DIALYSIS SYSTEM

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Filed: Feb. 28, 1977

Int. Cl. 2B01D 13/00
U.S. Cl. 210/22; 210/321 B

Field of Search 210/22, 23, 321 B

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The improved hemodialysis system utilizes a second polymeric membrane having dialyzate in contact with one surface and a urea decomposition solution in contact with the other surface. The membrane selectively passes urea from the dialyzate into the decomposition solution, while preventing passage of positively charged metal ions from the dialyzate into the solution and ammonium ions from the solution into the dialyzate.

57 ABSTRACT

19 Claims, 4 Drawing Figures
**Fig. 1**

SPENT DIALYZATE

UREA + UREASE

\[ \text{NH}_4^+ \]

\[ \text{HCO}_3^- \]

DIALYZATE

**Fig. 2**

ARTERIAL BLOOD

PURIFIED DIALYZATE

**Fig. 3**

**Fig. 4**

ARTERIAL BLOOD

UREASE + UREA

\[ \text{NH}_4^+ \]

\[ \text{HCO}_3^- \]

TO VEIN

TO VEIN
DIALYSIS SYSTEM

ORIGIN OF THE INVENTION

The invention described herein was made in the performance of work under a NASA contract and is subject to the provisions of Section 305 of the National Aeronautics and Space Act of 1958, Public Law 83-568 (72 Stat. 435; 42 USC 2457).

BACKGROUND OF THE INVENTION

1. Field of the Invention
The present invention relates to a hemodialysis system and, more particularly, to an improved system for selectively removing urea from dialyze.

2. Description of the Prior Art
A sizable fraction of the estimated 50,000 people who die of kidney failure each year in the United States are free of other complications and might be restored to useful life if their kidney function could be provided artificially. At present, artificial kidneys (using hemodialysis) and clinical procedures have been developed to the point where long-term sustenance of life by periodic hemodialysis is practical in many cases.

The limitations in using hemodialysis are the small number of patients who can be treated with a given kidney machine and the considerable expense of maintaining and staffing a kidney-treatment center. Obviously, a desirable solution lies in the development of an artificial kidney which is inexpensive, portable and capable of being operated outside the confines of a hospital with a minimum of medical attention. Attainment of this solution will require increased efficiency of mass transfer and further optimization in design of artificial-kidney systems.

In recent years, considerable attention has been focused on methods of reducing the size of the artificial kidney. This requires miniaturization of the membrane-containing dialyzer and a significant reduction in the volume of dialyzing fluid. It is generally conceded that the toxin primarily responsible for the uremic syndrome has not yet been identified. Even though urea is not considered particularly toxic, its removal is one of the chief objectives of dialysis as practiced today. The reason for the concentration on urea removal is that, in the absence of more specific knowledge, dialysis based on this principle is obviously beneficial. At least two explanations suggest themselves: (a) Unidentified toxicants are removed along with the urea. (b) Urea produces toxic products.

In order to increase the efficiency of hemodialysis, it is desirable to maintain the trans-membrane concentration gradient of waste metabolites as high as possible. Low waste concentrations in the dialyzing fluid have in the past been maintained by two methods. The more widely used method is the continual dilution of the dialyzed substances in a large reservoir of fluid, usually 100 to 300 liters. A second method of maintaining the gradient is to use the dialyzing fluid in a single-pass operation, where the waste-bearing effluent is discarded. Even then, more than 100 liters of fluid are required. The current research trend in obtaining low concentrations of wastes is to remove them selectively from the dialyzing fluid. Such an approach would allow the use of much smaller volumes of dialyzing fluid. Among all waste products, urea is by far the major waste metabolite which must be removed daily from the body fluid. Three major methods of urea removal from dialyze have been reported.

The first procedure utilizes an activated carbon bed which removes urea by adsorption. However, the demonstrated capacity for urea is only 0.2-0.8 grams per 100 grams of carbon. In another method urea is reduced by enzymatic hydrolysis either inside microcapsules or by the combination with other absorbents. However, enzymatic decomposition of urea produces large concentrations of ammonium ion which is toxic. Therefore, it is essential to achieve rapidly removal of the ammonium ion or it can accumulate in the dialyze and enter the blood. A commercial apparatus utilizes sodium zirconium phosphate to remove the ammonia produced by enzymatic decomposition of urea in the presence of urease. Though this system does remove urea from dialyze it also removes essential metal ions such as strontium and calcium which must be replaced. Furthermore, large amounts of zirconium phosphate are required and the process is expensive since the spent zirconium phosphate absorbent is not regeneratable and must be discarded.

SUMMARY OF THE INVENTION

The improved hemodialysis system in accordance with the invention obviates the need for an ammonia absorbent in the urea decomposition solution. The system of the invention permits purification and recirculation of dialyzed fluid in an efficient manner and substantially reduces the quantity of dialyze needed for dialysis making it feasible to produce a portable, or wearable artificial kidney system. The degradation products produced by the dialyze treating portion of the apparatus forms a soluble toxic component and a soluble nontoxic component. The toxic component is retained in the treating section of the apparatus while the nontoxic component may migrate or diffuse back into the dialyze for safe elimination in the body of the patient. The system of the invention also prevents diffusion of essential metal ions from dialyze into the treating solution.

Urea is continuously removed from dialyze in accordance with the invention by passing the urea in contact with a polymeric membrane selectively permeable to urea. The urea passes through the membrane into a solution containing a urea decomposition agent such as the enzyme urease. The urea is decomposed into ammonium and bicarbonate ions. The membrane is selectively impermeable to ammonium ion but may pass the bicarbonate back into dialyze and eventually through the primary membrane into the blood. However, bicarbonate is nontoxic and is readily decomposed and eliminated by exhalation as carbon dioxide. The membrane used in the dialyze purification section is also selectively nonpermeable to essential positive cations such as strontium and calcium which remain in the dialyze obviating the need to replenish these metals as is practiced in commercial systems. Preferred membranes are positively charged membranes, suitably polyquaternary substituted cation exchange resins, since such membranes do not require gradient effects for providing the desired nonselectivity to passage of cations in either direction.

The dialyze treating apparatus of the invention has demonstrated the capability of removing almost half the urea content of test dialyzates in 20 hours while retaining up to about 90% ammonium ions in the treating chamber. Operation is continuous and regeneration
simply involves replacing the low cost urease enzyme.
The system substantially reduces the amount of dialy-
zate required and a small size is indicated for use in
current clinical dialyzers in a typical thrice weekly
dialysis regimen.

These and many other features and attendant advan-
tages of the invention will become apparent as the in-
vitation becomes better understood by reference to the
following detailed description when considered in con-
junction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic illustration of a spent dialyzer
urea removal unit in accordance with the invention;
FIG. 2 is a schematic illustration of an artificial kid-
ney hemodialysis unit incorporating the dialyzate treat-
ing unit of the invention;
FIG. 3 is a schematic illustration of a hollow fiber
hemodialysis apparatus in accordance with the invention;
and
FIG. 4 is a schematic illustration of an artificial kid-
ney machine incorporating a single cationic membrane
and having the urease present in the dialyzate.

DESCRIPTION OF THE PREFERRED
EMBODIMENTS

Referring now to FIG. 1 the dialyzate treating unit 10
of the invention includes a container 12 divided into a
dialyzer chamber 14 and a urea decomposition cham-
ber 16 by a common membrane 18. Spent dialyzer
enters chamber 14 through inlet 20 and purified dialy-
zate leaves through outlet 22. The membrane 18 is per-
meable to the urea which diffuses into chamber 16
which contains a solution of urease enzyme. The en-
zyme decomposes the urea into ammonium ion which is
repelled by the membrane 18 and is retained in chamber
14 and into bicarbonate which may permeate through
the membrane 18 into the dialyzate. The purified dialy-
zate may be recycled to the dialysis section of a hemodi-
alysis unit.

The membrane 18 is formed of a high molecular
weight synthetic polymer having good tensile strength,
elongation and flexural strength. The membrane is se-
lectively permeable to solvated urea molecules while
preventing passage of larger molecules and preventing
passage of cationic ammonium or metallic ions in either
direction. Preferred membrane materials are synthetic
 polymers containing cationic groups such as phospho-
nium, sulfonium or quaternary nitrogen. A suitable
membrane material is RAI P-4025 which is a polyethyl-
ene containing 45% grafted vinylpyridine having an
ion-exchange capacity of 5 meq/gm and a resistance of
1 ohm-cm². The membrane may be utilized in various
thicknesses depending on the desired flow rate and
mechanical properties required in the purification unit.
The thickness may be from 1–15 mil, generally around
2–10 mil in thickness. The surface area membrane is
selected so as to give adequate removal of urea from the
dialyzate. From experiments to date, it is estimated that
the surface required would be about 10 to 40 square
inches.

The treating chamber 16 should contain concentra-
tions of low molecular weight ingredients equal to that
contained in the dialyzate chamber 14. For example,
buffer concentration should be equivalent as should
saline concentration to prevent diffusion from dialyzate
into the treating solution. The urease concentration
should be sufficient to significantly decrease the amount
of urea in the dialyzate. Usually the urea concentration
should be at least 25–300% the concentration of the
urea in the dialyzate in order to provide adequate peri-
ods before the need to recharge urease to the treating
chamber.

The dialyzate treating unit of the invention can be
combined with many diverse types of hemodialysis
units. In its simplest form shown in FIG. 2 the dialyzate
chamber 24 would have one wall formed by the pri-
mary membrane 26 and another wall portion formed of
the secondary treating membrane 28. Blood from an
artery enters the inlet 30 to continuous flow through
chamber 32 and leaves through outlet 34. As the blood
flows past primary membrane 26 such as a cellulose
ester, preferably a cuprammonium treated cellulose
acetate, urea diffuses through membrane 26 into the
dialyzate chamber 24. The urea in turn will diffuse
through secondary positively charged membrane 28
into the treating section 36 where it will be decomposed
by urease into ammonium and bicarbonate ions. The
bicarbonate ions will build up in concentration and can
flow backwards through membrane 28 into the dialy-
zate and in turn through membrane 26 into the blood.
The blood will leave through outlet 34 and will be
returned to a vein of the subject by intravenous injec-
tion.

In the typical artificial kidney machine a very thin
film of flowing blood is separated from the surrounding
dialyzate solution by an approximately 3 mil thick semi-
permeable cellulose acetate membrane. This membrane
allows substances in normal molecular solution and the
solvent to pass through its pores but it prevents the
passage of very large molecules such as proteins and
cellular constituents of the blood. The membrane does
not permit the passage of bacteria and viruses so that
sterilization of the apparatus located outside the mem-
brane is not required. Since the apparatus operates by
diffusion and osmosis the dialyzate liquid must contain
physiological concentrations of all membrane-passing,
dissolved normal constituents of the blood, electrolytes
in particular, which are required to be maintained in
the blood. The dialyzate may also contain high concen-
trations of substances which it is desired to introduce into
the blood stream by diffusion such as drugs, dextrose,
etc. The dialyzate must be at the same temperature as
the blood this usually being effected by thermostatic
control. Oxygen may be bubbled into the dialyzate so as
to maintain the oxygen content of blood in a normal
condition. The kidney machine may also contain a
pump and means to introduce anticoagulants such as
hirudin or heparin into the blood to prevent clotting of
the blood on all surfaces of the apparatus that are in
contact with blood.

A principle requirement of a kidney machine is that
the semipermeable membrane should have a large sur-
face area to insure adequate osmotic interchange be-
tween the blood and the dialyzate. This usually requires
that the blood flow in a very thin film to provide maxi-
mum contact with the membrane bathed by the dialy-
zate liquid. Many configurations of kidney machines
have been devised and are all compatible with the dialy-
zate treating section or unit of the invention. The blood
dialyzate portion of the equipment may be in the form
of a rotary drum apparatus in which a blood-filled flat
cellophane tube is wound in helical fashion around a
rotating drum made of wire mesh, the drum being
bathed or submerged in dialyzate. A sandwich-type
apparatus has been devised and can more readily be
utilized for ultrafiltration under pressure. In this form of construction a flat cellophane bag is sandwiched between grooved plates of plastic. The dialyzate liquid flows through the grooves in the opposite direction to the flow of blood in the cellophane bag. However, this configuration provides dead flow spaces providing an inherent danger of clotting unless large amounts of anticoagulants are used. Another configuration is a twin-coil apparatus in which the semipermeable membrane is in the form of a flat, wide cellophane tube which is coiled in two tiers around the hollow core. The coils are mounted inside a container through which the rinsing liquid is passed. A very thin film of blood flows through the coils which present a large area of contact with the surrounding liquid. This has the advantage that the modules can be supplied, sterilized and ready to use inside the container and can be quickly and easily exchanged.

Hollow fibers also offer the advantage of high surface area in a very compact volume. Hollow fibers may be utilized for either or both of the membranes discussed herein. A more complete artificial kidney machine employing hollow fibers is illustrated in FIG. 3. In the kidney machine 40 of FIG. 3 a cylindrical container 42 houses the dialyzate chamber 44. The container 42 is surrounded with a heating jacket 46 such as an electric resistance heater powered by thermostatically controlled power unit 48. The cellulose acetate membrane is in the form of a plurality of fine filamentary hollow fibers 50 having their inlet ends potted to a common inlet header 52 and their outlet ends connected to a common outlet header 54. Each of the headers 52 and 54 can be threadingly and sealingly received into the side walls 56, 58 of the container 42.

The second membrane may also be in the form of a plurality of hollow fiber tubes containing the urease solution and connected to the common inlet and outlet headers as in the blood chamber described above. However, since there is no need to recirculate the urease solution the dialyzate treating chamber can be in the form of a cartridge 60 in which the plurality of hollow fibers 62 have their inlet ends inserted to a base 64 which is threadingly received into a wall 68 of the container 42. A further replaceable cartridge element 64 may be provided in the chamber containing an effective absorbent such as activated carbon to remove other impurities from the dialyzate.

The kidney machine 40 of FIG. 3 is utilized by filling the chamber 44 with dialyzate through inlet plug 66. The absorbent cartridge 64, dialyzate treating cartridge 60 and blood cartridge 68 are inserted. The heater 48 is turned on and a first catheter 70 is inserted into a vein of the subject and connected to blood outlet 72 and a second catheter 74 is inserted into an artery of the subject and connected to the pump 76. The pump is then energized and as blood is drawn from the artery and through the hollow fiber tubes 50 of the blood cartridge, urea passes into the common body of dialyzate and then through the walls of hollow fiber tubes 62 of the cartridge 60 where urea is decomposed and retained therein. However, the positively charged walls of the hollow fibers prevent the ammonium ions from entering the dialyzate and prevent metal cations from the dialyzate from entering the tubes 62. Other impurities are absorbed onto the granules 78 of activated carbon within the cartridge 64. As the urease containing cartridge 60 is exhausted a new cartridge is inserted. Similarly, the activated carbon cartridge 64 can be replaced as needed. Should the hollow fibers of the blood cartridge 68 become damaged or worn out, that unit can be replaced. Any of the cartridges can be readily removed for sterilization.

An example of practice follows.

Two cylindrical chambers of about 30 mls capacity were separated by a positively charged membrane (RAI P-4025 membrane) having a surface area of about one square inch. Synthetic test solutions were introduced on each side of the membrane. The synthetic dialyzate contained about 2 gm/liter of urea, 4.5 gm/liter of sodium acetate trihydrate and 5.8 gm/liter of sodium chloride. The urease chamber test solution contained about 1 gm/liter of urea, 4.5 gm/liter sodium acetate trihydrate and 5.8 gm/liter of sodium chloride.

After six hours analysis showed that the quantity of urea in dialyzate had dropped about 25% and that significant concentrations of ammonium were present in the urease chamber. After 20 hours, urea concentration had dropped 45% and about 90% of the ammonia was present in the urease chamber, but the urease chamber now is found to contain no urea.

The above test demonstrates that urea readily diffuses through the membrane and is rapidly hydrolyzed to ammonium bicarbonate. The initial rate of removal of urea from dialyzate was about 0.1 gm/hr and about 0.05 gm/hr after 20 hours for the 4–5 mil thick film utilized. Higher diffusion rates can be expected with thinner membranes. The positively charged membrane also demonstrated the ability to isolate the toxic ammonium ion from the dialyzate and to retain the essential metal cations within the dialyzate. Preliminary estimates indicate that the dialyzate membrane need only require 24 in² of surface area to be compatible with the urea production of conventional hemodialysis units. A cartridge or treating chamber could readily be housed in a 1 ft. × 2 in. × 2 in. unit which is well within design constraints for continuous operation in portable or wearable artificial kidney apparatus for a typical thrice weekly dialysis regimen. Urease enzyme is not expensive and can readily be recharged for the next dialysis treatment.

The urease solution could be pumped past the membrane and removed from the chamber for continuous replenishment of urease and removal of ammonium ions. Similarly the dialyzate could be continuously pumped in concurrent or countercurrent flow past both membranes to increase urea transfer rate from the blood into the dialyzate. Another configuration would be to encapsulate the urease within a positively charged polymeric membrane and place the capsules in-line in the dialyzate flow path to absorb urea from the dialyzate while retaining ammonium salts within the capsules.

The cationic polymer membrane can also be utilized to form a single membrane, low dialyzate volume artificial kidney machine. Referring now to FIG. 4, the machine 70 includes a container 72 divided into a blood chamber 74 and a dialyzate chamber 76 by means of a cationic membrane 78. The membrane 78 repels and prevents passage of NH₄⁺ ions 80 and M⁺ ions 82. Therefore the dialyzate need not contain equilibrium concentrations of the essential cations such as strontium or calcium.

The blood chamber 74 contains an inlet 84 and an outlet 86. As the blood flows past the membrane 78, essential large proteins, cellular constituents and cations are retained in the blood, while urea 88 traverses the membrane 78, enters the dialyzate chamber 76 and is
decomposed into NH₄⁺ and HCO₃⁻. The ammonium ion is retained in the dialyzate chamber. Substantially smaller amounts of dialyze are required compared to dilution and continuous flowing dialyzate configurations.

It is to be realized that only preferred embodiments of the invention have been described and that numerous substitutions, modifications and alterations are permissible without departing from the spirit and scope of the invention as defined in the following claims.

What is claimed is:

1. A system for selectively removing urea from an aqueous liquid containing urea and positive metal cations comprising in combination:
   a container divided into a first chamber and a second chamber by means of a continuous sheet of cationically charged polymeric membrane selectively permeable to urea and having low permeability to cations;
   said first chamber including means for receiving said liquid; and
   said second chamber receiving a solution containing a urea decomposition agent whereby said cations are repelled by said membrane and retained in said liquid and urea permeates through the membrane into the solution and is decomposed into bicarbonate and ammonium, the ammonium being retained in the solution in the second chamber.

2. A system according to claim 1 in which the membrane contains quaternary ammonium groups.

3. A system according to claim 2 in which the membrane is a vinyl pyridine grafted polyethylene having a thickness from 1 to 15 mils.

4. A system according to claim 1 in which the membrane has an exchange capacity of from 1 to 20 meq/gm.

5. A system according to claim 1 in which the first chamber is a hollow body having said membrane as one wall thereof and having an inlet and outlet for flowing said liquid past a first surface of the membrane.

6. A system according to claim 1 in which the urea decomposition agent is urease.

7. A system according to claim 1 in which the urea concentration of the solution is at least 25% by weight of the urea content of the liquid.

8. A system according to claim 1 in which the liquid is dialyze containing urea and further including a blood dialysis membrane selectively permeable to urea having one surface in contact with said dialyze and a second surface for contacting a flow of blood.

9. A system according to claim 1 in which the urea containing blood is blood dialysis membrane selectively permeable to urea having one surface in contact with said dialyze and a second surface for contacting a flow of blood.

10. A method of selectively removing urea from an aqueous liquid containing urea and positive metal cations comprising the steps of:
    placing the liquid in contact with a first surface of a cationically charged polymeric membrane selectively permeable to urea and having low permeability to cations;
    placing an urea decomposition solution containing an urea decomposition agent in contact with a second surface of the membrane; and
    selectively permeating urea from the liquid through the membrane into the solution thereby decomposing urea into ammonium cations and bicarbonate whereby the ammonium cations are retained in the decomposition solution and the metal cations are retained in the liquid.

11. A method according to claim 10 in which the membrane contains quaternary ammonium groups.

12. A method according to claim 11 in which the membrane has an exchange capacity of from 1 to 20 meq/gm.

13. A method according to claim 12 in which the membrane is a vinyl pyridine grafted polyethylene having a thickness from 1 to 15 mils.

14. A method according to claim 11 in which the agent is urease.

15. A method according to claim 14 in which the urea concentration of the decomposition solution is at least 25% of the concentration of urea in the urea containing liquid.

16. A method according to claim 14 in which the urea containing liquid is dialyze from a blood dialysis unit.

17. A method according to claim 14 in which the urea containing liquid is blood.

18. An artificial kidney machine comprising in combination:
    enclosure means having an inlet and an outlet, and
    having a wall surface formed of a cationically charged membrane defining a channel for flowing urea containing blood past one surface of the membrane;
    urea removal means comprising walls defining a chamber, said chamber including a solution of urease having a concentration at least 25% by weight of the urea content of the blood; and
    means for supplying the urea permeate from the second surface of the membrane to the urease solution.

19. A machine according to claim 18 in which the membrane forms a common wall portion of said channel and chamber.