HEMODIALYSIS, PERITONEAL DIALYSIS, AND RELATED THERAPIES
FOR RENAL DIALYSIS AND THE ELDERLY/TECHNOLOGY
Contract #533-5850.0.

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A. BACKGROUND AND HISTORY

1. Hemodialysis

Thomas Graham, one of the early scientists to work in the area of colloid chemistry, was the first to show that colloids would pass through a semipermeable membrane while colloids did not, and named this process "dialysis" (1). However, it was not until 1913 that Abel, Rowntree, and Turner developed the first artificial kidney which was used for removal of solutes from the blood of experimental animals through a semipermeable membrane (2). The membrane consisted of celloidin tubes, the dialysate was saline or artificial serum, and the animal's blood was anticoagulated with hirudin obtained by crushing the heads of leeches. It is interesting that Abel and his co-workers suggested flattening of the celloidin tubes to increase their efficiency, reminiscent of present-day coil dialyzers, and noted that very small tubes "would undoubtedly prove valuable," thus predicting hollow fiber dialyzers. Abel and his colleagues carried out a series of experiments, developed a number of pieces of apparatus, and were interested in the possibility of using their new invention, which they had named an "artificial kidney," in humans (3). Nevertheless, the first human dialysis was not performed until 1924 by Georg Haas in Germany (4) using celloidin dialyzing tubes and hirudin as anticoagulant in what was essentially a larger version of the Abel, Rowntree and Turner device (5).

Over the next few years two important developments made dialysis of humans more feasible. First was the production of purified heparin as anticoagulant, and the second was development of a
commercially available cellophane membrane. As a result, in 1937 Thalhimer constructed a dialyzer similar to the Abel dialyzer using cellophane and heparin, and used this experimentally in dogs (6). However, the surface area was not sufficient and he did not pursue this further.

The first practical artificial kidney was developed by Kolff in Kampen, Holland, during the second world war. Kolff's dialyzer was a cylindrical drum on which was wound a 30-40m length of cellophane sausage tubing which was perfused with the patient's blood through a rotating coupling that was based on the Ford automobile water pump. The lower half of the rotating drum was immersed in a stationary tank containing a large volume of dialysis fluid. Blood was propelled through the tubing by rotation of the drum so that a blood pump was not required. Kolff attempted his first human dialysis in February 1943 but the patient died (7). A number of technical difficulties had to be overcome such as membrane leaks, hemolysis, blood line disconnections and hemorrhages; but Kolff and his colleagues continued their efforts, concentrating on treating patients with acute reversible renal failure. However, it was not until their 17th patient was treated in 1945 that one survived who clearly owed their life to treatment with the artificial kidney (8). Following the second world war, Kolff rotating drum machines were sent to London, New York, Montreal, Amsterdam, and Poland. Meanwhile, Murray and co-workers in Toronto had also developed an artificial kidney which was first used in 1946 (9). The Kolff machine was
modified at the Peter Bent Brigham Hospital in Boston (10) and was used in a number of centers around the world to treat acute renal failure.

Other dialyzers were developed following the second world war. Alwall in Sweden devised a stationary upright drum dialyzer which was the precursor of coil dialyzers (11), but the prototype of the present-day coil dialyzer was developed in 1953 by Inouye and Engleberg in Philadelphia (12,13). This used cellophane tubing wound in a helix around a stainless steel core, with plastic mesh acting as a spacer. The coil, with a surface area of 0.9m², was placed in a pressure cooker through which dialysis fluid was recirculated from a 50L tank. Blood was circulated with or without a blood pump, and ultrafiltration was regulated by controlling the rate at which dialyzing fluid was drawn into the dialyzer by a water pump. This was the model for the "twin coil kidney" developed by Kolff and Watschinger (14,15) and which was eventually produced commercially by Travenol Laboratories in the United States, gained rapid popularity, and was very widely used in the 1950's and 1960's. Its disadvantages were that it required a blood pump, had a high blood pressure in the extracorporeal circuit, required priming with blood before dialysis, and used a large open tank of dialysis fluid which could easily become contaminated.

Other dialyzers were developed during these years. MacNeill and co-workers in Buffalo devised a dialyzer using short lengths of flattened cellophane tube which was the prototype of parallel flow dialyzers (16,17), and Skeggs and Leonard at Western Reserve developed
a similar dialyzer (18,19). This latter used the countercurrent principle in which dialyzing fluid passed through the dialyzer in the opposite direction to the blood.

Throughout the 1950's and early 1960's dialysis was used primarily for the treatment of acute renal failure, and while a number of units continued to use variations of the original Kolff rotating drum machine, the availability of the twin coil artificial kidney enabled the spread of dialysis to many new centers. Interest increased because during the Korean war dialysis had proved invaluable in the management of military personnel with traumatic acute renal failure (10).

Blood Access and the Development of Chronic Maintenance Dialysis

Originally, hemodialysis required multiple arterial and venous cut-downs, one of each for each dialysis. Alwall attempted to obviate this by the use of siliconized glass tubes which were joined together between dialysis treatments by a narrow glass capillary (20). Heparin was injected into the tubing, but this approach was abandoned because of frequent clotting and local infection (21). The era of modern dialysis stems from development of the teflon arteriovenous shunt by Scribner and co-workers in Seattle (22), the first of which was implanted in March 1960. Two cannulae, made from thin-walled teflon tubing with tapered ends, were inserted into the radial artery and cephalic vein near the wrist and bent through a 180° turn before passing through the skin. Between dialyses the
external ends were connected to a curved teflon bypass tube using
two Swagelock couplings fixed on a stainless steel arm plate.
Because the rigidity of the teflon tubing caused mechanical damage
to the vessel walls, this shunt was modified when flexible silastic
tubing became available (23), and eventually a silastic shunt system
with a single break joined by a single short teflon connector and
with teflon vessel tips was developed (24). This, the "Scribner
shunt," and its various modifications became widely used throughout
the world during the 1960's (25).

At the same time as the development of the shunt, Scribner and
his colleagues developed a new dialysis system for use with patients
with chronic renal failure. This originally evolved from a system
to treat acute renal failure with continuous low-flow dialysis
using using a low resistance dialyzer to make a blood pump unneces-
sary and a large volume of dialysis fluid which was cooled in order
to minimize bacterial proliferation. Originally a Skeggs-Leonard
dialyzer was used, but in 1960 a device originally developed as a
blood oxygenator began to be used for dialysis, the Kiil dialyzer
(26,27). The Kiil dialyzer was modified to reduce its blood volume,
and a different cellophane, Cuprophan, was used as the membrane.
The first patient, Clyde Shields, started treatment in March 1960
and lived for 11 years on maintenance dialysis, dying in 1971, aged
50, from a myocardial infarction. Of the two other patients who
started treatment at the same time, one is still alive 25 years
later, having had a living-related donor transplant in 1968. As a
result of the success of this new treatment for chronic renal failure,
the Seattle Artificial Kidney Center was developed as the first outpatient community dialysis center. This was the first dialysis unit to be situated outside a hospital and the first unit in which dialysis was carried out primarily by nurses and not by physicians (28).

Further modifications of the dialysis system were made in Seattle, including the use of a single pass dialysate circuit in order to improve efficiency and reduce bacterial counts. Efforts also led to automation of the fluid supply system based on development of a system using a concentrated solution of electrolytes and dextrose which was diluted with tap water by means of an accurate proportioning pump system. This concentrated dialysate required the substitution of acetate for bicarbonate to avoid precipitation (29). A central dialysis system based on proportioning was built in Seattle to treat 15 patients using dialysate concentrate diluted 1:34 (31). It was while these developments were occurring that the Seattle Artificial Kidney Center developed its committee to select patients for this expensive and unusual treatment (28,31).

**Home Hemodialysis**

The next step in reducing the cost of hemodialysis was to move it to the home. Apparently, the first home dialysis was carried out in Japan in 1961 (32), but home dialysis as we know it today was introduced in 1964 in Boston (33), London (34), and Seattle (35). Besides being less expensive, home dialysis was also found to be
better for many patients in terms of increasing independence and the opportunity for rehabilitation (36). The Seattle group developed a modification of the proportioning system which became the standard for single patient dialysis systems (34). This system included several monitors and alarms with the intention of making overnight dialysis in the home a safe procedure to be carried out by patient and family member.

The Arteriovenous Fistula

While the Scribner shunt had made maintenance dialysis possible, problems with clotting, infections, and the need to replace the shunt plagued most patients. This was resolved in 1966 with the development of a surgically created arteriovenous fistula by Brescia and colleagues (37) which rapidly became the standard form of access for hemodialysis. Following this, for patients whose own veins are not suitable for development of an arteriovenous fistula, various grafts have been developed (38,39,40), but it is still true to say in 1985 that the "native" arteriovenous fistula remains the gold standard of blood access. Consequently one of the most important measures in the management of patients with chronic renal failure before they require dialysis is preservation of the forearm vessels so these can be used for development of a fistula when required (41).
The Square Meter-Hour and Middle Molecule Hypotheses

The Seattle group was also involved in the early development of intermittent peritoneal dialysis (see below). Quite early on, Scribner noted that patients treated by chronic peritoneal dialysis were often underdialyzed in terms of blood chemistry but nevertheless did not show evidence of peripheral neuropathy, or if this was present when they started dialysis it did not progress (42). He suggested that the peritoneal membrane was more permeable than cellulose membranes and that peritoneal dialysis removed more of substances with a higher molecular weight than did hemodialysis. This led to the suspicion that so-called "middle molecules" might play an important role in the toxicity of uremia, and the hypothesis that for a given membrane prevention of peripheral neuropathy depends on a minimum number of hours of dialysis per week rather than on maintenance of specific blood levels of urea and creatinine. This, the square meter-hour hypothesis (43,44) and its modification, the middle molecule hypothesis (45), suggested that inadequate removal of middle molecules (molecular weight between 300 and 2,000 daltons) may be the cause of complications such as peripheral neuropathy and pericarditis. Since removal of middle molecules through a conventional hemodialysis membrane is slow, the diffusion gradient remains high throughout the dialysis, unlike the situation with small molecules. Thus the net removal rate for middle molecules remains constant during a protracted dialysis, and net removal is proportional to the total hours per week of hemodialysis, unlike
small molecules which have flow-dependent removal that decreases with the decreasing plasma concentration as dialysis proceeds.

These hypotheses had a major effect on dialysis equipment and strategies, even though the isolation, identification and toxicology of middle molecules remains clouded in uncertainty (46). However, they led to shortening of dialysis schedules using larger surface area dialyzers or increased frequency of dialysis, usually with less total dialysis hours per week. With the development of hollow fiber dialyzers using cellophane, Cuprophan and other membranes, large surface area dialyzers have become widely used during the 1970's with shorter dialysis times. Scribner and his colleagues also noted the importance of residual renal function with a short dialysis schedule, and its contribution to the removal of middle molecules (47,48). Residual kidney function should be measured and taken into account in planning short dialysis schedules (49). Average dialysis time has decreased by more than 50% between 1968 and 1978 (50).

The Redy System

Hemodialysis generally uses a large volume of water which must be pretreated, and requires access to a water supply and a drain. This interferes with portability. Consequently, efforts have been made to reuse dialysis fluid, and Gordon et al (51,52) developed a system to continuously regenerate a small volume (5.5L) of dialysate using a multilayer disposable cartridge containing urease, zirconium resins, and activated carbon. This, the Redy system, has been
available for some 15 years, and is relatively portable and can be used by dialysis patients who wish to travel. This interesting approach to dialysis has not been as widely used as might have been anticipated because of the large amount of supplies and accessories that have to be carried, and because the equipment itself has some disadvantages (53).

**Sequential Ultrafiltration**

During hemodialysis fluid is removed by ultrafiltration, usually in present-day machines by application of a negative pressure to the dialysate compartment. During dialysis, episodes of hypotension, muscle cramps, and other symptoms are common, particularly when a large volume of fluid is removed during a short dialysis. Bergstrom et al (54) were the first to observe that rapid ultrafiltration was better tolerated when performed without simultaneous dialysis by applying negative pressure while the dialysate bypassed the dialyzer. This process, sequential ultrafiltration, allowed the removal of as much as 4L of fluid in an hour, and could be followed by dialysis without producing a significant adverse effect on blood pressure (55-57).

**Bicarbonate vs. Acetate**

As noted earlier, the development of a dialysate proportioning system required the use of sodium acetate rather than sodium bicarbonate in order to produce concentrated dialysis fluid (29). This
was necessary in order to prevent precipitation of calcium carbonate. In recent years it has become apparent that many patients with acute renal failure and some sick patients with chronic renal failure may accumulate acetate in the blood and tissues during rapid large surface area dialysis, leading to acetate toxicity with vascular instability and hypotension (58,59). Similar undesirable side effects occur in other chronic renal failure patients dialyzed with large surface area dialyzers, particularly those who metabolize acetate slowly (60). Not only is the rapid infusion of acetate and the inability to metabolize it quickly a problem, but simultaneous loss of bicarbonate occurs from the blood through the dialyzer. It has been shown that use of bicarbonate dialysate frequently will relieve these symptoms (61) and consequently bicarbonate dialysis is being used more widely, this despite the fact that the equipment is somewhat more complicated and the dialysis is slightly more expensive.

Dialyzer Reuse

Dialyzer reuse was first developed in 1964 by Shaldon et al who refrigerated twin coil dialyzers and their tubing sets, together with the contained blood, between dialyses (62). In 1967 Pollard et al in Seattle developed a technique for reuse of the Kiil dialyzer--a flat plate, nondisposable dialyzer (63). This technique allowed patients to put together their dialyzer and reuse it for as many as six dialyses. After dialysis the dialyzer was rinsed, cleaned with bleach, and sterilized using formaldehyde. With availability of
cheap disposable dialyzers, dialyzer reuse continued to be practiced at only a small number of centers, but with reduction in federal funding dialyzer reuse has again become important.

Dialyzer reuse is a safe procedure when carried out properly (64) but has been perceived by some patients as a means by which facilities may make money, and so during the late 1970's there was a strong patient movement against dialyzer reuse in the United States. This continues, but nevertheless more than 60% of patients in this country now are treated with reused dialyzers.

2. Peritoneal Dialysis

Peritoneal lavage was first described by the Reverend Steven Hales in 1744 (65), but it was not until 1877 that Wegner perfused the abdominal cavity of rabbits with a cold saline solution and observed a decrease in temperature (66). He went on to note an increase in the volume when concentrated sugar solutions or glycerol were placed in the abdominal cavity. A number of other studies on changes in outflow volume with solutions of different concentrations were reported over the next 40 years, but it was not until 1918 that the ability of the peritoneum to absorb fluid was first used clinically to treat children with gastrointestinal problems that prevented oral intake (67). Throughout the 1920's and 1930's studies were made on the diffusion of substances across the peritoneal membrane and the effect on blood levels, the mechanism for the increased outflow volume using hypertonic glucose, and the effect of vasodilatation and vasoconstriction on diffusion (68).
The first use of peritoneal dialysis to remove uremic toxins was by Ganter in 1923 in animals made uremic by ureteric ligation (68). He was also the first to report the use of peritoneal dialysis in the human, studying the effects of a physiological saline solution introduced intraperitoneally in a patient with ureteral obstruction due to uterine carcinoma, noting that her clinical condition showed slight improvement. Peritoneal dialysis was used clinically in a few patients during the 1930's, but the next major step was the publication of a report on the use of peritoneal dialysis in acute renal failure by Fine et al in 1946 (69). By 1950 there were reports on more than 101 patients treated by either intermittent or continuous peritoneal dialysis (70), and in the next 10 years peritoneal dialysis was used more widely for treatment of acute renal failure in adults and children, and to treat hypercalcemia and various poisonings.

Early Peritoneal Access Devices

Peritoneal access, originally achieved by means of a trochar and cannula, was a problem for repeated peritoneal dialysis. In the early 1960's there was intensive study of methods for repeated access, and various indwelling "buttons" and other devices were developed. Leakage and obstruction were serious problems, and generally these devices were not successful because of flow problems and lack of a closed dialysis system. However, in 1965 Weston and Roberts improved upon the Maxwell catheter by inserting a pointed
stylet (71). This became commercially available as the Trocath and it simplified access for temporary peritoneal dialysis considerably. However, access continued to be a major problem for patients on long-term peritoneal dialysis until the description by Palmer of a permanently implanted silastic catheter with a long subcutaneous tract (72). Working from this concept, Tenckhoff in Seattle attached dacron felt cuffs to the catheter just below the skin and immediately outside the peritoneum. Tissue ingrowth into these cuffs fixed the catheter in place and provided an effective barrier against bacterial invasion of the sinus tract around the catheter. This, the Tenckhoff catheter (73), originally implanted using a special trochar, has become the standard access device for long-term peritoneal dialysis, and a modification with a single cuff is widely used with acute renal failure.

Developments in Chronic Peritoneal Dialysis

The modern era of peritoneal dialysis was ushered in by publication of the monograph by Boen in the Netherlands in 1959. This classic work, published in the United States in 1964 (74), describes studies on the kinetics of peritoneal dialysis and discusses the indications, techniques, and complications of this treatment. This, together with the report by Maxwell et al from the United States (75), established the use of peritoneal dialysis in the treatment of acute renal failure. Because of its simplicity and because hemo-dialysis was not widely available at this time, peritoneal dialysis became widely used for acute renal failure.
In 1962 Scribner invited Boen to the University of Washington, Seattle, to continue his work on peritoneal dialysis and extend its application to the treatment of chronic renal failure. Equipment previously used for the experimental treatment of chronic renal failure by gastrodialysis was modified to make the first closed-system peritoneal dialysis cycler using dialysate sterilized in 40L glass bottles (76). This closed system dramatically reduced the frequency of peritonitis because it eliminated repeated connections to fresh dialysate containers during the course of the dialysis (77). In 1963 Boen started treatment of a 28-year-old woman with chronic renal failure by outpatient intermittent peritoneal dialysis (IPD), and this continued successfully for four years until the patient was transferred to home hemodialysis. This patient is alive today, having had a successful related donor transplant in 1971.

Boen and Tenckhoff continued work on development of peritoneal dialysis equipment which would eliminate the need for large containers of sterile fluid and on equipment for home IPD. The first such equipment, using heat sterilization, became available in 1970 (78) but was bulky and heavy, and while successfully used by a small number of patients, was never a commercial success.

The early 1970's showed increasing interest in IPD for chronic renal failure, primarily as a result of the continuing work of Tenckhoff, supported by the National Institutes of Health. He next developed a peritoneal dialysis fluid supply system using a reverse osmosis device to produce sterile pyrogen-free water. It was this
equipment which made long-term IPD feasible (79). In the late 1970's there was renewed interest in the use of pharmacologic agents to improve peritoneal clearance and so reduce the long duration of a peritoneal dialysis, and the possibility of using dialysate regeneration also was explored (80,81). However, IPD was still used for less than 5% of patients in the United States, in part because of lingering suspicions based on the high infection rate associated with the use of open peritoneal dialysis systems in the 1960's.

The most notable advance in peritoneal dialysis in the 1970's was the brilliant conception by Popovich, a biomedical engineer who had previously worked on hemodialysis kinetics at the University of Washington in Seattle, of the principle of continuous ambulatory peritoneal dialysis (CAPD) (82). This technique of portable self-dialysis has undergone an astonishingly rapid increase in use worldwide (83) and now accounts for about 13% of dialysis patients in the United States (84).

The recent increased interest in peritoneal dialysis has also led to the development of another approach. In 1979 Scribner first proposed nightly automated peritoneal dialysis, together with daytime ambulatory peritoneal dialysis (85). This concept was developed by Diaz-Buxo and co-workers and has become known as continuous cycling peritoneal dialysis (CCPD). It may prove a very useful further form of treatment (86).
The Enhancement of Peritoneal Dialysis Efficiency

Various pharmacological and physiological factors may affect peritoneal dialysis efficiency, but most of these have been studied in experimental animals and have not made a significant contribution to the management of patients. Peritoneal dialysis is inherently inefficient, and peritoneal mass transport can also be altered by both peritonitis and by generalized vascular diseases such as diabetes or scleroderma which affect the splanchnic blood vessels. A major factor affecting the rate of transport is the concentration gradient, but for larger molecular weight substances which diffuse slowly, increasing the rate of exchange beyond about 2L an hour has little effect on clearance. To improve mass transport requires either increasing peritoneal permeability or surface area, or increasing blood flow.

Blood flow to the peritoneal membrane is primarily related to mesenteric blood flow rate, since the visceral peritoneum is much greater in area than the parietal peritoneum. Thus factors which affect the splanchnic vascular bed can affect blood flow. Pharmacologic manipulations can produce vasoconstriction and vasodilatation of the vascular bed, and in particular vasoconstriction can be prevented by use of the alpha receptor blocking agent phenoxybenzamine. Prostaglandins have also shown to be involved in the control of vascular dynamics, again by modification of vasoconstrictor responses (87).
Convective transport can also be improved by increasing the osmotic activity of the dialysate or increasing capillary hydrostatic pressure by causing greater constriction of venules than of the arterioles, as with dopamine (88).

A number of vasodilator agents have been tested. For example, isoproterenol at a concentration of 0.06mg/L in the dialysate does improve peritoneal transport, although the effect is transient (89). No systemic effects were noted at this dosage. Isoproterenol inhibits catecholamine response and relaxes the mesenteric vascular bed. Theophylline (90) and nitroprusside (91) have also been used. Dipyridamole is interesting as it increases peritoneal transport and can be given orally. It is a smooth muscle relaxant and also has an antiplatelet aggregating effect which may be helpful with systemic diseases that produce platelet thrombi in the mesenteric circulation (92). Other substance that have been used include dopamine (93), hydralazine (89), diazoxide (94) and tolazoline (95).

Prostaglandins alter regional blood flow by their effect on vasoconstrictor responses (87), but studies of prostaglandin synthetase stimulators and inhibitors have not shown significant changes in peritoneal transport (96). Various vasodilator gastrointestinal hormones have also been investigated, and in experimental animals both glucagon and secretin can increase mesenteric blood flow (97). It has also been shown that methylprednisolone increases peritoneal clearance significantly (98).
From the foregoing, it is obvious that a number of drugs and hormones affect the peritoneal membrane and splanchnic blood flow, but to this date these have not proved applicable to clinical practice. Further knowledge of the effects of drugs and their interactions may eventually enable enhancement of peritoneal transport.

3. Other Technologies

Hemoperfusion

In 1948 Muirhead and Reid found that urea was absorbed from animal blood by passing this through an exchange column, so initiating the principle of using sorbents for blood purification (99). Yatzidas then described attempts to treat uremia by perfusing heparinized blood through a column of activated charcoal (100). However, while activated charcoal is an effective sorbent for several potential uremic toxins such as creatinine and uric acid, it does not absorb urea or correct the water and electrolyte abnormalities associated with chronic renal failure. In addition, it soon became obvious that the charcoal had to be coated or micro-encapsulated to prevent particles from entering the bloodstream (101).

Hemoperfusion using coated activated charcoal or Amberlite resin presently is used as treatment for severe overdosage with several hypnotic drugs including barbiturates, glutethamide, chlorpromazine, and methaqualone (102-104). It has also been used experimentally as an adjunct to dialysis treatment for chronic renal failure (105-107) but does not appear to be a complete alternative
to either hemodialysis or peritoneal dialysis. In addition, hemoperfusion with coated charcoal has been used to treat hepatic failure, but with inconsistent results (108,109).

**Hemofiltration**

Hemofiltration was introduced by Henderson and co-workers in 1967 (110), although the concept was originally described by Brull in 1928 (111). It has the advantage that it removes solutes by diffusion, as with conventional dialysis, and also by convection—a process which more clearly resembles the performance of the human kidney. Small and large molecules are removed at a similar rate. Introduction of the middle molecule hypothesis in the early 1970's stimulated work with hemofiltration, and a number of clinical trials have been undertaken (112-115). Different filters with different membranes can be used, including polysulfone, polyacrylonitrile, and asymmetric cellulose acetate membranes. Rather a large volume of fluid has to be ultrafiltered (20-40L 3 times weekly depending on body size), and an approximately equal amount of replacement fluid has to be added to the system either before (predilution mode) (116) or after the filter (postdilution mode) (113), and this replacement is one disadvantage of this treatment. The use of sorbent regeneration and reinfusion of ultrafiltrate has also been attempted and may be a feasible alternative (117).

Hemofiltration is an effective method to replace renal function, but removal of small molecules is somewhat less efficient than
with hemodialysis, and some loss of protein through the membrane of
the ultrafilter has been described (118). On the other hand,
better control of hypertension, improvement in peripheral nerve
function, and other advantages have been reported (119). Never-
theless, for the present time, hemofiltration is expensive and
rather cumbersome.

Hemodiafiltration

Hemodiafiltration is a combination of hemodialysis and hemo-
filtration which uses both diffusion and convection. It allows use
of a shorter dialysis time, together with a smaller volume of
replacement fluid than with hemofiltration (120). Intradialytic
morbidity is said to be reduced, and small molecular weight clear-
ances enhanced (121).

Plasma Exchange

Plasmapheresis was originally suggested by Abel and colleagues
in 1914 "for the relief of toxemia" (3). Plasma exchange became
feasible in the late 1960's and early 1970's with developments in
the technology of working with extracorporeal circulation. Consi-
deration has been given to the use of plasma exchange to treat a
number of very different diseases, several of them being thought to
have an autoimmune pathogenesis (122,123).

Two methods of plasma exchange are available--one of these is
continuous flow separation--plasma separation, and the more recent
one is membrane plasma separation—plasmapheresis, which has become the treatment of choice since the availability of suitable membranes (124,125). Vascular access is usually by means of an arteriovenous shunt or subclavian catheter. During treatment, 4-5L of plasma are removed and replaced by fresh frozen plasma, reconstituted dried plasma, or an albumin electrolyte mixture (122,123). Treatment is usually carried out daily or on alternate days.

Other techniques are being developed such as use of two hollow fiber filters with different pore sizes. The first separates plasma from whole blood and the second separates filtrate from larger molecular weight substances. This filtrate is then mixed with the cell-rich residual blood from the first filter and returned to the patient (126). Other developments include selective plasma component removal (127) and plasma exchange with immuno-adsorption (128).

Plasma exchange is frequently combined with immunosuppressive therapy for the treatment of acute hypersensitivity glomerular diseases such as Goodpasture's syndrome and rapidly progressive glomerulonephritis. It has also been used for autoimmune and other diseases including thrombotic thrombocytopenic purpura, systemic lupus erythematosus, myasthenia gravis, Guillain-Barré syndrome, rheumatoid arthritis, scleroderma, and Raynaud's syndrome. Success has been variable, and treatment of these conditions requires further evaluation.
4. **Important Medical Issues**

**Viral Hepatitis**

About 1965 it was first recognized that hepatitis was a hazard in dialysis units, and in the next few years a number of serious outbreaks occurred in several centers in Europe and the United States. Both patients and staff were affected, and a number of deaths occurred (129,130). At the same time, considerable research was being carried out on viral hepatitis, and it was soon realized that after hepatitis B infection, persistent Australia antigenemia (HBsAg) could occur. Such individuals are potentially infectious to others, endangering both other patients and staff. As recently as 1984, in Europe there were 2,174 new cases of hepatitis in dialysis patients, of which most were due to hepatitis B (131). There were 360 cases in dialysis staff with one death, a significant improvement over 1980 when there were 566 staff cases and 11 deaths.

Recommendations were developed in both the United States and Europe to help to control the spread of hepatitis in dialysis units, including isolation of affected patients, encouragement of home dialysis, and use of hyperimmune gamma globulin for protection following needle stick injury. Development of a successful vaccine for hepatitis B is now beginning to have a significant impact on the rate of infection for staff (132). Vaccination should be considered for all staff working in dialysis units who do not have antibodies to hepatitis B, and can also be used to protect patients, also, although it may be less effective in hemodialysis patients (133).
Other varieties of hepatitis also occur in dialysis patients. Hepatitis A may result from transmission from acute cases but does not pose a long-term hazard in dialysis units. However, with the introduction of reliable serological tests for hepatitis B infection, it soon became obvious that apart from a small number of cases due to cytomegalovirus, Epstein-Bar virus and drugs, there was yet another cause of hepatitis in dialysis patients. This, non-A, non-B hepatitis, results from an agent which is transmissible from man to chimpanzees (134), and for which a new antigen-antibody system has been distinguished (135). Like hepatitis B, non-A, non-B hepatitis infection does result in the carrier state and consequently can be a source of hepatitis in dialysis units. Unfortunately, non-A, non-B hepatitis is much more likely to result in chronic liver disease than is hepatitis B (136). Specific serological tests towards a specific non-A, non-B antigen called hepatitis C antigen are being developed.

In addition, a further hepatitis agent named "delta" has also been identified which is invariably associated with progressive liver injury in human carriers. This agent has an obligatory association with hepatitis B virus and cannot replicate without the latter's presence. So far, delta agent has not become a major problem in dialysis units, but is more commonly described in intravenous drug abusers (137).

Thus, while hepatitis B should be screened for on a regular basis in dialysis units and should no longer be a serious problem
with the availability of the vaccine, occasional brief outbreaks of hepatitis A may occur, and non-A, non-B hepatitis is appearing as a serious problem for some patients.

**Anemia**

Chronic renal failure is almost always associated with anemia, except in the case of a small number of the patients with polycystic kidney disease. The major cause for this anemia is the reduced production of erythropoietin by the kidney causing a reduction in red cell production (138). Several other mechanisms may be involved, including shortened red cell survival (139), toxic depression of erythroid proliferation and heme synthesis by uremic inhibitors (140,141), and blood loss occurring to a variable degree in association with the dialysis procedure (142). Anemia remains one of the major factors in the lack of well-being of dialysis patients and is important in preventing rehabilitation of such patients.

Institution of thrice-weekly dialysis in good time and a dietary protein intake of 1 to 1.5/g/kg/body weight/day helps to produce a higher hematocrit level in patients starting dialysis (143). Transfusions, because of their potential erythropoietic suppressive effect and the risk of transmitting hepatitis, should be given only when there is clear evidence of tissue hypoxia such as angina or where required as part of a transplant program. The serum ferritin level should be monitored regularly to check for development of iron deficiency, but unless there are unusually great
blood losses the patient who starts dialysis with normal iron stores takes six months to two years to develop iron deficiency. Once this occurs, it should be treated with oral iron taken before or after a meal, and without cocomitant ingestion of phosphate-binding gels (144). For patients who cannot tolerate oral iron or in whom it does not produce improvement, parenteral iron-dextran can be used. However, this carries the risk of occasional systemic reactions (145) and the danger of producing iron overload. Dietary supplementation with folic acid and histidine should also be considered (146). In patients with refractory anemia, androgens may be of help but are associated with side effects (147). In addition, peritoneal dialysis, and in particular, CAPD, has been said to be associated with higher hematocrit levels.

Perhaps the most exciting recent development is the availability for investigation of human erythropoietin produced from recombinant DNA. If, as is hoped, this will produce a marked improvement in the anemia of patients with renal failure, this could be one of the most significant steps in improving the well-being of patients and increasing their activity and opportunity for rehabilitation (138).

**Aluminum Toxicity**

In 1972 a new clinical syndrome was described in a number of patients who had hemodialyzed in Denver, Colorado, for several years. This consisted of dyspraxia, speech abnormalities, myclonus,
seizures, personality changes, and an abnormal electroencephalogram, and progressed to death within a few months. All patients had been dialyzed with untreated Denver city water. Analysis of brain tissue for trace elements showed few differences from that of controls and of uremic patients who had died without signs of encephalopathy except for some reduction in the amount of rubidium and potassium and an increase in the content of tin (148). Aluminum was not estimated at that time. By 1976, 19 cases had been observed in Denver, and suspicion had been raised that aluminum was responsible as tissue studies showed brain aluminum to be four times higher than in dialysis patients who died from other causes and ten times higher than in nondialyzed patients, the aluminum being localized in the gray matter. Aluminum concentrations in muscle and bone were also higher than in controls (149).

At the same time, similar cases were being reported in England and in Canada from cities with a high aluminum content in tap water, frequently as a result of an aluminum precipitation method used to reduce any undesired color in the water (150). Further studies showed that dialysis encephalopathy had a geographical distribution which appeared to be related to the aluminum content of untreated or inadequately treated water used for preparing dialysate. More recently other symptoms associated with aluminum toxicity have been described including vitamin D-resistant osteomalacia, proximal muscle weakness (151), and a hypochromic microcytic anemia (152).
The kinetics of aluminum in dialysis patients are complex. Aluminum is bound to plasma protein, and uptake from dialysate may continue even when the total plasma aluminum concentration exceeds that in the dialysate. Transfer is also related to pH and is increased by increasing the pH of the water or by use of bicarbonate dialysate (153). A pH below 6.5 has a similar effect.

The other major source of aluminum which has become of increasing concern recently is the aluminum-containing phosphate binders which are routinely administered to dialysis patient to control phosphate intake (154, 155). Efficient aluminum-free, and preferably magnesium-free, phosphate binders are currently under investigation.

Recently, the administration of desferrioxamine during dialysis has been shown to help remove aluminum from the body (156). Even so, because of the serious dangers associated with aluminum intoxication, it is important that water be pretreated by reverse osmosis or other means for all dialysis patients. Routine monitoring of serum aluminum levels should also be considered.

Osteodystrophy

Renal osteodystrophy, previously seen primarily as renal rickets in children, became a serious problem with the availability of maintenance dialysis. The association of hyperparathyroidism with renal disease has been known for some time (157), and calcium malabsorption has been found in such patients and is resistant to vitamin D treatment (158). However, it was found that renal
osteodystrophy can also be improved with large doses of vitamin D or dihydrotachysterol, that vitamin D increases bone resorption and there is a long delay between giving intravenous vitamin D and its physiological effects. Thus the interactions between the kidneys, the parathyroids, bone skeleton, and vitamin D are complicated (159).

DeLuca and his colleagues eventually showed that vitamin D had to be hydroxylated before it is physiologically effective (160), and the lag period can be shortened by giving 25-hydroxyvitamin D3 which is also active in bone cultures. The 25-hydroxylation occurs in the liver microsomes and is a biofeedback-regulated process. However, 25-hydroxyvitamin D still did not appear to be the active agent. The next step was the finding that the kidney is a unique source of a potent hormone which stimulates intestinal calcium absorption and calcium resorption from bone. This was isolated and found to be 1,25-dihydroxyvitamin D3 (161).

As a result of these findings, treatment of renal osteodystrophy and other disorders with synthetic vitamin D metabolites and analogues is possible. However, while vitamin D and its analogues have been shown to be effective in treating renal osteodystrophy, the osteomalacia in dialysis patients does not always respond to this treatment, and as noted above, aluminum accumulation may be the prime cause of osteomalacia in some of these patients.

There is no doubt that this better understanding of the interrelationships between vitamin D and its metabolites, the kidneys, bones, and alimentary tract has been a major advance in the management of patients with end-stage renal disease.
Lipid Abnormalities

In 1974 Scribner and co-workers reported the high morbidity and mortality from atherosclerotic cardiovascular disease in long-term dialysis patients in Seattle (162). Similar data has been reported by the European Dialysis and Transplant Association (163), and it now appears that cerebrovascular and cardiovascular causes account for approximately 60% of deaths in dialysis patients. Plasma lipid abnormalities have been shown to occur in dialysis patients, including persistent hypertriglyceridemia associated with a delay of the peripheral catabolism of very low density lipoproteins, and impaired triglyceride removal from a defect in lipoprotein lipase, presumably associated with the accumulation of uremic toxins (164,165). Hypertriglyceridemia also may be increased by the use of dextrose in the dialysate (166) and also by use of acetate dialysate (167).

The major problem affecting long-term survival in dialysis patients is cardiovascular disease, and in addition to the lipid abnormalities described, the occurrence of hypertension appears to be a major factor. This underlines the importance of blood pressure control in all dialysis patients and also in patients with renal disease.
B. DESCRIPTION OF PRESENT-DAY PROCEDURES

1. Hemodialysis

Hemodialysis requires access to the bloodstream, a hemodialyzer, equipment to provide dialysate to the hemodialyzer, monitoring devices and alarms, treated water for preparation of the dialysate, and staff to carry out the treatment.

Hemodialyzers

More than 250 different dialyzers are available, of which about two-thirds are hollow fiber dialyzers and the remainder are parallel plate dialyzers. Coil dialyzers, which were very important in the past, are now used only infrequently.

The Membrane

There are three basic types of membrane used in dialyzers: cellulose acetate and cellulose-derived materials, Cuprophan, and membranes of synthetic materials such as polycarbonate, polyacrylonitrile, and polymethylmethacrylate. The type of membrane determines various characteristics of the dialyzer such as its thrombogenicity, its activation of complement, and the occurrence of allergic reactions during dialysis.

Dialyzers vary in their membrane surface area from 0.3m² to 2.5m², and they also vary in the thickness of the membrane. The latter determines the clearance and ultrafiltration characteristics of the dialyzer and normally ranges from 8 microns to 40 microns.
Blood volume in the dialyzer ranges from 25-185ml and is relatively fixed in a hollow fiber dialyzer, but in a flat plate dialyzer is influenced by transmembrane pressure. Clearance rates of most dialyzers are in the range of 55ml/min to 180ml/min creatinine clearance, and the ultrafiltration rate (UFR) usually ranges from 0.5ml/hr/mmHg to 10ml/hr/mmHg. Newer high flux dialyzers are becoming available which have an even higher UFR. Thus there is a very wide range of dialyzers available with different physical characteristics, and a physician has a great deal of choice in picking the most appropriate one for the individual patient. This may be particularly important for dialysis of the patient with acute renal failure who is extremely sick, for other unstable patients, and for pediatric patients. Excellent summaries and tabulations of the various dialyzers are available (168,169).

Hemodialysis is most often carried out three times weekly, the duration of dialysis generally being in the range of 3 to 5 hours, although the effects of even shorter dialysis times are being studied (170). Three-times-weekly dialysis is a compromise between the increase in the time taken to prepare and to clean up after dialysis and the advantages to be gained from more frequent dialysis. Empirical experience has shown that for most patients three times weekly is the optimum. Some patients elect to dialyze more frequently; others, particularly those who may have significant residual renal function, may dialyze only twice weekly.
Dialysis is a remarkably safe procedure, and it has been estimated that the death rate from technical or human error is only about 1 in 75,000 dialyses (171). This is equivalent to one death every 480 years for dialysis 3 times weekly. There are several problems which can occur with dialysis. Blood leaks due to imperfections in the membrane are extremely rare, as are blood leaks related to human error. However, other problems that may occur with dialyzers include anaphylactic and allergic reactions during dialysis (172,173). These may relate to inadequate removal of sterilants from the dialyzer before use, the leaching of substances from the potting material in hollow fiber dialyzers, or allergic reactions to the membrane itself. Most reactions have occurred with Cuprophan membranes; they have been less common with dialyzers using regenerated cellulose or other cellulosic membranes, and affected patients do not react to synthetic membranes such as polyacrylonitrile.

Probably the most important single cause of an allergic reaction is the presence of residual ethylene oxide, and ethylene oxide-related sensitization has been found in a proportion of hemodialysis patients but not in patients treated only by peritoneal dialysis (174). In addition, in many of the patients who experience an acute allergic reaction it is possible to demonstrate the presence of IgE against human serum albumin exposed to ethylene oxide (175). Unfortunately, ethylene oxide cannot be completely removed by the usual rinsing process, but changes in the manufacturing process are already
occurring because the rate of severe hypersensitivity reactions has declined since 1982 when it was 3.5 reactions per 100,000 hollow fiber dialyzers sold (176).

**Dialysate and the Dialysate Supply System**

Currently, most dialysis equipment uses dialysate prepared from a concentrate which is diluted with treated water and which is then delivered to the artificial kidney. Usually, the dialysate is then discarded to the drain—single pass dialysis. The concentrate is diluted 1:34 with water, and the concentrate most commonly used includes acetate rather than bicarbonate as anion because this allows concentrate preparation without precipitation of calcium salts (29). Generally, dilution is performed in a proportioning unit which is part of the dialysis equipment. Bicarbonate dialysate has also been used with greater frequency recently, even though it requires somewhat more complex equipment and is more expensive.

The dialysis equipment also includes various monitors required in order to make the procedure relatively safe, and in fact, single patient dialysis equipment was developed in Seattle in order to make overnight hemodialysis a safe procedure for patients to carry out at home. Typical monitors include a monitor of pressure in the blood circuit, a blood leak detector, a temperature monitor, a negative pressure monitor which permits estimation of transmembrane pressure and may directly allow measurement of ultrafiltration, and an air detector to prevent the occurrence of air embolism with breaks in the extracorporeal circuit (177). Appropriate alarms are connected
to the monitors and can be set to specific limits. Typically the equipment includes a blood pump as, while pumpless dialysis can be done with cannulas and a low resistance system, the pressure in an arteriovenous fistula is generally insufficient and a blood pump is required to achieve an adequate blood flow rate. In addition, the equipment includes a heparin pump to maintain anticoagulation of the patient throughout dialysis.

Dialysate composition, adjusted according to the choice of the physician and the needs of the individual patient, is generally such as to match normal blood electrolyte levels or to induce changes in the patient's blood levels to more closely approach normality. Generally, the dialysate sodium concentration is set between 136-147mEq/L. This is somewhat higher than in the early years of dialysis because it has been found that use of a higher dialysate sodium concentration is associated with less dialysis morbidity, presumably related to prevention of a sudden fall in plasma osmolality with dialysis (178,179). The problem with using a high dialysate sodium content is that this may increase thirst and consequently produce greater weight gain and may result in hypertension and pulmonary edema between dialyses (180). Most patients tolerate a sodium concentration of 135mEq/L, and only in the minority is a higher or lower sodium concentration required to control problems during dialysis. Generally, if the sodium concentration of acetate dialysate has to be increased, this should be done by addition of sodium bicarbonate.
The dialysate potassium concentration is generally 2.0mEq/L, but the patient's serum potassium should be monitored and the dialysate concentration altered as needed. Patients with predialysis potassium levels of greater than 6.0mEq/L usually need a lower potassium concentration in the dialysate. Contrarywise, acutely ill patients, those with severe acidosis, those receiving parenteral glucose and/or bicarbonate, and particularly those using a digitalis preparation, may require a higher dialysate potassium concentration to prevent the occurrence of cardiac arrhythmias during dialysis associated with a rapid reduction in serum potassium level (181).

The calcium content of dialysate is adjusted in order to result in a slight net flux of calcium into the patient during dialysis so as to help to counter the calcium deficiency which occurs in patients with chronic renal failure. The recommended dialysate calcium concentration is between 3 and 3.5 mEq/L. Patients dialyzed against a lower level than this frequently develop secondary hyperparathyroidism and increasing renal osteodystrophy, whereas a higher level than 3.5mEq/L results in hypercalcemia (182).

The recommended dialysate magnesium concentration is between 0.5 and 1.0mEq/L. Higher levels may result in hypermagnesemia which can result in abnormal mineralization, and magnesium-free dialysate can result in magnesium deficiency (183).

Glucose was used in dialysate originally in order to enhance fluid removal during treatment, also providing extra calories and
reducing symptoms. However, the usual dialysate glucose concentration of 200mg% appears to have little impact on the quality of dialysis, and as glucose is one of the more costly constituents of dialysate its use is probably not required.

The buffer base in dialysate is used to correct the metabolic acidosis and bicarbonate deficiency which occurs in uremic patients, and to replace bicarbonate which diffuses from blood to dialysate if bicarbonate is absent in the dialysate. Because calcium and magnesium bicarbonate are relatively insoluble, particularly at higher pH levels and in concentrated solutions, acetate was substituted for bicarbonate when dialysate concentrate was first developed for proportioning systems (29). Acetate is a physiological buffer which is metabolized to bicarbonate in the body. In a relatively inefficient dialysis, acetate dialysate creates no problem because acetate is presented to the body at a rate which was easily metabolized. With development of large surface area dialyzers the rate of acetate influx and bicarbonate loss increased, and many patients develop clinical symptoms such as headache, vomiting, nausea, cramps, and hypotension (184). Symptoms appear to relate to an increase in organic acid and acetate levels in the blood, and comparison of infusion of acetate and of other organic acids has shown that hypoxemia and decreased serum potassium, phosphate and glucose levels occur only with acetate infusion (185). Acetate has also been shown to cause myocardial depression and vasodilatation (186), may affect lipid synthesis (187), and is more likely to cause hemodynamic instability and symptoms during dialysis (184).
Bicarbonate dialysate may also have long-term benefits. Patients on acetate dialysis generally have a lower predialysis bicarbonate level and this chronic acidosis may be harmful to bone mineralization. Aluminum complexes are less dialyzable in the pH range 7-7.4, and more rigid pH control with bicarbonate may help to reduce the influx of aluminum from dialysate to blood (153). The effect of long-term bicarbonate dialysis on the lipid profiles is still disputed, but several studies have shown that growth hormone release may be suppressed by acetate (188,189). It has also been suggested that plasma ketone levels may increase with increase of plasma acetate levels, suggesting hormonal variations facilitating fatty acid oxidation during acetate dialysis (190). On the other hand, bicarbonate dialysate is relatively unstable, is more expensive, and is nonbacteriostatic, although recently use of a stabilizer has been reported to deal with this problem.

Water

The water used for preparation of dialysate is usually tap water from the local supply, and as such, likely contaminants include particulate matter, bacteriological contaminants, and chemical contaminants.

Particulate matter does not cross the dialysis membrane but may obstruct conduits in the dialysate supply system, and so an appropriate filter in the water line is required to protect the system from damage.
The dialysis membrane also acts as a barrier to both bacterial and pyrogenic materials, and so dialysate does not need to be pyrogen-free or completely sterile. However, a major membrane leak with unsterile dialysate may result in septicemia, although small leaks are not usually a cause for concern.

Pyrogenic reactions may result from use of water for dialysate with a high bacterial count because of endotoxins passing the membrane, but not all febrile reactions are related to bacterial contamination. Nevertheless, bacterial growth in the dialysate and water supply system should be controlled. Methods have included the use of filters, ultraviolet light exposure, reverse osmosis, use of safe and nondialyzable disinfectants, and various combinations of these methods. Periodic culture of the water supply and of dialysate as it leaves the dialyzer is recommended. A colony count in the water of greater than 200 colonies/ml, and in the postdialyzer dialysate of greater than 2,000 colonies/ml, should trigger search for a source of contamination.

Various chemical contaminants may be present in water, and suggested maximum levels for these have been set based on EPA standards for drinking water (191). Use of appropriate water treatment equipment should prevent many of the hazards associated with chemicals, but in dialysis centers which do not use water treatment the possibility of chemical contamination of the water should be monitored regularly.
Water treatment devices include water softeners, cellular filters, reverse osmosis devices, and deionizers. Water softeners are the least expensive but are less reliable and serve to reduce calcium, magnesium, iron, and manganese levels. They are particularly useful in areas with hard water but have a limited spectrum activity--sodium is exchanged for cations, and fluoride and other toxic substances may not be removed.

The most effective means of chemical purification include deionization, reverse osmosis, and distillation, choice depending on demand and the type of contamination. Deionizers are effective against most chemical contaminants, while reverse osmosis is good for bacteriological, organic, and pyrogenic contamination. Generally, with small demand situations deionizers are more suitable, while for larger installations reverse osmosis, with or without one or more deionizers, has proved better. Charcoal filters are also valuable for removal of chloramines, dimethylnitrosamines, and pyrogens. Distillation requires a bulky apparatus, is energy-inefficient and expensive, and is rarely used.

**Technique of Dialysis**

During hemodialysis, movement of solutes and water occurs along the concentration gradients. The process of diffusion from an area of higher concentration to one of lower concentration is a net transfer of mass as a result of random thermal movement. However, the dialyzer also has another type of transfer, the process of ultrafiltration of plasma water along with those solutes of small
enough molecular size to cross the membrane—this is called convective transport. The latter is independent of the concentration gradient and depends chiefly on the mechanical pressure difference between the two sides of the membrane. Both diffusive and convective processes occur during conventional hemodialysis.

Diffusion of a solute depends mainly on molecular size rather than permeability of the membrane. As the size of the molecule increases, the net mass transfer decreases. Thus smaller molecular weight solutes are rapidly removed by dialysis and removal rate is influenced by blood and dialysate flow rates. In contrast, larger molecular weight substances are removed less efficiently, and the rate of removal is not influenced by blood or dialysate flow rates, but rather by duration of the dialysis procedure.

2. **Peritoneal Dialysis (192)**

Peritoneal dialysis is dependent upon access to the peritoneal cavity without undue risk of bacterial contamination and the development of peritonitis. For patients with chronic renal failure a permanent indwelling silastic catheter is the only practical method for long-term treatment, and the usual catheter is the Tenckhoff catheter (73). As described previously, this has one, or more commonly two, dacron felt cuffs, the inner of which is placed immediately outside the peritoneum, and the outer of which is located just below the skin exit. The catheter is inserted either at the bedside using a trochar and cannula or may be inserted surgically.
Once in place the catheter must be kept clean and dry, and before and after each dialysis the catheter exit site should be cleaned with betadine or hydrogen peroxide. Careful attention must be paid to connection and disconnection from the catheter during peritoneal dialysis.

Various other peritoneal dialysis catheters have been devised, the one most commonly used at the present time being the Toronto Western Hospital catheter (193).

Complications associated with placement of indwelling peritoneal dialysis catheters include leakage of dialysis fluid, bleeding, reflex ileus and, rarely, bowel perforation.

There are a number of long-term complications associated with peritoneal catheters including skin exit infection, most commonly due to staphylococcus aureus or epidermidis. Tunnel infections also occur and may extend deep into the abdominal wall and can be a cause of repeated episodes of peritonitis. Catheter cuff erosion and prolapse may occur due to pressure and necrosis of the skin at the exit site. This requires elective catheter replacement.

Catheter malfunction often presents as a failure to drain the peritoneal cavity at the start of dialysis, and outflow obstruction is much more common than inflow obstruction. Common causes include involvement of the catheter in adhesions, catheter malposition, catheter entanglement in the omentum and catheter obstruction by incarceration of tissue. Dye injection and X ray is often helpful in elucidating the problem. Catheter revision may be required.
Failure to drain also frequently occurs as part of a functional problem and responds to bowel stimulation by an enema. This treatment should always be tried first before looking for a mechanical cause of catheter failure.

The Peritoneal Membrane

The peritoneal membrane has a surface area of between 1 and 2m\(^2\). Solute removal occurs by diffusion from the blood in the peritoneal capillaries to the dialyzing solution infused into the peritoneal space (194). Solutes with molecular weights of up to 30,000 daltons may cross the peritoneal membranes. Solute removal depends on dialysate flow rate, temperature, pH, and osmolality. Fluid removal with peritoneal dialysis is carried out by osmosis, using a dialysate of higher dextrose content. Dextrose is poorly absorbed across the peritoneal membrane and therefore creates an osmotic gradient for fluid removal (195).

Intermittent Peritoneal Dialysis (IPD)

Intermittent peritoneal dialysis generally is performed using a machine to deliver sterile dialysate to the peritoneal cavity. After a suitable dwell time, the machine may pump the fluid out or siphonage may be used. Spent dialysate can be collected in a container or may be delivered to a floor drain. The simplest piece of equipment is a cycler which operates by gravity or a pump and feeds a fixed volume of sterile peritoneal dialysate stored in several
large bags through an octopus head of tubing, through a heater chamber, and into the patient's peritoneal cavity for a preset dwell time. The peritoneal cavity is then drained automatically and the cycle repeated (196). The second type of equipment used for IPD, which unfortunately is no longer manufactured, depends on reverse osmosis to prepare sterile, pyrogen-free water which is then mixed with sterile concentrate by a proportioning pump in order to produce sterile peritoneal dialysate (79). The dialysate is then pumped into the peritoneal cavity and timers are used to preset the duration of inflow, dwell time, and outflow. While reverse osmosis equipment is more complex and more expensive than a cycler, the supplies required for each dialysis are much less expensive because the dialysate is prepared in the machine and less plastic tubing is used. Treatment is usually carried for 10-12 hours overnight, 3 nights weekly. While peritonitis does occur, this should be less than one episode per 2 years.

The main problem with IPD is the eventual occurrence of under-dialysis as the patient's residual renal function declines, so requiring either longer dialysis time than many patients find convenient or more frequent dialysis. In addition, the mortality rate appears to be greater with IPD than with long-term hemodialysis (197), although this may be more a question of patient selection.

Continuous Ambulatory Peritoneal Dialysis

Continuous ambulatory peritoneal dialysis (CAPD) is a form of home peritoneal dialysis in which the patient dialyzes continuously
by infusing 2 liters of sterile dialysate from a flexible plastic bag into the peritoneal cavity (198). The bag is then rolled and carried in a pocket or belt during a dwell time of 4 to 6 hours or overnight. During the dwell time the patient can be active and carry on most normal activities. At the end of the dwell time the dialysate is drained into the empty bag. This is then detached and replaced by a fresh bag which is used in turn to refill the peritoneal cavity. This process of drainage, disconnection, connection, and infusion takes 30 to 45 minutes. New techniques which allow disconnection from the bag during dwell time are being evaluated. Various techniques and equipment for connection and disconnection are available, but so far none has been shown to be superior to normal connection and disconnection. CAPD is simple to carry out, does not require the assistance of a second person, allows the patient greater mobility, does not require use of a machine, and is well tolerated by many patients. Its major problems are its continuous nature, 7 days weekly, from which the patient has little or no respite, and the risk of the occurrence of peritonitis which occurs an average of slightly more than one episode per year (199). Repeated episodes of peritonitis may lead to technique failure due to reduced efficiency of dialysis, and it is then necessary to transfer the patient to hemodialysis.
Continuous Cycling Peritoneal Dialysis

Continuous cycling peritoneal dialysis (CCPD) is a combination of IPD and CAPD in which the patient uses a machine (either a cycler or reverse osmosis equipment) for peritoneal dialysis overnight while sleeping (196). Prior to disconnection in the morning, 2 liters of fresh dialysate are instilled into the peritoneal cavity, and this remains in place until connection for the next dialysis that evening. This technique reduces the number of connections as compared with CAPD and so may lessen the risk of peritonitis. It also avoids the need and inconvenience of making bag changes during the day. However, it requires nightly IPD for 8 hours or more to provide adequate dialysis.

Complications of peritoneal dialysis

The complications associated with peritoneal dialysis include mechanical problems, infections and peritonitis, metabolic effects, cardiovascular and pulmonary problems.

Mechanical complications include the occurrence of pain in the rectum or bladder area due to malposition of the catheter. In addition, pain in the shoulder may be referred from the diaphragm and associated with abdominal distention with air or excess dialysate. Bleeding may occur into the peritoneal cavity, but despite appearances this is usually not a serious problem. Leakage of dialysate may occur around the catheter, and subcutaneous dissection with dialysate can occur when one of the catheter holes is outside the
peritoneal cavity, or with leakage through the peritoneal membrane into the muscles and subcutaneous tissues. The most serious mechanical complication is bowel perforation, and the risk of this can be minimized by careful attention to detail during insertion of the peritoneal catheter.

Peritonitis remains the single most important complication with all forms of peritoneal dialysis. The incidence rate varies from facility to facility, but with IPD should be less than one episode per two years of treatment. The latest United States data on CAPD shows an infection rate of slightly more than one episode per year of treatment, and this has been slowly improving for several years (199). Bacteria can gain entry into the peritoneal cavity through the lumen of the catheter or by way of the catheter tract, and meticulous sterile technique during connection and disconnection is essential. Peritonitis usually presents with fever, abdominal pain, tenderness, discomfort, and/or a cloudy peritoneal fluid on outflow. A specimen of fluid should be sent for gram stain, cell count and culture, and appropriate antibiotic therapy started. Many episodes of peritonitis can be treated at home by suitably trained patients and without admission to hospital. Infection may also occur along the catheter tract, and this requires meticulous local care and the use of systemic antibiotics. Catheter replacement may be required with resistant or repeated episodes of catheter tract infections.

Infection with hepatitis B virus can also be a problem for peritoneal dialysis patients. Such patients should be vaccinated
against this and should be tested routinely for hepatitis B because of the risk associated with the presence of high concentrations of virus in the peritoneal fluid. Whether a similar risk applies to patients who have antibodies to HTLV-III or who have acquired immune deficiency syndrome remains to be determined.

Metabolic problems associated with peritoneal dialysis include protein loss, which may be as much as 9 to 10g of protein daily. However, most patients eating a diet containing 1.2g of protein/kg body weight/day probably will not have problems with this. A second common problem is hyperglycemia and hyperlipidemia associated with absorption of glucose from the dialysate.

The pulmonary complications of peritoneal dialysis include pneumonia and atalexis as a result of abdominal distention and limited respiratory movements. With marked abdominal distention, the volume of the exchange can be reduced to provide relief. Pleural effusion, when it occurs, is usually right-sided, presumably due to dialysate passing through a defect in the diaphragm. Cardiovascular problems can also occur, particularly in patients with preexisting cardiac problems who become either severely overdistended or severely volume depleted.

3. **Sequential Ultrafiltration**

Sequential ultrafiltration is the separation in time of the ultrafiltration process and diffusion dialysis (54-57). This may be particularly helpful in patients with hemodynamic instability.
During ultrafiltration, as fluid is removed cardiac output and stroke volume decrease but systemic vascular resistance increases, and as a result, blood pressure remains stable. This is in contrast to the diffusion dialysis process which, if associated with ultrafiltration, results in a reduction in cardiac output and stroke volume associated either with a decrease or with no change in systemic vascular resistance, so resulting in hypotension. Thus isolated ultrafiltration permits easier removal of a larger volume of fluid at a faster rate without the development of hemodynamic symptoms. Hemodynamic stability during ultrafiltration may relate to the fact that proteins are not removed during ultrafiltration, so that the plasma oncotic pressure rises, with consequent refilling of the plasma space and maintenance of blood pressure. In contrast, in diffusion dialysis, as the osmotic pressure of extracellular fluid declines, fluid moves into the cells and extracellular fluid volume is lost to both dialysate and the intracellular space, resulting in a fall in blood pressure. A combination of initial ultrafiltration followed by diffusion dialysis, so-called sequential ultrafiltration, is helpful in many patients with hemodynamic instability.

Complications of ultrafiltration include worsening of the metabolic acidosis, possibly due to movement of intracellular fluid into the extracellular space, thus lowering bicarbonate concentration; loss of bicarbonate with ultrafiltration (200); and development of lactic acidosis (201). Hyperkalemia has also been reported, perhaps related to movement of intracellular fluid into the extracellular space and the associated metabolic acidosis. Hypotension
may occur if the ultrafiltration rate exceeds 0.5ml/min/kg body weight. In the long term, sequential ultrafiltration may lead to hypercalcemia and hyperphosphatemia, together with an increased parathyroid hormone level and a decline in nutritional status in some patients (202).

Hemofiltration

This is the process of ultrafiltration with associated removal of uremic toxins by the convective process, and has some resemblance to glomerular filtration. Hemofiltration depends on use of a relatively porous membrane to carry out the ultrafiltration, and equipment to provide a carefully metered volume of fluid to replace the plasma that has been ultrafiltered (110). Originally called diafiltration, hemofiltration differs from ultrafiltration in that the ultrafiltered fluid is replaced by an electrolyte solution similar in composition to plasma.

The restraint offered by the membrane to passage of a solute is measured by the sieving coefficient. This is the ratio of the concentrations of solute on the filtrate side and the blood side of the membrane. A solute which passes freely across the membrane will have a similar concentration on both sides of the membrane and a sieving coefficient of one. On the other hand, a solute which does not pass the membrane at all will have a sieving coefficient of zero. Different solutes have sieving coefficients between these two values (203). Small molecules such as urea and creatinine pass
freely through a regular dialysis membrane, and if the concentration gradient is favorable, large quantities will be cleared by diffusion. In contrast, larger molecules will not be cleared as readily and their clearance is negatively correlated with the size of the molecule. With convective clearance, clearance is largely size-independent and is dependent on solvent drag of water moving through the membrane under a pressure gradient resulting in bulk movement carrying solutes with it in about the same concentration as plasma. Thus for solutes which pass the membrane clearance is approximately equal to the volume of water filtered in unit time. Other factors which influence the transport of solutes are the Gibbs-Donnan effect of protein and the effect of ionic charge. The viscosity of the blood, related to hematocrit and protein concentration, can also affect passage of solute through the membrane.

The technique of hemofiltration requires passage of blood from the patient through a hemofilter where ultrafiltration of plasma occurs as a result of a pressure gradient. This can be generated either by increasing pressure on the blood side or reducing pressure on the ultrafiltrate side. Replacement fluid containing glucose and electrolytes in similar concentrations to plasma is infused either before the blood enters the hemofilter (predilution) or after the blood leaves the hemofilter (postdilution). Predilution hemofiltration is believed to result in better clearance of solutes (116), while postdilution is less expensive and more convenient as it uses a smaller volume of replacement fluid (113). A combination of these
two techniques can be used. The size of the equipment is related to the need for accurate replacement of fluid, and an automated system which removes and replaces 20-120L of fluid in 4 hours has to be technically complex to avoid the risk of an imbalance between the volume removed and that replaced. In addition, unlike dialysate for hemodialysis, the replacement fluid must be sterile and pyrogen-free. The cost and complexity of the equipment is one of the major reasons why hemofiltration has not gained more popularity in the United States. Its advantages are the increased clearance of large molecular weight substances, the occurrence of less morbidity during dialysis, and better tolerance of the procedure.

Hemodiafiltration

Hemodiafiltration is a combination of hemodialysis and hemofiltration in order to obtain the advantages of both (120,121). Thus it relies on both diffusion and convection. Hemodiafiltration requires a smaller volume of replacement fluid, and allows the shortening of dialysis time by as much as 40% without signs or symptoms of underdialysis. At the same time, small molecular weight clearances are enhanced, including phosphate clearance, and intradialytic morbidity is reduced. Investigation of the role of this treatment is continuing.

Continuous Arteriovenous Hemofiltration

Recently continuous arteriovenous hemofiltration using a small hemofilter and without a blood pump has been used in some patients
with acute renal failure requiring dialysis (204). Initial results have been encouraging, and this technique is worthy of further evaluation.

4. **Dialyzer Reuse**

Dialyzer storage and reuse was first attempted in 1964 using anticoagulation and refrigeration of twin coil dialyzers, the attached blood tubing sets and the contained blood (62). In 1967 a reuse technique was developed in Seattle to save home dialysis patients the time and trouble of rebuilding the nondisposable Kiil dialyzer for each dialysis (63). A similar technique was developed for disposable flat plate dialyzers and hollow fiber dialyzers when these were first introduced, primarily to reduce the cost before the enactment of the Medicare ESRD Program in 1973. However, following 1973, with the relatively generous reimbursement for outpatient hemodialysis, there was little incentive to reuse dialyzers.

In recent years dialyzer reuse has become much more widespread in an attempt to contain the cost of dialysis, but there has also been considerable concern on the part of some patients regarding both the short- and long-term safety of reused dialyzers. Two major studies have concluded that dialyzer reuse is safe, efficacious, and not associated with any increased rate of complications (64,205). Many patients in Seattle have reused each of their dialyzers 6 or more times for 5 years or more without adverse effects. Apart from the economic considerations, a reprocessed dialyzer also carries a
lesser risk of causing allergic reactions, is associated with a lesser degree of leukopenia during dialysis, and is generally better tolerated (206). In recent years automated equipment has been developed for cleaning and disinfection of dialyzers, and this equipment can also check dialyzer functions such as fiber bundle volume and ultrafiltration rate.

The use of formaldehyde as the disinfecting agent for reuse of dialyzers has been one major cause of concern. Recently, the Center for Disease Control has recommended use of a 4% formaldehyde solution for dialyzer reprocessing because of seasonal variation in the risk of bacterial contamination with relatively resistant organisms such as the mycobacterium species. Use of 4% formaldehyde solution requires a larger volume of rinsing fluid to remove formaldehyde from the dialyzer, and testing is necessary to insure that there has been complete removal prior to connection to the patient. Four percent formaldehyde is an unpleasant substance to work with, and spills require special handling. Development of antinuclear-like antibodies may occur as a response to residual formaldehyde reaching the patient, and these antibodies have been implicated as a cause of hemolysis in some dialysis patients (207). Because of these and other problems, new disinfectants such as Alcide are being examined as possible replacements for formaldehyde.

Another concern with reuse is the possibility of inadequate dialysis, either because of diminished effective membrane surface
area or because of alterations to the membrane itself. However, most studies have shown that ultrafiltration and clearance of small molecular weight substances are not impaired with reuse.

A number of substances are available to clean the membrane for dialyzer reuse before it is disinfected. Hypochlorite bleach, reverse ultrafiltration, water flush, hydrogen peroxide, peracetic acid and sodium hydroxide have all been used. While bleach is widely used, some membranes deteriorate with this; and in addition, cleaning may be so complete that bleach-cleaned dialyzers may behave like new dialyzers in producing the first-use syndrome and are more likely to be associated with significant complement activation.
C. DIALYSIS SETTINGS AND PRESENT-DAY PRACTICE IN THE UNITED STATES

1. Acute Renal Failure

Acute renal failure is most commonly caused by acute tubular necrosis, generally following ischemia, and is most often associated with cardiovascular or hepato-biliary surgery, traumatic injury, sepsis or pancreatitis. Consequently, almost all patients with acute renal failure are hospitalized because of the underlying cause and associated complications, and treatment is by in-hospital dialysis.

Generally it is preferable to use single patient dialysis machines for this purpose rather than to have a separate area set aside for dialysis of patients with acute renal failure. Sicker patients require dialysis in the intensive care unit, but with appropriate plumbing and electrical connections it is possible to dialyze other patients who are less sick in a regular hospital room. Generally, the equipment is the same as that used for patients with chronic renal failure, including the use of water treatment as may be necessary.

2. Chronic Renal Failure

The dialysis of patients with chronic renal failure can be done in a hospital, in a freestanding dialysis unit, or at home. The nomenclature is somewhat confusing.
Hospital Dialysis

A hospital may perform two forms of dialysis: inpatient dialysis for hospitalized patients who suffer from chronic renal failure, and outpatient dialysis for outpatients with chronic renal failure.

Inpatient dialysis for hospitalized patients with chronic renal failure is often managed in the same way as described previously for hospitalized patients with acute renal failure. However, in smaller hospitals which have an outpatient dialysis unit, patients with acute renal failure may be treated in the dialysis unit. This is not necessarily in the best interests of the patient and staff because the patient with acute renal failure may require much closer surveillance than the outpatient with chronic renal failure. Also, it may be disturbing to stable patients with chronic renal failure to be treated in proximity to a patient with acute renal failure and multiple complications. Thus, wherever possible, inpatient dialysis should be provided either in the intensive care unit or in the individual patient's room. Only the stable patient with chronic renal failure who is an inpatient for a condition such as minor elective surgery and who has relatively little in the way of complications should be treated in a hospital outpatient dialysis unit.

Hospitals also may provide outpatient dialysis for patients with chronic renal failure. The Medicare ESRD Program divides institutions that provide outpatient dialysis for chronic renal failure into two categories: dialysis centers which are hospital
units that also provide all the usual services provided by hospitals, and dialysis facilities which are outpatient, freestanding dialysis units (see below) which contract with a hospital to provide in-hospital services for their patients. There are 662 hospitals out of a total of 1,368 institutions approved to provide chronic dialysis services in the United States (208). In Europe, in contrast, until recently at least, the majority of outpatient dialysis was carried out in hospital units. This can create confusion in comparing European and American statistics, as in Europe "hospital dialysis" for chronic renal failure generally means outpatient dialysis.

The major advantage of a hospital dialysis unit is that it uses the existing administrative structure of the hospital, but the disadvantage is the higher overhead and other costs associated with hospital services. Also, there is evidence that hospital units may treat a sicker patient population than outpatient dialysis units.

Out-of-Hospital Dialysis

As noted above, more than half the institutions providing outpatient dialysis in the United States are "out of hospital," and these are categorized by the Medicare ESRD Program as dialysis facilities. They have also been called freestanding, limited care or out-of-hospital dialysis facilities. It is only recently that such facilities have been developed in Europe.

Typically, an out-of-hospital dialysis facility provides staff-assisted outpatient dialysis and, like a hospital dialysis unit, can
provide all modalities of treatment other than inpatient dialysis. Freestanding units may be associated with hospitals or may be independent. They may be nonprofit institutions or may be for-profit and, in the latter case, may be owned by individuals or by a corporate chain. One such entity, National Medical Care, currently dialyzes about one quarter of the patients in the United States.

Self-Care Dialysis

In the early 1960's it was realized that one of the major factors contributing to the cost of dialysis was personnel. By training the patient and family or other helper to perform dialysis at home the cost could be reduced significantly. This requires a specific home dialysis training program, and both hospital and freestanding dialysis units may have such a program. Patients may be trained for home dialysis, or more recently, some patients have been trained to do self-care dialysis in the dialysis unit.

Home dialysis involves the patient and a family member, or in some programs a paid dialysis helper when a family member is not available, in order to assist the patient to do their dialysis at home (209). While originally developed because of its cost-saving potential, home dialysis was soon found to have other advantages, and in particular, increasing patient independence, freedom, and opportunity for rehabilitation (210). Self-care dialysis in a dialysis unit has also been used for similar reasons, usually in a
situation where a number of patients dialyze themselves, perhaps with the assistance of family members, and with minimal assistance from the staff.

Self-care dialysis, whether in the home or in a unit, requires an organized patient training program. Training should begin as soon as possible after the patient is started on dialysis so that independence can be encouraged. The staff providing training should be selected for their teaching abilities as well as their knowledge of dialysis, and training should, if possible, be carried out in an area separate from that used for regular maintenance dialysis. The training program should include information about kidney disease and its complications, blood access, diet, medications, and the various procedures for the form of self-dialysis selected by the patient. Training may be on a one-on-one basis or may be in groups. Written materials, slides, posters, and videotape programs have all been used to assist with training. Training for home IPD and for CAPD and CCPD is of shorter duration than for home hemodialysis. Generally, peritoneal dialysis training takes one to two weeks, and hemodialysis training takes from three weeks to three months. Patient progress needs to be assessed during training, and it is important that as far as possible the patient be made responsible for their own care in order to avoid becoming overly dependent on the spouse or other helper. The availability of a paid home dialysis helper permits some patients to be trained for home dialysis who do not have a family member or whose family member is not
willing to undertake this (209). Successful home dialysis requires a careful initial assessment of patient and family and the availability of good social work follow-up.

Self-care dialysis requires blood access that is easy to use, and most patients can be taught to insert their own needles into a suitable arteriovenous fistula or graft. The dialyzer used, duration of dialysis, and ultrafiltration rate should be selected individually for the patient so as to minimize the occurrence of symptoms during dialysis. Similarly, hypotensive drugs should be used with care in self-care dialysis patients. Dialysis equipment and water treatment should be chosen because of reliability, ease of use, adequacy of monitoring, and availability of repair service and maintenance support.

Home dialysis requires well organized follow-up services. Generally, the patient is reviewed monthly in the physician's office and can mail in ahead a monthly predialysis blood sample for analysis, reports being sent to the physician, the training program, and the patient. Records should be kept of each dialysis and forwarded to the training program. Arrangements must be made for provision of supplies and for maintenance and repair of equipment. Ongoing social work support, vocational rehabilitation services, and nutritional advice are also important. In addition to being able to contact the physician, a home dialysis patient should at all times have ready access to a nurse from the training program who can advise as to what services are required in the event of a problem or emergency.
Selection of Patients for Various Modalities of Dialysis

This is discussed in a further section.

D. MANPOWER NEEDS

Little has been published on the manpower needs associated with dialysis in different settings (211,212). Thus this section will consist of general comments on manpower requirements for direct patient care and those for supporting and administrative services.

1. Acute Renal Failure

Patients with acute renal failure are hospitalized, and in many cases will be sick enough to require treatment in an intensive care setting.

Nephrologists and other physicians

Because acute renal failure usually occurs as a complication of another condition, many of these patients will have an attending physician who is not a nephrologist. Nevertheless, dialysis of patients with acute renal failure should always be supervised by a nephrologist. With the availability of dialysis equipment in many hospitals and the growth of outside services which will provide dialysis equipment and dialysis nurses to hospitals which do not possess these, dialysis for acute renal failure is being carried out in many hospitals which do not have a chronic dialysis program. Nevertheless, with the large number of nephrologists in the United
States, it should always be possible for a nephrologist to be involved in the care of a patient with acute renal failure.

**Registered nurses**

Dialysis for acute renal failure should always be carried out by an experienced registered nurse trained in provision of both hemodialysis and/or peritoneal dialysis in patients with acute renal failure. Where a facility does not have nurses trained in dialysis and is using dialysis services provided from elsewhere, the procedure should always be done by a suitably trained registered nurse provided by the outside agency.

**Dialysis technicians**

Because of the severity of the patient's illness, dialysis in patients with acute renal failure generally should not be done by a licensed practical nurse or a patient care technician. Equipment technicians will be required to maintain, service and repair the equipment, the number being dictated by the quantity of equipment available.

2. **Chronic Renal Failure**

**Inpatient hospital dialysis**

The patient with chronic renal failure who requires in-hospital dialysis has other medical problems, and so it is important that the dialysis be carried out by an experienced registered nurse. Because all patients with chronic renal failure should already be under the
care of a nephrologist, he or she should continue to be responsible for the patient's dialysis. Generally speaking, licensed practical nurses and patient care technicians should not do the dialysis of the hospitalized patient with chronic renal failure.

**Outpatient hospital dialysis and limited care staff-assisted dialysis**

Almost all ESRD patients are followed by a nephrologist who is responsible for their care. In addition, units providing outpatient dialysis, whether hospital-based or freestanding, should be under the supervision of a medical director who is a nephrologist, and who may or may not be the nephrologist caring for the individual patient.

As a general rule, outpatient dialysis should be under the supervision of a registered nurse trained in hemodialysis or peritoneal dialysis as the case may be. Nevertheless, the hands-on dialysis care can be given by registered nurses, licensed practical nurses, or patient care technicians, provided that all have had appropriate training. As a general rule, one staff member should be able to care for at least three dialysis patients. Because administration of drugs may be required during dialysis, it is generally advisable to have a registered nurse available, even if the dialyses are performed by patient care dialysis technicians. In some states, the law requires that a registered nurse be present to supervise dialysis in an outpatient unit. In situations where a large number of stable patients are being dialyzed, the patient-nurse ratio may be 4:1, 5:1 or greater, at the discretion of the unit. There are
also units which treat a large number of unstable patients with cardiovascular instability and other medical problems during dialysis. In these circumstances, one nurse may be required for each two patients on dialysis. However, this should not be necessary for the majority of dialysis patients.

Equipment technicians are required to maintain, service, and repair the dialysis equipment. No information is available on the number of machines that can be cared for by one technician, and there is a lack of good job definitions.

As a general rule, all the staff involved in the care of the patient treated in an outpatient dialysis unit should be familiar with dialysis, should have been appropriately trained, and this training should be documented.

**Self-care dialysis training**

Self-care dialysis training is best provided by staff who are experienced in dialysis and who are chosen for their abilities to teach patients, to allow them to learn by making mistakes, and to encourage independence. These qualities are difficult to define, but training staff need to be selected carefully if a self-care dialysis training program is to be successful.

**Self-care dialysis in a dialysis unit**

Patients trained to perform their own dialysis require relatively little assistance and supervision during dialysis. Consequently, one staff member can manage five, and perhaps as many as
ten, patients carrying out self-dialysis. Such an individual need not necessarily be a registered nurse, but could be a suitably trained licensed practical nurse or patient care technician. However, as a general rule, it is still preferable to have an experienced registered nurse available on the premises.

**Home dialysis**

Home dialysis generally requires the presence of a second person during dialysis, with the exception of continuous ambulatory peritoneal dialysis. Generally, a patient should be trained to carry out their own dialysis, utilizing a family member or a paid dialysis helper to provide a second pair of hands and to assist the patient in carrying out the dialysis. Such family members or dialysis aides need to be trained in the same way that the home dialysis patient is trained. Occasionally, very independent patients may feel they can carry out their own home hemodialysis or home IPD without the assistance of a second person. In the case of home hemodialysis, this is particularly inadvisable as fatalities have occurred, usually associated with a blood leak or bleeding, when the patient has become unconscious and unable to resolve the problem. Consequently, no home hemodialysis patient should dialyze without a second individual readily available who knows enough to be able to discontinue dialysis and who is trained to handle likely emergencies. In the case of home IPD and CCPD, this may not be necessary as the problems that occur related to the dialysis are unlikely to be so
acute as to render the patient unable to help themselves. CAPD by its very nature is a procedure that the patient carries out themself during their daily activities, and there is no need for the assistance of a family member or paid helper. The only exception is in the case of infants and very small children treated by CAPD or CCPD. The latter treatment may be preferable in such children because CAPD, with its need for frequent changes, becomes a major time commitment for the mother or other family member involved.

Supporting and administrative staff

Supporting and administrative staff are required for patients dialyzing as outpatients, and for patients dialyzing at home. Again, no good information is available as to how many patients can be supported by one such individual.

Nurses

For successful home hemodialysis, it is important that patients have good supporting services from the home dialysis training program or from the dialysis unit following the patient. A nurse should be available 24 hours daily on call by telephone and pager in order to answer the patient's questions during dialysis, to discuss problems, and to make the decision as to whether the patient requires to speak to their physician, whether they should continue the dialysis, whether the patient should be referred to other individuals or services such as a social worker, equipment repair
technician, etc. One nurse can provide on-call support for a large number of patients, and at the Northwest Kidney Center one nurse is on call for more than 200 patients dialyzing at home. Similarly, patients treated by any form of peritoneal dialysis should have a nurse who can be contacted at any time to answer questions that may arise.

In addition, the training staff or other dialysis staff must be available to see home dialysis patients at the unit if there are questions to be answered or minor technical issues to be resolved. Generally this is not a major need for hemodialysis patients, but for CAPD patients a nurse is required for various services such as tubing changes, and one nurse can be responsible for the care of 10-20 such patients.

**Equipment technicians**

The equipment of the home dialysis patient must be maintained, serviced, and repaired. These services can be provided by equipment technicians from the manufacturer or supplier, or may be provided directly by the facility. Because the home dialysis patient is usually well dialyzed, there is no need to have a 24-hour repair service available. Arrangements should be such that an equipment problem in the home can be attended to promptly the following day so as to avoid the patient having to come to the unit for a backup dialysis. Patients should be taught the basic maintenance of their equipment, but the equipment service technician should provide routine major servicing, as well as responding to patient problems.
Suppliers

Home dialysis patients, whatever form of home dialysis they may be undertaking, require provision of an adequate quantity of supplies. In many cases, this function is delegated to the manufacturer or an outside supplier, but it behooves the facility to insure that appropriate supplies are ordered. Some facilities may provide supplies directly, allowing better inventory control, but otherwise inventory management and accounting should be coordinated between the unit and the supplier.

Social workers

Dialysis, whether as an outpatient or at home, puts stress on patient and family, and many readjustments are required at the time when a new patient first starts dialysis. At a later stage, patients and their families may develop problems requiring the services of a social worker. Medicare regulations require that all dialysis facilities have the services of a social worker, but no criteria have been laid down as to how many patients one social worker can follow. The social worker must be familiar with dialysis and the problems of dialysis patients. Generally, it is preferable for all new patients to be interviewed by a social worker prior to the start of dialysis, and during the early months of treatment a social worker should be available to provide advice and counseling, including advice on rehabilitation services and employment. Once the patient is established on dialysis social support must continue to be
available, but generally is not required to the same degree. In the Northwest Kidney Center program, one social worker is responsible for approximately 100 patients, including both center and home dialysis patients. Unfortunately, some facilities do not have a social worker who is closely involved in patient care, but rather have a part-time social worker who serves merely to meet the requirements of the Medicare regulations.

**Financial counselors**

Some facilities employ financial counselors who specialize in the finances of end-stage renal disease and who can establish the patient's financial responsibilities, the availability of various funding sources, and counsel the patient as to the best use of their resources. Such individuals can be invaluable to both patient and facility by insuring that patients take maximum advantage of the financial services available to them. As with social work support, financial counseling is particularly important at the time that a patient commences dialysis. It is also helpful if the patient's financial situation is reviewed on a regular basis in order to insure that the patient continues to make the best use of available resources.

**Nutritionists**

Diet is an important part of the management of patients with chronic renal failure, and recent evidence suggests that nutrition
may be important in delaying the onset of dialysis (213). Once a patient starts dialysis there is an ongoing need for nutritional services. New patients should spend time with a nutritionist, and a careful program of nutritional advice, support and regular review should be available for all dialysis patients. Generally, one nutritionist can support as many as 100 dialysis patients.

Administrative and other staff

In the case of a hospital, most of the administrative services required by the dialysis unit are provided through the hospital. Nevertheless, each unit, whether in a hospital or freestanding, must have a medical director who should be a nephrologist. Many freestanding units also have an administrator who is responsible for such services as billing and accounting, personnel functions, and the general supporting functions required in operating a dialysis unit. In some smaller units and in units that belong to larger organizations, much of the administrative services may be provided off-site by a central administration.
E. CURRENT EXPERIENCE WITH DIALYSIS

1. The Present-Day Patient Population

Patient demographic data from the Health Care Financing Administration are shown in Tables I through 4. The changes in the patient population which ensued with passage of the Medicare ESRD legislation and subsequent general availability of dialysis and transplantation have been described (214). This paper examined the dialysis patient populations in 1967 and 1976, and showed the increase in the number of elderly patients, minorities, especially blacks, the less educated and the less well-to-do. These changes have continued. Most striking is the large percentage of patients aged 65 and older who are on dialysis. Such patients accounted for 25% of all dialysis patients in 1981 (215). There has also been a marked increase in the incidence of patients with diabetic end-stage renal disease, and this now accounts for more than 25% of new patients. These changes are important for two reasons. First, until recently patients over the age of 65 have not been considered as suitable candidates for kidney transplantation, although this may change with more experience with the use of cyclosporine. Second, the increase in the number of elderly patients and diabetic patients means that a much greater portion of the ESRD patient population is likely to have vascular and other complications which affect survival and also increase morbidity. The frequency of hospitalization is greater in these patients, with consequent financial impact on the cost of the Medicare ESRD Program. It is uncertain whether all the
patients with diabetic end-stage renal disease and all the elderly patients who might benefit from treatment are being referred. However, the proportion of elderly ESRD patients will continue to increase because of aging of the general population, and the dialysis population in the United States is not likely to stabilize before the year 2030 (216).

Transplantation is a factor which will affect the future number of patients on dialysis. Assuming an increased availability of cadaver kidneys, it is likely that in the future the great majority of younger patients will receive a kidney transplant. Although there will continue to be a significant failure rate for cadaver grafts, with the patients then returning to dialysis, and while some of these patients will have high levels of cytotoxic antibodies making retransplantation both less probable and less successful, nevertheless, the number of patients on dialysis aged 35 and under is likely to decline in the future (216). Consequently, the proportion of elderly patients on dialysis is likely to increase even further.

2. **Selection of Treatment for the Individual Patient**

Patient and physician have a number of options to select from in deciding which modality of treatment is best for the individual patient. While some general guidelines are available, there remains the problem that good comparative information on the best form of
treatment for the individual patient is sparse. Much of the survival information available does not take into account the effect of patient selection for different modalities of treatment.

Friedman has listed the important factors governing selection of treatment as patient age, cause of renal failure, physician bias, patient bias, economic realities, and the use of investigational treatments (217).

**Patient age**

Infants and children under the age of one generally do not do well with hemodialysis, and CAPD or CCPD, which reduce the time demands on the parents, may be the preferred forms of dialysis. Transplantation in very small children has been more successful with the use of adult living-related donors (218), although short-term results with cadaver transplants are also said to be improving (219). In older children, hemodialysis, CAPD and CCPD are all effective forms of treatment, but in general home hemodialysis, CAPD or CCPD are to be preferred rather than outpatient dialysis in order to give the best opportunity for schooling and leisure activities. Unfortunately, growth tends to be subnormal in children on dialysis, but may improve following transplantation. Consequently, transplantation should be considered for all children, and it also offers the best opportunity to return to school and other activities (220).
As noted earlier, almost half the new patients starting treatment in the United States are aged 55 or older, and almost half the patients enrolled in the Medicare ESRD program are 55 or older. These numbers will continue to increase. Survival is less good than in younger patients, but nevertheless, the results of treatment with dialysis are such as to warrant treatment of patients at all ages. The question remaining to be answered is the role of transplantation in patients aged 55 to 70 now that cyclosporine is available. Prior to cyclosporine, this age group did not do well with transplantation, primarily because of lesser tolerance for steroids and their side effects. Now, if enough kidneys become available, more such patients may be transplanted.

Meanwhile, for patients over the age of 55 the best treatment probably is hemodialysis, and home dialysis is to be preferred when practical, but CAPD or CCPD are reasonable alternatives for some patients.

For patients in the age range from adolescence to late middle age—say 55 years—survival with both dialysis and transplantation is at its best. Nevertheless, assessment of comparative morbidity and mortality of patients in this age group is difficult because of the need to compare equivalent subpopulations in terms of age, sex, race, socioeconomic status, and diagnosis. Transplantation will depend on availability of a living-related donor or a cadaver kidney. Generally, transplantation should be encouraged, particularly in younger patients, in order to maximize independence and rehabilitation.
Where this is not available, home hemodialysis, CAPD or CCPD are preferable, but many patients will, by default, be treated by long-term outpatient hemodialysis.

**Cause of Renal Failure**

This is also important in considering treatment. Some diseases recur following transplantation, and so oxalosis, focal segmental glomerulosclerosis, and membranoproliferative glomerulonephritis may be relative contraindications to transplantation, and cancer, either primary or metastatic, is an indication for delaying or avoiding transplantation.

A significant number of patients who start dialysis may recover sufficient renal function to stop dialysis for a period of time. These include some of the patients with malignant hypertension, gouty nephropathy, renal cortical necrosis, and also patients with renal failure due to toxic nephropathy, especially in the elderly. Patients with renal failure due to these causes should be observed on dialysis for 6-12 months before transplantation is considered to give opportunity for any improvement in residual renal function.

For patients with serious cardiovascular problems, peritoneal dialysis may be the treatment of choice, and CAPD may be preferred for patients who want home dialysis but who do not have a partner. The overall role of CAPD remains uncertain. Enthusiasts argue that this should be the primary treatment for most patients today, but some are beginning to question the long-term use of CAPD because
the peritonitis rate is not improving, even after 7 years of experience (221). For selected patients CAPD is a very satisfactory form of treatment; but unfortunately, because of the relatively high rate of technique failure, only a minority of patients will be able to continue on CAPD for more than 3 years. Ideally, patients who can no longer be treated by CAPD should be encouraged to undertake home hemodialysis in order to maintain their independence, but this is not always possible. Peritoneal dialysis is in no way a contraindication to either living-related donor or cadaver donor transplantation.

Intermittent peritoneal dialysis (IPD), while relatively simple to undertake, is expensive, even when used at home, and as residual renal function declines patients may require prolonged hours of treatment making this unacceptable. Continuous cycling peritoneal dialysis (CCPD) may be a reasonable alternative, but its long-term value has not yet been established. Thus maintenance hemodialysis remains the usual mode of therapy for the majority of patients, particularly the elderly.

**Physician Bias**

Examination of data from around the world shows a wide variation in treatment distribution from country to country. In part, at least, these differences represent physician bias (222). For example, in Canada peritoneal dialysis is used to treat 35% of the dialysis patient population, whereas in the United States this is 15%. Home hemodialysis is widely used in Australia and Canada, to a
lesser extent in the United States and Britain, and yet in Japan it accounts for less than 1% of patients. The use of all forms of home dialysis varies widely in different parts of the United States, sometimes markedly in adjacent states; for example, the home dialysis rate in Indiana is much higher than in Illinois.

Individual physician biases also occur. Transplant surgeons generally favor this over dialysis, and some nephrologists favor home dialysis or CAPD much more than others (223).

Patient Bias

The patient should be actively involved in selection of their treatment, and they may ignore the best intentioned medical advice. Fear, anger and hostility may all affect patient behavior at the time when treatment is started. Many patients are not seen by a nephrologist until the time to start dialysis, and patients are influenced by the attitudes of the physicians they meet. Religious beliefs also may affect their decision. It is important that patients have access to as much relatively unbiased information as possible. One approach to this is a specific orientation program during the first two months of dialysis to give the patient a better understanding of the various options available to them (224).

Economic Situation

Treatment choices also may depend on economics. In western nations, politics and economics may influence use of various forms
of treatment, and this is illustrated by comparing the treatment of end-stage renal disease in the United States and the United Kingdom (225).

**New Treatments**

As of today, maintenance hemodialysis remains the standard against which other treatments must be judged, age for age and diagnosis for diagnosis, in terms of survival and morbidity. Nevertheless, hemodialysis is not ideal. The complications of uremia persist, rehabilitation is often incomplete unless the patient is treated at home, and treatment remains expensive.

Hemofiltration and hemodiafiltration were used to treat 2,867 patients in 25 countries throughout Europe in 1983, as compared to 76,179 patients on hemodialysis (226). Comparable data is not available for the United States. The drop-out rate with hemofiltration is less than one third of that with CAPD (115), and patients managed first by hemodialysis appear to tolerate and even prefer hemofiltration because of fewer symptoms. However, long-term patient experience with hemofiltration is still minimal, and it remains an investigational procedure.

**Conclusion**

The choice of treatment for a uremic patient is still far from an objective exercise. Only with much more statistical information, and preferably with comparative trials of age- and diagnosis-matched
treatments, will physicians and patients be able to review the options objectively, reflect on the various pressures, and make an informed decision as to which treatment is best for the individual patient.

3. **Major Complications**

   Table 5 illustrates the common causes of death in the dialysis population based on data from the Northwest Kidney Center. The major cause of death remains cardiovascular and cerebrovascular disease, and this may relate to both hypertension before and after starting on dialysis, and also to the lipid abnormalities which are common in these patients. Smoking has also shown to be a major adverse factor in mortality from cardiovascular disease in dialysis patients (227). With patients now surviving for 20 years or more following the start of dialysis, the importance of prevention of vascular disease is paramount. Also, apart from progression of the renal disease itself, the major cause of progression to renal failure in patients with primary kidney disease is poorly controlled hypertension (228), and the diseased kidney appears particularly prone to further damage from hypertension (229). Consequently, it is becoming obvious that control of hypertension is perhaps the single most important factor that can be manipulated to prevent progression to renal failure, and this is true whether or not dietary means can also slow the progression of renal disease.

   The one change in causes of death that has occurred is the increase in the number of patients in whom dialysis is discontinued,
either at the patient's request or, in the case of incompetent patients, at the request of relatives. Recent data from Minneapolis (230) and on our experience at the Northwest Kidney Center is that about 10% of all deaths occur after cessation of treatment. Diabetics and elderly patients are the most likely to have dialysis discontinued because the quality of their life has deteriorated.

In a population which dies predominantly from complications of cardiovascular disease and hypertension, a significant proportion of the morbidity is also associated with cardiovascular disease. This accounts for 20% or more of the hospitalizations of patients with end-stage renal disease in our program.

Another major problem for patients with end-stage renal disease is the occurrence of complications related to blood access. The preferred mode of blood access is the native arteriovenous fistula (231), and where this is not available a number of other techniques are available, the most common being an arteriovenous graft of Gortex or a vein graft (232). As many patients have the potential to survive for long periods of time, circulatory access requires careful planning and great attention to detail. Problems with access often relate to events occurring long before the patient requires dialysis. Casual placement of indwelling intravenous catheters in forearm veins during an intercurrent illness can result in thrombosis and loss of veins so that it is not possible to establish a native arteriovenous fistula. It is therefore essential
that patients with early renal failure be aware that they should warn medical and nursing personnel not to use forearm veins for any purpose unless absolutely necessary.

A well-functioning, mature fistula can be used for many years; we have one patient who has now used the same arteriovenous fistula for 20 years. Access surgery, whether an arteriovenous fistula or a graft, should be performed only by vascular surgeons who devote a considerable part of their time to access surgery and who, with the nephrologist, can assume long-term responsibility for maintenance of satisfactory circulatory access to each patient (233).

The common problems with arteriovenous fistulas and grafts include thrombosis and infection. For thrombosis, percutaneous angioplasty, injection of urokinase or streptokinase, or thrombectomy may be used; and in patients who have a tendency to recurrent clotting, a small dose of aspirin or other antiplatelet agent may be helpful. Thrombosis occurring in a mature fistula is usually due either to a hypotensive episode or to pressure on the fistula during an unrelated procedure. Infection in fistulas is often related to needle punctures for dialysis and usually responds to antibiotics. In a small proportion of cases, aneurysmal dilatation of the fistula may occur but can usually be corrected surgically. Other complications include venous hypertension and ischemia of the hand, and occasionally cardiac and hemodynamic complications may be associated with the high blood flow through a fistula. Endothelial hyperplasia at the anastomosis sites and consequent thrombosis is
more common in arteriovenous grafts than with fistulas; transluminal angioplasty may be used to correct this problem.

Access surgery is uncomfortable, and if it has to be repeated frequently is discouraging to the patient. Consequently complications due to access should be minimized. Nevertheless, access problems remain one of the major reasons for hospitalization and for morbidity in dialysis patients, accounting for 15% of hospitalizations in our program.
F. SURVIVAL RESULTS WITH DIFFERENT MODALITIES OF TREATMENT

Over the years there have been a number of reports on survival of patients with end-stage renal disease with the various modalities of treatment. These have come from individual facilities and from national registries such as the European Dialysis and Transplant Registry (131), the Canadian Registry (234), and the Australian and New Zealand Registry (235). Unfortunately at this time, there is no comparable national ESRD registry in the United States. Consequently, in order to illustrate the effects of treatment, the following results, except when stated otherwise, relate to patients treated through the regional program based on the Northwest Kidney Center in Seattle. Over the years, this program has treated more than 2,000 patients by the various modalities of dialysis and by transplantation (236).

What has been clearly demonstrated is that survival of patients with end-stage renal disease depends on a number of factors. Age at the time of starting treatment is one of the most significant of these. When survival curves are drawn based on ten-year age intervals, irrespective of the form of treatment, there is a smooth decrease in survival with increasing age, which suggests a linear relationship (Figure 1). Linear, quadratic, and cubic models have been developed, but neither the quadratic nor the cubic model give any significant improvement in fit over the linear model for describing the effect of age on survival. In our experience, the only exception to this age relationship is in patients under the age of 15, and this presumably reflects the lesser survival in the youngest patients (those under the age of 5). Similar results have
been found by others (237). What should be noted is that for patients aged 65 and over, the 5-year survival, irrespective of treatment, is approximately 25%. There was no difference in survival between males and females.

When patient survival was studied by race, there appeared to be slightly better survival in "other" patients—primarily Asians and American Indians—than in blacks or whites, but this was not of statistical significance (Figure 2).

Another major factor affecting survival is the cause of the renal disease. This has been analyzed for the commoner causes of chronic renal failure—chronic glomerulonephritis, diabetic nephropathy, congenital renal disorders, polycystic kidney disease, pyelonephritis, and primary hypertensive disease (Figure 3). Patients with renal failure secondary to congenital disorders have somewhat better survival, presumably because of their younger age. Those with renal failure due to diabetic nephropathy or primary hypertensive disease showed significantly poorer survival, presumably related to their generalized vascular disease.

A further major factor affecting survival is the presence of pre-existing disease or diseases at the time of starting dialysis. Figures 4 through 7 illustrate the effect of the presence of severe hypertension, cerebrovascular disease, cancer, and coronary artery disease on survival. There are significant differences related to all these preexisting problems. Survival is also related to the number of preexisting associated diseases the patient has at the time of starting treatment, whether or not these are comparable in severity (Figure 8).
The other remaining major issue is whether survival is comparable in patients with the different modalities of treatment. Patient survival has been compared with related donor transplantation, cadaver donor transplantation, and hemodialysis (238). The patient population was subdivided into those with diabetes or primary hypertensive disease as the cause for their renal failure, and those with other causes. While the duration of survival was less in the diabetic and hypertensive patients, the results of comparison of the modalities of treatment were similar in both population subgroups. Related donor transplantation clearly had better patient survival than the other modalities of treatment, but patient survival with hemodialysis and cadaver transplantation was not significantly different when account was taken of the time spent on dialysis prior to transplantation, and of the differences in age, number of associated diseases, and year of treatment in the patient populations treated by the different modalities. This analysis used the Cox proportional hazards model (239).

This leaves unanswered the question of comparison of survival with the different forms of dialysis. Conventional wisdom is that home hemodialysis patients have a better survival than center hemodialysis patients, that survival with CAPD may or may not be similar to that with hemodialysis, and that survival with intermittent peritoneal dialysis may be inferior. However, again, the problem is the different patient populations selected for the various treatments, selection being based on both medical and nonmedical factors. Consequently, the results in the patient population treated in the Northwest Kidney Center program between 1975
and 1985 has been analyzed using the Cox proportional hazards model. Comparisons were made between the different modalities of dialysis and with cadaver transplantation. When known risk factors were taken into account, intermittent peritoneal dialysis was found to be significantly inferior in terms of survival in comparison with center hemodialysis, home hemodialysis and CAPD. Home hemodialysis survival was somewhat better than center hemodialysis, but not significantly so, and there was no significant difference in survival between home hemodialysis, CAPD, and cadaver transplantation. These analyses also confirmed the importance of age and number of associated diseases as factors affecting survival, and showed that patient educational level had no bearing on this. Again, the year of treatment affected survival, patients treated more recently having better results than patients treated in the early years of the last decade. Unfortunately, there were not sufficient patient numbers to examine survival with CCPD.

The importance of these results is the assistance they give in selection of treatment. Rather than survival, the decision as to the form of dialysis for a given patient should be based on an evaluation of differences in the complications associated with the various forms of dialysis, and the potential effects of these on the patient's lifestyle, opportunity for rehabilitation, and family and social responsibilities. These same considerations should apply in making the decision as to whether a dialysis patient should receive a cadaver transplant. In this regard, the various reports on quality of life studies with different modalities of treatment are of importance (240,241). It also is apparent
that intermittent peritoneal dialysis, at least three times a week IPD as practiced over the last ten years, is a form of treatment which results in inferior survival, presumably because of inadequate dialysis as suggested previously (197). Consequently, it becomes important to gather information on CCPD to see whether results with this may more closely resemble those with CAPD.

These findings also suggest that an integrated program providing all modalities of dialysis and transplantation gives the greatest opportunity for optimal treatment of patients with end-stage renal disease. Unfortunately, at this time there is not enough information to compare survival with transplantation and dialysis in patients over the age of 65, but presumably these will not differ significantly from those illustrated here from a population representing all ages of patients.
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continuous peritoneal dialysis in the treatment of chronic renal failure.


OTA References - 31 -


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### TABLE 2
Medicare ESRD program incidence rates per million population, by age, sex, and race: 1978-80 average.

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<td>Female</td>
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<td>12</td>
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<tr>
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<td>37</td>
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<tr>
<th>TABLE 3</th>
<th>Primary diagnosis for newly entitled ESRD persons: 1973-80</th>
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<td>NUMBER OF PERSONS</td>
<td>13,320 6,553 6,805 6,245 7,226 7,505 8,315 9,310</td>
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<tr>
<td>Percent distribution</td>
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<td>ALL CAUSES</td>
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<td>Primary hypertensive disease</td>
<td>13.2 13.9 15.0 15.8 20.4 22.2 22.1 23.4</td>
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<tr>
<td>Diabetic nephropathy</td>
<td>7.0 11.9 12.2 14.0 15.8 18.0 18.7 21.8</td>
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<tr>
<td>Polycystic kidney disease</td>
<td>8.7 7.5 6.5 7.0 6.7 6.4 6.1 5.9</td>
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<tr>
<td>Collagen vascular disease</td>
<td>1.5 2.0 1.8 1.8 1.3 1.7 1.4 1.4</td>
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<tr>
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<tr>
<td>Etiology unknown</td>
<td>9.0 11.0 12.8 12.4 9.6 9.5 10.1 8.8</td>
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1 Less than 1 percent.

<table>
<thead>
<tr>
<th>TABLE 4</th>
<th>Medicare ESRD program incidence, by diagnosis and age: 1980</th>
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<tr>
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<td>NUMBER OF PERSONS</td>
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<tr>
<td>ALL CAUSES</td>
<td>%</td>
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<td>Glomerulonephritis</td>
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<td>Primary hypertensive disease</td>
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<tr>
<td>Diabetic nephropathy</td>
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<td>Collagen vascular disease</td>
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<td>Interstitial nephritis, other</td>
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<td>Amyloidosis</td>
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<table>
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<th>Cause of Death</th>
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<th>After Two Years</th>
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<td>Cardiovascular</td>
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<tr>
<td>CVA</td>
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<tr>
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<td>3.7%</td>
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<tr>
<td>Infection</td>
<td>13.5%</td>
<td>13.7%</td>
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<tr>
<td>Stop Treatment</td>
<td>12.7%</td>
<td>9.7%</td>
</tr>
<tr>
<td>Cancer</td>
<td>2.9%</td>
<td>2.0%</td>
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</table>

Figure 1 - Patient survival by age.

Figure 2 - Patient survival by race.
Figure 3 - Patient survival by renal failure diagnosis.

Figure 4 - Patient survival with and without preexisting severe hypertension.
Figure 5 - Patient survival in patients with and without preexisting cerebrovascular disease.

Figure 6 - Patient survival in patients with and without a history of cancer.
Figure 7 - Patient survival in patients with and without preexisting coronary artery disease.

Figure 8 - Patient survival based on number of associated diseases.