PROPHYLACTIC HEMODIALYSIS IN THE TREATMENT OF ACUTE RENAL FAILURE*

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with comments by

PAUL E. TESCHAN AND RAYMOND M. HAKIM


INTRODUCTION

FOLLOWING the introduction of clinically usable artificial kidneys by Kolf,1 Alwall,2 Murray3 and Skeggs and Leonard,4 and the pioneering clinical investigations by Merrill5,6 hemodialysis has been widely employed in the treatment of acute renal failure § according to certain conventional indications: (1) define clinical uremia, and/or (2) hyperkalemia with myocardial potassium intoxication, when either or both progress in spite of a suppressive medical regimen, including cation exchange resins for potassium removal.7–15 Such dialysis treatment usually results in a more nearly normal blood chemical pattern and a gratifying clinical improvement, at least in the absence of significantly symptomatic underlying disease.16 The latter is vitally important because underlying sepsis, hypoxemia and a variety of other states sometimes mimic the uremic syndrome itself.17,18 Unless diuresis and renal function return, however, the improvement is transient.

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§ In this presentation, patients with acute renal failure are identified by oliguria, urinary volume of less than 400 ml/24 hours, with a compensated circulation, patent renal vascular supply, and patent post-renal urinary tracts, in the absence of significant chronic renal disease. The phases of acute renal failure are further defined as follows: The oliguric phase is characterized by urinary volume of less than 400 ml/24 hours; the oliguric phase continues until the urinary volume equals or exceeds 1,000 ml/24 hours. The day on which this first occurs is termed, for convenience, the “day of diuresis.” The “early diuretic phase” begins on the day of diuresis and continues until the day on which azotemia reaches its peak. The latter is the first day of the “late diuretic phase.” The late diuretic phase ends on the day that the declining non-protein nitrogen reaches 30 mg%. The recovery phase begins at that time. Other workers have defined these terms in a variety of other ways; the conclusions drawn from the experience reported here do not appear to be affected by such differing definitions, however. “High output acute renal failure” refers to the situation in which acute renal failure with significant azotemia is associated with urinary volume greater than 400 ml/24 hours, i.e., those instances in which oliguria does not occur.
and repeated dialyses on the same indications produce the familiar, fluctuating chemical and clinical course\(^{19}\) (figure 1).

When hemodialysis is used in treatment, clinical uremic illness is generally easier to control. However, a clear reduction in mortality has been difficult to demonstrate. Mortality remains high among patients who have been referred to centers for possible dialysis treatment, especially among patients who develop conventional indications for dialysis and are so treated. As emphasized by Bluemle,\(^{20}\) the data in table 1 (which presumably already reflect the beneficial effect of dialysis) contrast starkly with the inference that acute renal failure is a benign disease with a low mortality when it is properly treated,\(^{8,9}\) even by medical measures alone.\(^{26}\) Attentive reading reveals that published optimism about prognosis is carefully reserved, however, for the “uncomplicated” cases. In our experience, instances of uncomplicated acute renal failure have been rare.

Instead, regardless of dialysis treatment, wasting, anemia, sepsis (especially pneumonia), and delayed healing of wounds occur frequently in patients with acute renal failure.\(^{20,27}\) While these are most conspicuous in traumatized patients,\(^{27}\) they are often found in fatal cases, regardless of the cause of the renal failure, and appear to cause death in many instances.\(^{20}\) In contrast, such “complications” are rare in the larger number of patients who do not develop acute renal failure (or who develop milder forms, e.g., “high output” acute renal failure) in similar etiologic settings, such as surgical or accidental trauma, hemolytic transfusion reactions, exposure to poisons, etc.\(^{27}\) Hence the anemia, wasting and impaired wound healing in patients with oliguric acute renal failure may not be “complications” at all. Rather, they appear to be a part of acute renal failure itself (and possibly of chronic renal failure as well), in that they may reflect a damaging influence of uremia on many recuperative or homeostatic processes and physiologic defense mechanisms. Furthermore, in all series, occasional patients survive following severe trauma or even prolonged oliguria. This suggests

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**Fig. 1.** Participants in the Study Group on Acute Renal Failure, at the U.S. Army Surgical Research Unit, Brooke Army Medical Center, Fort Sam Houston, Texas, October 13–16, 1959. Seated, left to right: Drs. George Schreiner, Hadley Conn, Donald Pomerantz, Paul Doolan, Bill McMillan, Graham Bull (Belfast), Paul Teschan, Paul Bluemle, Sam Mason, John Merrill, John Kiley, Arthur Nosel, John McDermott, Edouard Richet (Paris), Milton Rubini.

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Data from a 40 year old patient with acute renal failure following accidental trauma. Brigham-Kolff rotating drum dialyzer was used three times, with chemical and clinical benefit.
that virtually all instances of acute renal failure must be considered to be reversible, even though oliguria may persist for three weeks or longer, and that mortality, like severe morbidity, should somehow be avoidable in a larger proportion of these patients.

HYPOTHESIS

Accordingly, for patients with acute renal failure (and possibly for chronic renal failure as well), the following postulates formed the basis of this investigation:

1. The uremic syndrome is often largely reversible by dialysis procedures.

2. Uremic patients frequently develop sepsis and other complications which are not reversible by dialysis and commonly cause death.

3. These complications may reflect a cumulative injury of many tissues by the same toxic, dialyzable substances that presumably produce the uremic syndrome.

4. Therefore, prophylactic dialysis, applied before uremic symptoms appear, should prevent both the uremic syndrome and many of its commonly lethal sequelae.

MATERIALS AND METHODS

Patients: This report deals with our initial experience in testing this hypothesis in the first 15 patients who were referred to the Renal Center, U. S. Army Surgical Research Unit, for treatment of oliguric acute renal failure, and who could be treated with a series of prophylactic hemodialyses before the nonprotein nitrogen reached 200 mg.%* and obvious symptoms of uremia appeared.† Pertinent data are summarized in table 2 and figures 2, 3, and 4. Twelve of these patients had acute tubular necrosis, six of them following severe trauma; two had bilateral renal cortical necrosis; and one, a four year old boy, had acute poststreptococcal (Group A, type 12) glomerulonephritis. In aggregate, during 398 oliguric days they were treated with 193 dialyses, each lasting approximately six hours, either daily, or often enough to maintain the

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* The initial nonprotein nitrogen was higher in one of the two patients with bilateral renal cortical necrosis; this patient is included, however, because of the unusual amount of information she contributed.
† A preliminary report of initial findings has been published.28

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<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>No. of fatalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swan, Merrill (1953)</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Albright (1954)</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Cubison and Henry (1957)</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>Study group on acute renal failure (1957)</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>Bleecker et al. (1959)</td>
<td>50</td>
<td>25</td>
</tr>
</tbody>
</table>

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**Table 1: Acute Renal Failure—Mortality Rates**

- **No. of patients**: number of patients treated with dialysis.
- **No. of fatalities**: number of deaths among the treated patients.
- **% Fatalities**: percentage of fatalities among the treated patients.

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Six of the 10 reports since 1957 compared "early" or "intensive" dialysis with historical series, and contain firm assertions about improved patient survival, dietary, caloric intake, cerebrovascular control, and improvement in bleeding, less wasting, normalized wound-healing, and easier ambulation. However, only two were prospective studies of concurrent, matched-patient pairs. One of these indicated similar results, the other did not. Two reports attribute an improved morbidity and mortality to the severe underlying injuries and uncontrollable infection beyond influence by dialysis.

My perception over the last 50 years is that high mortality rates in acute renal failure continue to occur in progressively more severely sick patients. It seems that more effective anesthetics and dialysis techniques have served to sustain more patients with previously lethal injuries for referral to our more obliging dialysis units.

Some Consequences of Our Experience with Prophylactic Dialysis: In developing a model of spontaneously reversible acute renal failure in rats, we quantified reversible behavioral deficits in trained mice, performance that paralleled the animal's reversible azotemia. Thus, whole-organism illness behavior in animals, and possibly in humans, might be quantified, including responses to dialysis. These possibilities were first demonstrated in monkeys in which reversible azotemia was induced by uptake, reinfusion, or by nephrectomy with peritoneal dialysis (independent variables) in primates that were operatively conditioned for quantifiable behavioral program, with electroencephalogram (EEG) recording and frequency analysis (independent variables). Similar increases in deficits were found in patients quantified EEG and measures of cognition within the increasing deficits of their progressive, chronic renal failure, followed by measured improvements on multiple diagnosis and after successful renal transplantation. Reduction in the amount of dialysis in 10 patients from a Kt/V of approximately 1.0 to a Kt/V of approximately 0.67, then back to 1.0, produced reversible EEG abnormalities and the regression of slow-wave EEG power versus Kt/V revealed it. The minimum amount of dialysis to prevent EEG abnormalities beyond the control level is a Kt/V of approximately 1.0. Then, development of techniques in conscious, ambulatory rats for chronic peritoneal dialysis and for chronic EEG recording (quantified by power spectrum analysis) allowed us finally to explore the chemical basis of dialysis-reversible uremic illness behavior.

No peer review group really existed at National Institutes of Health for our four applications, and much appreciated...
### Table 2
Clinical Data on Patients Treated with Prophylactic Hemodialysis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Etiology</th>
<th>Post-onset Day of Admission</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>A. Acute Tubular Necrosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>19</td>
<td>M</td>
<td>Heat stroke</td>
<td>3</td>
<td>Survived</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>F</td>
<td>Cardiac arrest and hemorrhage at and after closure of intra-atrial septal defect; vaso-presors for 48 hours postoperatively</td>
<td>4</td>
<td>Survived</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>M</td>
<td>Traumatic rupture of spleen</td>
<td>4</td>
<td>Survived</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>M</td>
<td>Stab wound, left chest, laceration of pulmonary artery</td>
<td>6</td>
<td>Survived</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>M</td>
<td>Carbon tetrachloride poisoning</td>
<td>3</td>
<td>Survived</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>F</td>
<td>Self-induced abortion</td>
<td>5</td>
<td>Survived</td>
</tr>
<tr>
<td>7</td>
<td>21</td>
<td>M</td>
<td>Fractures of ribs, femur, tibia in motorcycle collision</td>
<td>3</td>
<td>Survived</td>
</tr>
<tr>
<td>8</td>
<td>47</td>
<td>F</td>
<td>Hemolytic transfusion reaction</td>
<td>3</td>
<td>Died suddenly with ventricular arrhythmia</td>
</tr>
<tr>
<td>9</td>
<td>35</td>
<td>F</td>
<td>Hemolytic transfusion reaction</td>
<td>2</td>
<td>Survived</td>
</tr>
<tr>
<td>10</td>
<td>37</td>
<td>M</td>
<td>Crushing injury with fractures, both lower legs</td>
<td>4</td>
<td>Survived</td>
</tr>
<tr>
<td>11</td>
<td>27</td>
<td>M</td>
<td>Epigastric shotgun wound, requiring 60% gastrectomy, splenectomy, excision of splenic flexure of the colon, repair of lacerations of small bowel vessels and liver, partial pancreatectomy</td>
<td>3</td>
<td>Died; intracerebral hemorrhage and necrosis; fat embolism</td>
</tr>
<tr>
<td>12</td>
<td>25</td>
<td>M</td>
<td>Multiple arm and leg fractures; auto accident</td>
<td>5</td>
<td>Died following aspiration of gastric contents; total (lt.) and partial (rt.) renal infarction due to renal artery thrombosis; infarcts and lacerations of spleen and liver</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>B. Bilateral Renal Cortical Necrosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>27</td>
<td>F</td>
<td>Abruptio placenta</td>
<td>5</td>
<td>Died; sudden fall in blood pressure</td>
</tr>
<tr>
<td>14</td>
<td>35</td>
<td>F</td>
<td>Abruptio placenta</td>
<td>9</td>
<td>Died; sudden fall in blood pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>C. Acute Glomerulonephritis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>4</td>
<td>M</td>
<td>Pharyngitis due to group A, Type 12 streptococcus</td>
<td>4</td>
<td>Survived</td>
</tr>
</tbody>
</table>

Because much of the clinical response of these patients could not be quantitated, color-sound cinematography was used in some instances to document clinical interviews and examinations.

**Dialysers:** Both MacNeill-Collins § and Travenol || twin-coil dialyzers were used. The dialyzers and circuits were usually assembled, filled with compatible blood and operated by an Army enlisted Clinical Technician (one Technician per patient) under a physician's direct supervision.

**Clinical Management:** The dialyses were used in conjunction with a basic medical regimen which included the following:

1. Fluid intake during oliguria was restricted to from 300 to 400 ml. per day in excess of measured losses. This allowance was frequently liberalized when ultrafiltration during dialysis was used to increase extrarenal fluid losses. During diuresis, *ad libitum* fluid intake was permitted.

2. Each patient selected a diet from the hospital menu, unrestricted in amount or composition, and including protein and potassium-containing foods *ad libitum*. Carbohydrate-fat mixtures were specifically avoided, since a balanced diet might be needed to supply essential nutrients.

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|| Manufactured by Baxter Laboratories, Morton Grove, Illinois.*
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Ambulation was vigorously encouraged between dialyses in patients not confined to bed by associated disease.
4. When present on admission, indwelling urethral catheters were removed and were not used. Blood which would flow spontaneously from the dialyzer and/or that remaining from the initial priming was usually given to the patients during or following each dialysis. The few drugs used were given in reduced, stat doses; antibiotics were given only on specific indication, in doses adjusted according to their probable loss by dialysis.29 Other measures have been well discussed in innumerable publications in this field.

_Chronic Vessel Cannulation:_ The principal requirement of easy and repeated access to the patient's circulation was met by surgically cannulating an artery and a vein (usually the radial artery and the antecubital vein) shortly after admission to the Center. The tapered plastic cannulae remained in place between dialyses, sealed by a short, closed tygon tube or by a threaded nylon fitting with a stopcock through which heparinized saline was instilled at hourly intervals (figure 5). The cannulae were taped to the patient's extremity to permit unencumbered ambulation. Patients were under constant surveillance by members of the enlisted technician-team while the cannulae remained in place.

Regional Heparinisation: In patients with recent bleeding or fresh wounds, only the extracorporeal blood circuit was heparinized.13,30 Syringe driver pumps* were

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* Most recently, we have used Dual Infusion/Withdrawal Pumps, Model 600–910, Harvard Apparatus Company, Inc., Dover, Massachusetts.

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**Fig. 2.** Nonprotein nitrogen and potassium concentrations during oliguria in 15 patients with acute renal failure treated with prophylactic hemodialysis. Points represent the means, and vertical bars span ±1 standard deviation of each sample

\[
\sigma = \sqrt{\frac{\sum Y^2 - (\sum Y)^2/n}{n-1}}
\]

Values on admission to the Renal Center are noted for each patient by (X).

subject to depletion by dialysis; on the other hand, metabolites in excess of needs would be removed by dialysis.

3. Ambulation was vigorously encouraged between dialyses in patients not confined to bed by associated disease.
4. When present on admission, indwelling urethral catheters were removed and were not used. Blood which would flow spontaneously from the dialyzer and/or that remaining from the initial priming was usually given to the patients during or following each dialysis. The few drugs used were given in reduced, stat doses; antibiotics were given only on specific indication, in doses adjusted according to their probable loss by dialysis.29 Other measures have been well discussed in innumerable publications in this field.

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used to infuse calculated† amounts of heparin and protamine through the stopcocks of the arterial and venous cannulae, respectively, to prevent clotting in the dialyzer and to keep the patient's blood clotting time normal (figure 6). At first, heparin concentrations were monitored by a modified thrombin titration31 technic, but more recently, single-tube clotting times, determined on samples aspirated through a rubber cuff on the arterial cannula proximal to the heparin infusion (via the stopcock), have proved to be much simpler, and satisfactorily accurate.

Standard clinical laboratory methods were used for chemical, hematologic and bacteriologic determinations. Blood for chemical determinations was drawn in the morning; the resulting nonprotein nitrogen and potassium concentrations therefore represent peak values on days when dialysis was performed.

RESULTS

Technical: The enlisted technicians developed great skill in assembling dialyzers and circuits and in operating them, in performing the dialyses, in mixing and changing dialysates, and in performing and monitoring regional heparinization and related technical details, under the direct supervision of the physicians and nurses of the Renal Center Staff.

The average nonprotein nitrogen and potassium levels (± one standard deviation) recorded in figure 2 indicate the high degree of chemical control afforded by this procedure. Wide and sudden fluctuations in extracellular osmolality and pH—as, for example, those often brought about by conventional dialysis—were avoided. Such control was more difficult in those patients whose renal failure followed severe trauma, but was ultimately established in them and maintained despite prolonged oliguria.

Single-channel cannulae were usually placed initially in the radial artery and antecubital vein. Anterior tibial

† See Appendix for sample calculation.
arteries were also used, as well as a variety of other superficial veins. The cannulae delivered and accepted an adequate blood flow (75–250 mL/min); among arteries for an approximate average of 10 days (range, from one to 22 days) each, while the average life of a single-channel venous cannula was about seven days (range, from one to 20 days). Averages of 6.1 and 4.3 dialyses were served by the arterial and venous cannulae, respectively. When these cannulae became nonfunctional, surgical cannulation of further vessels, or of the same vessel at a different site, was undertaken. In addition, multichannel cannulae* were also used, and these were usually functioning and not associated with thrombi after from one to three weeks’ use. Insertion of the cannulae on the day prior to dialysis prevented oozing from cutdowns during dialysis, even under total heparinization.

Cultures from the lumen of the sealed cannulae sometimes revealed growth of organisms within a few days of the insertion. The organism recovered in such instances was usually an A. Aerobacter-Klebsiella, suggesting that contamination may have occurred in the process of handling the cannulae. Despite various technical maneuvers designed to eliminate this problem, most—but not all—dialyses in most of these patients were associated with a 30- to 60-minute shaking chill, beginning from 30 to 60 minutes after the start of dialysis, frequently with a rise in

* Fabricated by Cordis Corporation, 241 Northeast 36th Street, Miami 37, Florida.

Fig. 4. Number of dialyses employed prophylactically in 15 patients with acute renal failure.

Fig. 5. Plastic cannulae fitted for chronic vessel cannulation and heparin instillation.
temperature, and a blood culture positive for *Aerobacter-Klebsiella, Pseudomonas aeruginosa, Escherichia coli,* or *Staphylococcus aureus.* This bacteremia abruptly disappeared in the majority of instances; patients usually retained breakfast, and ate the midday meal (both served during dialysis) without further untoward effect. The number of organisms so introduced was apparently small, but it is nevertheless noteworthy that these patients suffered no apparent ill effect from these recurrent and threatening episodes.

Regional heparinization was performed in 66 of these dialyses. With the mechanical pump (see footnote, page 999) the procedure was simple, automatic and free of difficulty. Measured heparin levels usually approximated 10 μg./ml. or more in the dialyzer, and zero in the patient. Clotting times were normal, or were brought to normal by giving additional protamine sulfate intravenously. Although an occasional dialyzer clotted, this occurred no more frequently with regional than with general heparinization, and was rare in either circumstance. No discernible untoward effect resulted from the administration of as much as 550 mg. of heparin and 750 mg. of protamine daily over many days. With these methods, actual or impending hemorrhage seems to be effectively eliminated as a contraindication to hemodialysis.

**Clinical Findings. Mental and Neuromuscular State, Ambulation:** In general, the typical agitated depression, lethargy, drowsiness and twitching of uremia were either absent or barely detectable on admission, nor did these signs appear in the subsequent clinical course. As a rule, these patients remained alert and cooperative (figure 7). No hallucinations, convulsions or abnormalities in behavior occurred, with the exception of case 8, who developed typical (and unexplained) catatonia on her twelfth and thirteenth post-onset days, which vanished as suddenly as it appeared; and of case 10, whose relentlessly downward course to coma and death could be attributed to the extensive intracerebral hemorrhage and necrosis found at autopsy. It is noteworthy that abnormal behavior during oliguria and early diuresis did not occur, although it might have been expected in several instances: case 1 had been hospitalized for schizophrenia, was released one month prior to onset of acute renal failure, and only in the late diuretic phase required further psychiatric treatment; case 4 had stabbed himself; case 5 drank carbon tetrachloride in a suicide attempt; case 6 had attempted a criminal abortion.

These patients played cards, read, watched television, and maintained a sense of humor and an interest in the dialysis procedure, the ward routine and other patients. Cases 5, 7, 10, 11 and 12 were confined to bed largely because of injuries, and acute glomerulonephritis indicated bed-rest for case 15. After from six to eight weeks of oliguria, the patients with renal cortical necrosis preferred to stay in bed and complained of weakness. The remaining patients were able to ambulate between dialyses, despite continuing oliguria. Clinical crises, previously so common, especially at night, occurred only rarely in some patients and not at all in others.

However, on close observation after one or more dialyses, or on comparison of color-sound motion picture films documenting a series of clinical interviews, alert patients became even more alert after one or more dialyses, and subtle neuromuscular hyperactivity disappeared. In tests involving simple mental arithmetic (e.g., serial subtraction of seven from 100), seemingly alert patients were often unable to perform normally. Until tested, the patients themselves were apparently unaware of any such incapacity; they were usually surprised, and in one instance alarmed, at the discovery. This deficit persisted even in alert patients, but gradually improved during oliguria, presumably by virtue of practice, the effects of dialysis, general clinical improvement, or a combination of these.

**Appetite, Thirst, Diet, Gastrointestinal Function:** In general, patients having anorexia, nausea or marked thirst on admission experienced a return of appetite and less thirst following successive dialyses. Vomiting had occurred at least once prior to admission in most patients, in spite of low levels of azotemia, perhaps partly as an effect of the inciting episode; other patients did not vomit at all. Because unutilized metabolites could be removed by dialysis as they accumulated, patients were permitted an unrestricted selection from the hospital menu; between-meal feedings were encouraged. Protein-free, low-potassium carbohydrate-fat mixtures were specifically avoided, in the belief that a balanced diet would be needed to supply essential nutrients which might be depleted by dialysis. The estimated daily food intake provided between 1,000 and 3,500 calories and between 30 and 75 gm. of protein. Parenteral feeding was unnecessary except in case 5 (jaundice and vomiting due to hepatic injury), case 10 (progressive coma), and case 11 (during resolution of postsurgical ileus). Fluid intake could frequently be liberalized by means of ultrafiltration with dialysis, and this technic was used more often when
patients stated that they could eat more solid food if they had more fluid to drink. Vomiting also occasionally occurred in several patients later in the clinical course, e.g., with dialysis during episodes of chills, and (in case 7) prior to amputation of the lower leg, rendered necrotic by failure of a popliteal arterial graft. Diet was modified and partly limited by the gastrectomy and recurrent bouts of partial intestinal obstruction in case 11.

Mouth care, including brushing the teeth, irrigating all corners of the mouth, inspecting teeth and gums for adherent material, oil or ointment application to lips, every two to four hours, seemed decisive in avoiding or healing oral lesions in patients so treated. Improved nutrition and increased fluid intake may have contributed. Nevertheless, suppurative parotitis complicated the course in cases 5 and 6. Bowel function in most patients was normal except, as expected, in the first few post-onset days. Diarrhea of undetermined etiology occurred in case 14 in the latter weeks of hospitalization. Melena, hematemesis and “uremic colitis” did not occur.

Body Weight Changes: Despite the improved nutrition and high vitamin intake in these patients, weight loss was the rule. As expected, it proceeded more rapidly in the patients with continuing infection and tissue necrosis (e.g., an average of 0.4 to 0.6 Kg./day during oliguria in cases 7 and 11) than in the nontraumatized patients or those without residual, unhealed wounds (average, 0.12; range, 0.0 to 0.26 Kg./day). Associated liver injury may have favored the weight loss in case 5 (average, 0.26 Kg./day). Weight loss did not seem greater than could be reasonably anticipated in patients without renal failure hospitalized for similar illness or injury.

Resistance to Infection; Wound-healing: Both survivors and fatalities were conspicuously free of significant infection. “Uremic pneumonitis” did not occur. The tissue of the midportion of the epigastric laparotomy wound in case 11 (figure 8) was injured in the initial shotgun blast. Necrosis with infection resulted in a slow dehiscence of this part of the incision. However, the underlying intestine became adherent, and infection subsided. Stab wounds through which drains had extended into the pancreatic bed continued to drain purulent material, but these became shallower; by the time of discharge, on the seventieth hospital day, they had become narrow channels extending 3 to 4 cm. into the abdomen. Generalized peritonitis did not occur. The episodes of bacteremia during dialysis appeared to be self-limited, and did not progress to the clinical picture of septicemia. Except for aspiration pneumonia in case 12, the three patients with acute tubular necrosis and the two with bilateral renal cortical necrosis who died were free of infection at autopsy. Cutdown wounds rarely became infected, even those performed on cases 13 and 14 after 10 or more weeks of oliguria. Like other wounds in these patients, they also healed well. The wound in figure 8 (nineteenth post-onset day) shows clear evidence of healing and of granulation tissue formation, despite the fact that urinary output had averaged 72 ml. per day for the
preceding 15 days, and that the patient would excrete 1,000 ml. in 24 hours for the first time nine days later. The thoracotomy wound in case 4 is also shown (figure 9) 16 days following onset of renal failure with oliguria lasting 13 days. Wounds of amputation (case 7) and fasciotomy for relief of pressure of a hematoma (case 5) also healed well.

Hematology and Bleeding: During the first seven to 10 days of the oliguric phase, all of these patients became anemic, with individual hematocrits ranging as low (on one day) as 12%. Return toward normal occurred in late diuresis, the lowest hematocrit values being recorded in early diuresis. Anemia persisted despite the transfusion of 200 to 300 ml. of blood at the end of most dialyses. These transfusions consisted of the sedimented erythrocytes left over from priming the dialyzer circuit, and the blood which would flow spontaneously from the dialyzer and circuit. Studies of erythrocyte survival were not attempted because of frequent dialysis and transfusion; however, supernatant plasma of postdialysis samples revealed hemolysis on only one occasion. Figure 10 depicts the mean and range of hematocrit and reticulocyte counts in these patients in oliguria, before the “day of diuresis” and after it. Reticulocyte counts were generally highest when hematocrit and hemoglobin levels were lowest, and occasionally reached high levels, e.g., 9.6, 7.7, 8.0 and 7.2% in cases 2, 5, 7 and 13, respectively.

When dialysis was performed several hours after cannulation, bleeding from cutdown sites did not occur, even under general heparinization. This may have been a factor in the subsequent improved healing of these wounds. A spontaneous hemorrhage into the muscle and fascial spaces of the thigh occurred in case 5 despite regional heparinization. This was thought to follow a femoral venipuncture, but fasciotomy with exploration showed that the hematoma did not extend to the inguinal region; the exact explanation for the hemorrhage remains in doubt. The intracerebral hemorrhage in case 10 occurred despite adequately controlled regional heparinization; whether the dialysis procedures accelerated bleeding is not known. No other significant bleeding occurred. In the treatment of case 15, complement and globulin-free blood was used to fill the dialyzer and for other transfusions on all but one occasion. Washed, compatible erythrocytes were suspended in 5% human albumin in saline. This technic presumably avoided the transfusion of globulin and complement which could possibly continue or augment glomerular injury, as suggested by Schreiner.22

Mortality: Cases 8, 10 and 12 with acute tubular necrosis died during oliguria of 26, 11 and seven days’ duration, respectively. Autopsy was unrevealing in case 8, but revealed lesions adequate to explain the deaths of cases 10 and 12 (table 2). The portions of the right kidney in case 12 not involved in infarction revealed evidence of tubular necrosis. Cases 13 and 14 had complete atrophy of renal cortices after 73 and 92 days of oliguria, respectively. Both rapidly developed severe and unexplained metabolic acidosis prior to death, and died in shock unresponsive to adrenal steroids, vasopressors, etc. The autopsies failed to reveal obvious causes of death. The anterior pituitary in case 13 was necrotic, but this lesion was not found in case 14. Tissues were grossly in good condition.

DISCUSSION

The basis of this investigation is the conviction that the sickness of uremia may be caused in some way by a retention of dialyzable substances which interfere with the function of many cells and tissues. The clinical course of such sick uremic patients often suggests that, beyond a point, such potentially reversible chemical derangement may begin to do some fundamental damage which is no longer reversible by dialysis, and which is manifested clinically by such apparently irreversible phenomena as collapse of resistance to infection, progressive wasting, and failure of wound healing. Since certain of the manifestations of acute uremia in patients with acute renal failure such as nausea, vomiting and drowsiness, could be readily reversed by dialysis, the prophylactic use of dialysis, before clinical or chemical derangements became marked, might be expected to prevent other,
Other findings usually associated with symptomatic acute renal failure remained in some or all of these patients, despite their obvious general clinical health: (1) subtle deficits in certain mental processes persisted, though with improvement, in patients who seemed otherwise alert; (2) a loss in body weight continued at varying rates into late diuresis, despite the improved food intake; and (3) anemia occurred in spite of reticulocytosis, commonly reaching hemoglobin levels of 7 gm.% (hematocrit levels of 20%) in late oliguria and early diuresis. In addition, transient bacteremia with fever and chills occurred in some patients within an hour of the beginning of dialysis, possibly because of contamination of the indwelling cannulae. During this treatment, three patients with presumably reversible acute tubular necrosis died in oliguria, of intercurrent or underlying significant disease.

The persistence of these abnormalities suggests that not all of the manifestations of uremia are directly related to toxic substances which are dialyzable through cellophane. Thus it may be that a hemolytic process continues to contribute to the anemia of uremia and remains decisive even though a reticulocytosis occurs which indicates at least a partial release of bone marrow suppression. Persisting subtle mental deficits in alert patients, like the continuous loss of body weight, may indicate variable sensitivity of the brain or of anabolic processes in many tissues to the several chemical abnormalities of uremia. In any event, this experience obviously forms an insufficient basis for any final statement at this time; however, as indicated in the introduction, the repeated, generally stable or "uphill" clinical course of these patients contrasts markedly with our past experience in treating patients with acute renal failure, either without dialysis, or with dialysis on conventional indications.

The concept of prophylactic dialysis may be considered to be a logical extrapolation of the observations and recommendations of Anthonisen, Salisbury, Scribner and others, that a smoother clinical course and better prognosis are apparent consequences of "earlier" dialysis, namely, the application of dialysis before the patients are severely uremic or preterminal; dialysis is usually useless as a "last resort." Similar findings were reported by Houck in terms of fewer uremic symptoms and longer survival in bilaterally nephrectomized dogs when dialysis was begun within 20 hours of surgery, and performed three times daily in the first week and twice daily thereafter. Scribner has also recently reported his initial experiences with continuous dialysis, by which patients are connected to the dialyzer throughout each 24-hour period through the beginning of diuresis. This technic appears to be a further extension of the hypothesis and the technics invoked in the present study. In our opinion, continuous dialysis, like the foregoing technics, should receive more extensive application to determine whether further advantages accrue to patients so treated.

While there is increasing recognition of the value of earlier dialysis, the published consensus, and the practice in many centers at present, is still to apply dialysis to
relatively ill rather than to relatively healthy patients. This is implied by the usually quoted indications for dialysis, namely, definite or progressive clinical uremic illness and/or progressive potassium intoxication, occurring despite careful suppressive therapy.7-15 In many of these reports, the recorded, relatively high predialysis levels of azotemia11,38 clearly indicate the extent of chemical deterioration and, inferentially, of clinical deterioration which is imposed by the conventional indications for dialysis.

Certain effects of such conventional dialysis have been suggested, particularly in acute renal failure following trauma. Some reduction in mortality may be achieved, but this is not conclusively demonstrated.20 All series include patients who could not possibly have survived without dialysis treatment.15,39 The clinical course may be smoother. Fatalities live longer, and a larger percentage of them therefore tend to die in diuresis rather than in oliguria. But when death due to potassium intoxication is avoided, other complications and apparent causes of death, such as sepsis, wasting and impaired wound healing, seem to occur more frequently.

Opinion persists, however that acute renal failure is essentially a benign disease, responsive to careful medical management in the absence of complications.7-9 With such management, it is estimated that both morbidity and mortality should be very low and, in the absence of "lethal complications," should approach zero.9 The data in table 1, from centers where dialysis is readily available and frequently performed, belie these confident assertions. The reasons for this remarkable divergence between data and opinion are also pertinent to whether the results of prophylactic hemodialysis constitute a real contrast with, and improvement over, past experience. This judgment for each physician will depend largely on his own past experience and appreciation of clinical acute renal failure. The issue is extremely difficult to resolve objectively because (1) no two physicians are likely to see the same proportion of patients with "uncomplicated" acute renal failure; (2) there is a wide variation in severity between patients and between etiologic groups,7-9,20 and hence between physicians' personal impressions of the disease; (3) most large series of carefully studied patients come from centers to which they have been referred as possible candidates for dialysis; (4) similar data are not available on patients not so referred; and (5) some physicians tend to eliminate such patients, as Bluemle has stated, "this treatment would have been superfluous." We would urge that dialyses applied to patients who might otherwise survive should not under any circumstances be considered to be superfluous. Rather, the judgment of whether to undertake dialysis should also be made in have played in such events. Mortality statistics "corrected" by eliminating such patients, as Bluemle has stated, "ignore the detrimental influence which uremia may exert on the patient's potential for recovery from any illness or complication. They further tend to give a false basis for evaluating prognosis in any given case."20 In any event, it is difficult to explain the relatively high frequency of wasting or generalized sepsis (due to organisms which normally inhabit the skin, or the gastrointestinal or respiratory tracts) in patients whose renal failure follows nephrotoxic poisoning, hemolytic transfusion reaction or obstetric accidents. On the face of it, little in these etiologic settings seems to justify the incidence of complications, and the recorded 25 to 40% mortality which occurs at least among patients at Renal Centers who develop conventional indications for dialysis. In other words, "uncomplicated" acute renal failure with its favorable prognosis may be relatively uncommon. Conversely, perhaps some of the "complications" are properly a part of the uremic syndrome, which may be preventable but not treatable by dialysis; our hypothesis is partly based on this intriguing idea.

Further objection to prophylactic dialysis may be based on the occurrence in all series of survivors even from prolonged oliguria or from severe post-traumatic renal insufficiency after many dialyses on conventional indications.15,39 It should be noted, however, that such survivors tend to be the exception rather than the rule; one objective of prophylactic dialysis is to establish the reverse situation as the norm for these patients.

Again, objection to dialysis of any sort is often raised in the case of the mild instance of acute renal failure in which the patient accumulates nitrogen and potassium very slowly, maintains a moderate oliguria of 150 to 300 ml./24 hours, enters into diuresis in less than two weeks, and experiences only lethargy, nausea and vomiting. Certainly, dialysis hardly seems indicated in such instances. However, it should be noted that this situation may be relatively uncommon (as it is in our experience), and that the description is retrospective. It is most difficult—if not impossible—to predict such a mild course for any patient. Generally the smoothness of the clinical course and the fact of survival are known only at the end of the clinical course, and not at the beginning. In contrast, we have been impressed by the number of patients with nephrotoxic injuries, obstetric accidents or transfusion reactions who "should have had" a benign course but who died, often in the diuretic phase, even after oliguria of relatively short duration. A related example is given by Salisbury,14 in analyzing which of the previous patients in his series might have received dialysis treatment under a new policy of earlier dialysis. He found six patients who would have received dialysis treatment under the new criteria, but who in fact recovered without the use of the artificial kidney, and he concluded that "this treatment would have been superfluous."
view of possible risks in not employing this procedure. We would question both the wisdom and the safety of subjecting patients to several days of avoidable nausea, vomiting, drowsiness and thirst, which not only implies significant discomfort to the patient but may also impose considerable risk of aspiration, pneumonia and other unexpected “complications.”

At present we suggest that hemodialysis should be applied prophylactically in patients with acute renal failure before the nonprotein nitrogen reaches 150 mg.%, (blood urea nitrogen, 120 mg.%), however mild the clinical course may seem. This arbitrary choice of a level of azotemia does not imply that it is the figure of choice, or that the toxic substance(s) mentioned in the hypothesis is measured by or necessarily varies with nonprotein nitrogen concentration; subsequent experience may show that prophylactic dialysis is better applied at lower or higher levels of nonprotein nitrogen or other chemical parameter. With regional heparinization, there are no known contraindications to this technic. Present requirements for the procedure include at least one trained technician or nurse for each dialysis to be performed at any one time, operating under a trained physician’s direction. While it is obviously wise for a physician to supervise the start of dialysis when the circuit is connected to the patient and blood flow is begun, he is not otherwise needed, in most instances, for the technical conduct of these procedures. His function is rather to stand by for necessary clinical decisions or for possible emergencies.

Any dialyzer may be used for this technic. It seems obvious, however, that instruments featuring a low cost per dialysis and a small requirement for banked blood would be particularly advantageous for frequent or daily use. In our hands, the MacNeill-Collins dialyzer has been found to satisfy these requirements.

Furthermore, this technic is applicable to small children, as demonstrated by case 15, who was four years old. It is also possible that peritoneal dialysis might be used prophylactically. More experience is needed, however, before its application can be defined in patients with post-traumatic renal insufficiency, with and without recent abdominal wounding or surgery.

It is evident that frequent dialysis implies an organized, disciplined and well supported team of trained physicians, nurses and technicians. Even more important is the executive resolve to carry out management, including dialysis, on a systematic, routine basis, without allowing inertia in the face of a somewhat complex dialysis procedure to result in procrastination and delay. The relative rarity of these patients suggests that prophylactic dialysis should not be attempted in every hospital. Rather, as Strauss has suggested, the patients should be concentrated at Renal Centers serving populations of several millions each; adequate financing and communication should be sought for them. Such concentration affords the further priceless opportunity for careful clinical study and investigation of this disease, and hence for improving treatment further. Certainly, without a concentration of patients there can be no such opportunity.

**Summary**

Prophylactic hemodialysis has been employed in the treatment of 15 patients with acute renal failure due to acute tubular necrosis (12), bilateral renal cortical necrosis (two), and poststreptococcal glomerulonephritis (one). Dialyses, usually lasting six hours each, were begun before clinical evidence of uremia developed in each patient and/or before the nonprotein nitrogen reached 200 mg.%, and were repeated daily or often enough to maintain the nonprotein nitrogen below 150 mg.%. The hypothesis underlying this technic postulates (1) that wasting, sepsis and impaired wound healing in these patients may reflect tissue injury by the same dialyzable toxic agents which produce the uremic symptoms that are readily reversible by dialysis, and (2) that repeated dialyses should therefore prevent both clinical uremia and the later, often lethal sequelae.

The results contrast dramatically with our own past experience in treating patients with acute renal failure with a carefully executed medical regimen together with hemodialysis on conventional indications. Except in one instance of crush injury with progressive intracerebral damage, and one brief occasion in another individual, these patients experienced a stable, convalescent clinical course, remained free of uremic symptoms or chemical imbalances, ate at least three meals daily which were unrestricted in amount and composition, and were ambulatory between dialyses unless confined to bed by associated disease. Wounds healed well. Infection either did not occur, or subsided after appropriate therapy. Fluid restriction was liberalized by means of ultrafiltration with dialysis. Regional heparinization of only the extracorporeal circuit eliminated actual or impending bleeding as a contraindication to dialysis. Chronic vessel cannulation made the frequent dialyses possible, but may have provided the route for repeated, transient bacterial contamination of the blood stream in the first hour of many dialyses. Marked anemia, despite reticulocytosis, moderate to mild weight loss and some mental deficit persisted in spite of the general clinical improvement and well-being. Three patients with tubular necrosis died after seven, 11 and 26 days of oliguria; both patients with bilateral renal cortical necrosis also succumbed, on the seventy-third and ninety-second days of renal failure, and after 29 and 40 dialyses, respectively. At autopsy, evidence of sepsis was conspicuously absent. The remaining 10 patients survived. Thus some, but not all, clinical manifestations of acute renal failure appear to be favorably influenced by prophylactic dialysis treatment.

Our initial experience in this group of 15 patients does not of course prove that freedom from complications and a significantly better outlook for survival can be assured to patients with acute renal failure by these methods. However, it seems to offer a reasonable hope of this possibility which we cannot attach to management by medical measures alone, or by dialysis on conventional indications. If this hope is realized in greatly extended, subsequent series, then it seems inevitable that some
form of prophylactic dialysis, or some equally effective alternative, should be adopted in treating the majority of patients with acute renal failure.

APPENDIX

Regional Heparinization: Sample Calculation of Heparin and Protamine Dilutions

1. Heparin

Anticipated extracorporeal blood flow rate = 150 ml./min.

Desired extracorporeal blood heparin concentration = 10 µg./ml. × 150 × 10 = 1,500 µg./min. or 1.5 mg. heparin/min.

Position 7 on Infusion Pump with 50 ml. syringe delivers 0.382 ml/min.

0.382 ml/min. concentration

1.5 mg./min. = final heparin concentration

(10 mg./ml.) × (X ml.) = (3.93 mg./ml.)

(50 ml.)

X = 19.6 ml. of commercial heparin, qs. ad.

50 ml. in the syringe with sterile, isotonic saline.

2. Protamine

Assume a protamine SO₄ requirement of 1.33 mg./mg. of heparin.

X = 19.6 ml. (196 mg.) of heparin require 1.33 × 19.6 = 261 mg. or 26.1 ml. of protamine (also at 10 mg./ml. concentration for neutralization. This is also diluted qs. ad. 50 ml. in the syringe with sterile, isotonic saline.

References


* Concentration of commercial heparin.
† Volume of syringe to be used.


25. Proceedings (unpublished), Study Group on Acute Renal Failure, held at U. S. Army Surgical Research Unit, Brooke Army Medical Center, Fort Sam Houston, Texas, October 14–16, 1957.


