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Recent Advancement in Renal Replacement Therapy*

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1. Modalities of Treatment

In the early stage of the renal substitution therapy dialysis was the only one modality available clinically.

However, in 1964 hemoperfusion was introduced into this field by Yatzidis and in 1967 hemofiltration using synthetic filter was also indroduced by Henderson as an alternative mode to treat renal failure patients.

In 1978 plasmapheresis using membrane was introduced by Inoue and Yamazaki and CAPD also has become widely used in this year.

These situations have made it impossible to cover all the modalities involved in this field under the word "dialysis." Therefore, the word "blood purification" has been proposed by us to be used to cover all the modalities.

The mechanisms involved are shown in Figure 1 along with its combination. Hereafter, main topics will be introduced(Figure 1).

2. Recent Advancement in Dialysis Therapy

There are many aspects in the advancement of dialysis therapy. They are summarized in Table 1.

As for machine, those equipped with autoregulation, programming system using computor have become increasingly popular. Especially for ultrafiltration and sodium level control, they are very effectively used.

As for dialyzers hollow fiber has become more and more widely used, and variety of synthetic polymer membrances including polymethylmethacrylate(PMMA), ethylene-vinylalcohol copolymer(EVA), polysulfon, polyacrylonitrile(PAN) have been developed and incorporated in dialyzers.

Biocompatibility of these membrance especially degree of leukocyte reduction and complement activation have become a matter of concern as parameters of hypersensitivity reaction(Figure. 2, 3)

Other improvements are related to dialysate. They include the use of bicarbonate instead of acetate, alternate use of high sodium and low sodium dialysate, cell wash dialysis(introduced by Maeda et al.) and low temperature dialysis.

3. Hemofiltration

In hemofiltration, the mechanism involved in blood purification is similar to that observed in glomerulus. Therefore, it is the most physiological mode from the theoretical point of view.

In human kidney, ultrafiltrate produced by glomerular filtration is selectively reabsorbed in the tubulus to make complete urine. In conventional hemofiltration such a function

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is defective.

To substitute this tubular function, a fluid similar to the one absorbed in the tubulus is produced in a factory and infused to replace the removed water and solutes.

There are two modes in this process; predilution which means to add substitution fluid first and then remove the corresponding volume through the filter, and postdilution in which fluid is removed first through the filter and corresponding dose is substituted down stream to the filter. Clinically, postdilution method is more widely used to save substitution fluid.

The advantage of this mode is to reduce complications such as hypotension, nausea, vomiting and headache which accompanies during and after dialysis.

In Figure 4, shown are examples in which disappearance of side effects is obvious by observed in crossover study.

In Figure 5, shown are changes of body weight in crossover study. In hemodialysis, body weight after treatment elevates gradually after each treatment by insufficient removal of water. On the contrary during hemofiltration interval it gradually decreases to the patient's optimal level.

From these studies it has become apparent that the hemofiltration is a better treatment in terms of side effects.

The mechanism of this advantage of the modality lies in the effective removal of middle molecular substances compares to small molecules. Since change in osmolarity is low, disequilibrium syndrome and body fluid shift from extracellular to intracellular is not likely to occur.

The disadvantage of the hemofiltration, however, lies in the necessity of infusing substitution fluid. Usually in routine hemofiltration which is repeated 3 times a week, it is necessary to infuse 18～20 l of substitution fluid. The volume und accompanying labor, along with its cost impose a restriction upon its wide spread application.

To combine advantage of hemofiltration to the advantage of conventional dialysis which is known to be effective to remove small molecules, a new composite system is created which is known as simultaneous hemofiltration and hemodialysis, abbreviated as hemodiafiltration. Figure 6, is the diagram of the system. Using this mode of treatment removing small molecules by filtration and middle molecules by dialysis, it is possible to shorten the duration of treatment from 5 hours to 3 hours without causing serious complications(Figure 6, 7, 8).

In recent years continuous arterio-venous hemofiltration(CAVH) which was first introduced by Kramer in 1977, has gained increasing interest from doctors who have had difficulties in controlling overhydration refractory to diuretics.

The filter used in this mode is made from polysulfon hollow fiber, and using external shunt or catheters the blood circulates through the blood live connecting the filter. Without blood pump and intentional positive or negative transmembrane pressure, continuous hemofiltration is performed(Figure 9, 10, 11).

4. Hemoperfusion

Hemoperfusion using activated carbon has several defects as a mode used for renal substitution therapy. Since it can not remove water, electrolytes and urea in addition to the difficulty in controlling pH, it is only used as an adjunct to dialysis or filtration to improve the efficacy of removing middle

molecular substances. Its main object is now confined to hepatic assist and drug intoxication.

However, in recent years it has gained renewed interest as an effective meassure to be used in secondary process in plasmapheresis. A new sorvent IO-2 and IMP and other compound applicable to immune disease were introduced by several investigators including Yamazaki and Terman.

5. Implantable Kidney

Implantation of artificial kidney is a long awaited dream of investigators involved in dialysis therapy. The progress has three stages, namely portable, wearable and implantable stages.

Some technical inovations and advancements are necessary to move to the next stage. To be portable, an indepencency from waterworks is necessary, and to be wearable, total weight less than 10kg is requested. In this case a function to regenerate the dialysate should be equipped. To be implantable, it is necessary to develope membrane which functions over a year besides the weight and dialysate regeneration.

As for portable artificial kidney, small machines are already available and as for wearable kidney, a small filter with blood line and driving system has been developed.

This filter removes body fluid 6~8 l/day. However, since in this system no function is equipped to regenerate ultrafiltrate to be used for substitution fluid administered orally is used to compensate the fluid loss. Using this system we have succeeded to maintain anuric patient for couple of months.

To develop implantable kidney it is necessary to satisfy conditions listed in Table 2.

As a basic study to examine the long term function of a membrane, filters made from ethylene-polyvinyl alcohol copolymer were implanted in dogs and circulate the blood from femoral artery to femoral vein. In spite of the continuous use of heparin all tested filters thrombosed within a week, scanning election microscopic examination revealed a thick fibrin deposit with sequestered blood cell (Figure 12).

6. CAPD

As it is well known CAPD stands for continuous ambulatory peritoneal dialysis. It is a variation of intermittent peritoneal dialysis.

By changing a glass bottle to plastic bag and prolonging dwell time, intermittent peritoneal dialysis has transformed into semi implantable kidney.

The most important thing in CAPD treatment is to prevent infection. For this purpose development of clean and safe connection is mandatory. In our country Terumo has made their connecting device consisting of metal and ceramics. At the time of connection they are heated using alcohol lamp for several seconds. By heating, both ends are sterilized and at the same time metal joint enlarges which makes it possible to insert ceramic that remains at its original size (Figure 13, 14).

There are two other methods now under clinical examination. They are ultraviolet method introduced by Travenol and splice method of Dupont.

By these technical advancement the result will be improved.

As is abvious from the developments described above, we have now many moda-

lities of treatment with variety of specificity. Using these technology a better treatment of renal failure patients will be achieved.

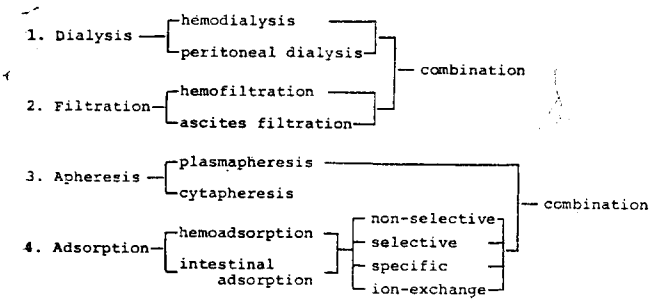

Figure 1. Principes and Modes of Blood Purification Therapy

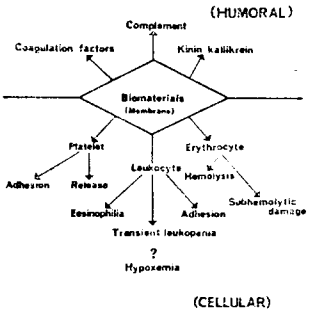

Figure 2. BLOOD MEMBRANE INTERACTION

Table 1

Improvement in Dialysis Type Artificial Kidney

1. Machine
   1) Autoregulation (TMP, UF Volume)
   2) Program (Sodium, UF Volume)
   3) Miniaturarization (Portable, Wearable)
2. Dialyzer
   1) Assembly (HFK, etc.)
   2) Quality Control (Leak, etc.)
   3) Sterilization (Antoclave, Radiation)
3. Membrane
   1) Material (PMMA, EVA, PAN, etc.)
   2) Wall Thickeness
   3) Structure
4. Dialyzate
   1) Alkalifying Agent (Acetate, Bicartonate)
   2) Concentration Control (Sodium, Cell Wash)
   3) Temperature Control (Hypothermia)
   4) Regeneration (Adsorption, Degradation)
5. Anticoagulation
   1) New Anticoagulants(FOY, FUT, Prostacycline)
   2) Non-Heparin

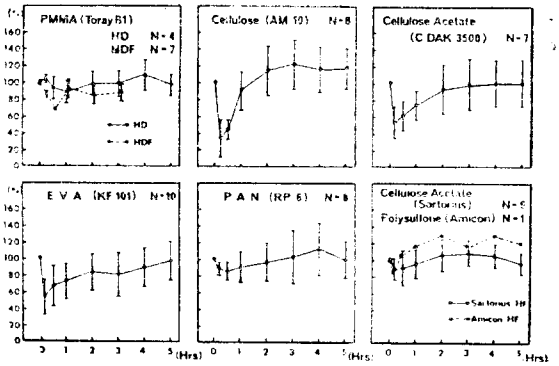

Figure 3. WBC Count During Hemodialysis & Hemofiltration with Various Membranes

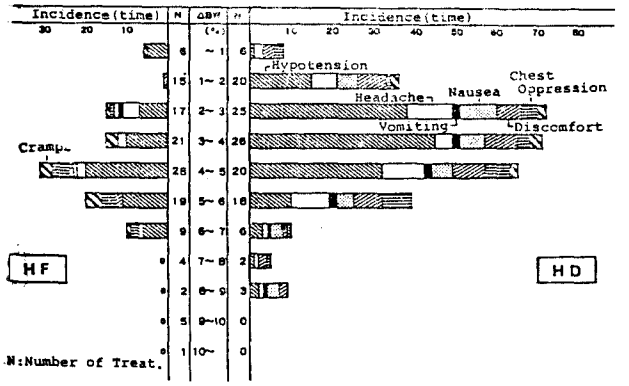

Figure 4. INCIDENCE OF DISEQUILIBRIUM IN RELATION TO BODY WEIGHT CHANGE

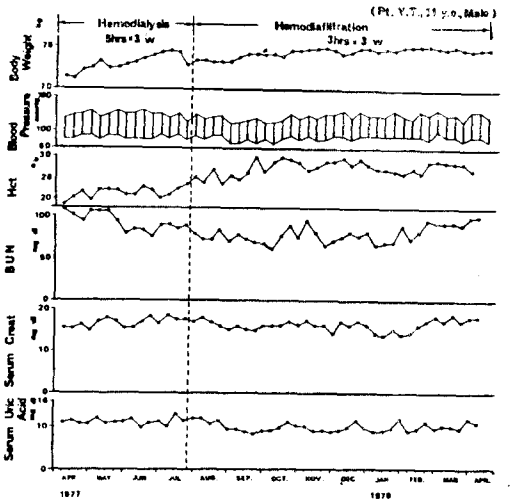

Figure 7. CLINICAL COURSE OF A PATIENT

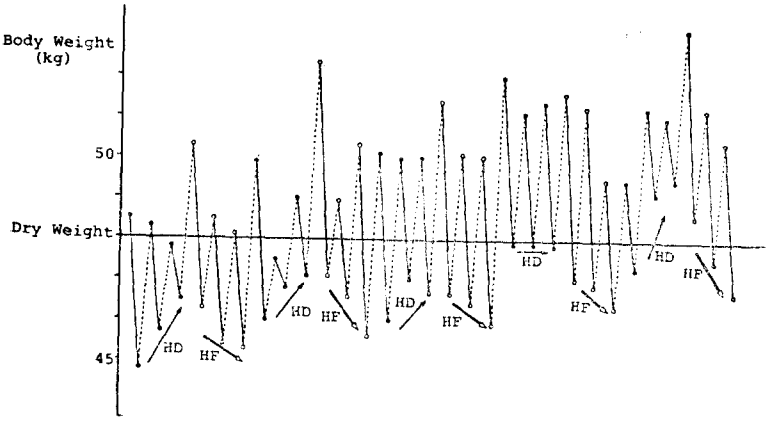

Figure 5. BODY WEIGHT CHANGE HD VS. HF

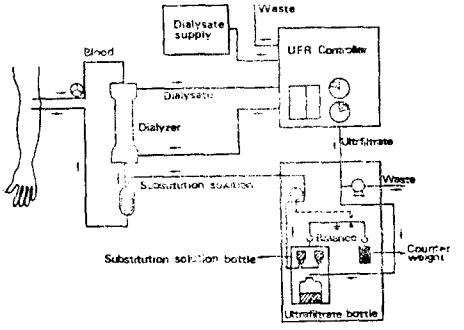

Figure 6.

Figure 8.

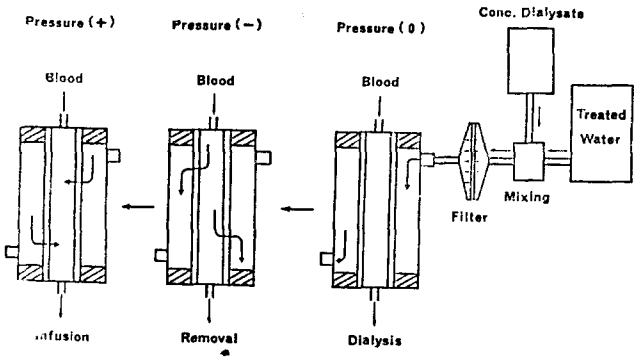

Figure 9. HDF USING CENTRAL SUPPLY SYSTEM

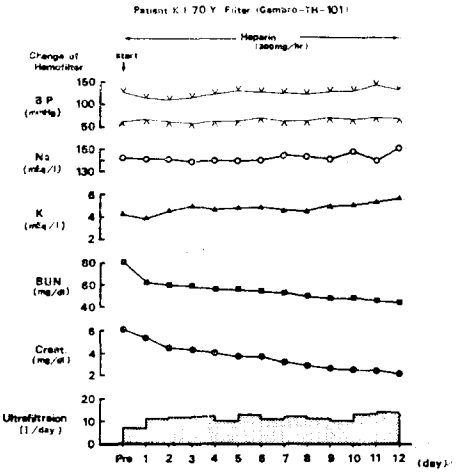

Figure 11. Clinical course of CAVH treatment

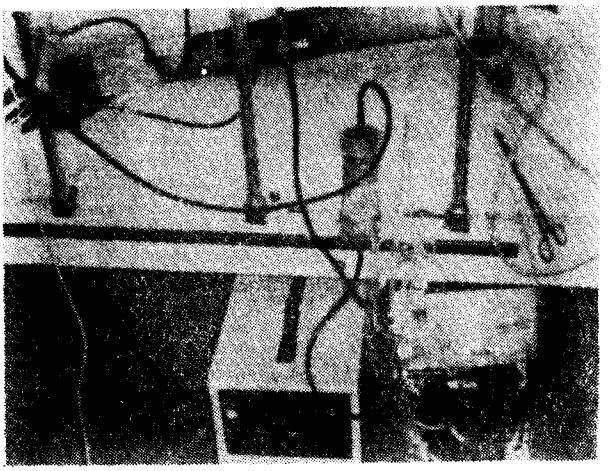

Figure 10.

Table 2

CONDITIONS REQUESTED TO IMPLANTABLE ARTIFICIAL KIDNEY

1. Implantable size and weight
2. Free from waterwork
3. Implantable energy source
4. Long term function of membrane
5. Long term functioning regeneration system
6. Antithrombogenicity
7. Abscence of severe tissue reaction

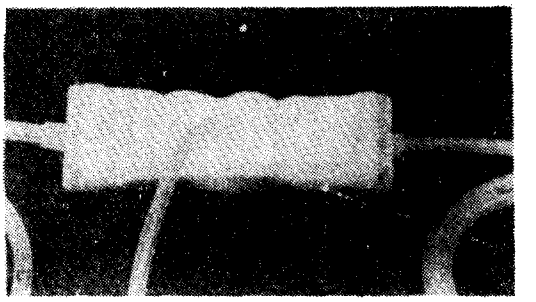

Figure 12.

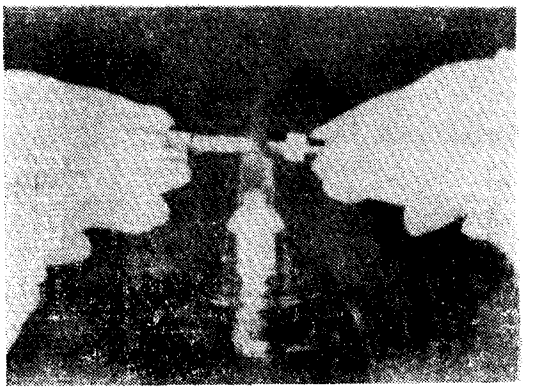

Figure 13.

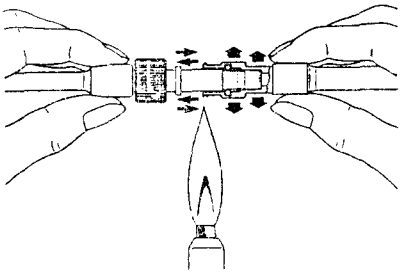

Figure 14.