team internalize and apply this approach, there is true synergy. I feel that Frank and I have had this type of a collaborative relationship where both of us have approached problems differently than we would have 30 years ago. This is the lasting contribution of this collaboration.

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