TECHNOLOGY ASSESSMENT

ON

FUTURE DEVELOPMENTS IN LIFE SUSTAINING TECHNOLOGIES FOR ELDERLY

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I. OVERVIEW

In order to sustain or provide an improved quality of life for the elderly, various types of artificial organ technologies are available and being successfully applied. One technology available is hemodialysis. Originally, the patient population on dialysis was relatively young; however, the life sustaining capability of hemodialysis has been such that the current average age of the dialysis patient is now considerably higher and is increasing yearly. The mean age of patients beginning chronic dialysis is rapidly increasing and in some centers approaches 60 years of age[1]. Some parts of the United States reported that over 40% of all patients treated in 1982 were older than 60 years[2]. Presently 20-25% of the patients are 70 years or older when started on dialysis[3]. These patients have a high risk for atherosclerotic heart disease, peripheral vascular disease, chronic obstructive pulmonary disease, diabetes mellitus, malignant tumors and cerebrovascular accident (Table 1, Figure 1).

While the increased incidence of cancer [4,5], abnormality of lipid metabolism[6], abnormality of bone metabolism[7], and inhibition of immune system [8] in patients on maintenance hemodialysis have been reported, these problems may be related to the dialysis system itself in terms of biocompatibility and/or ineffectiveness of the therapy to remove so called "uremic middle molecules". The middle molecule" hypothesis is that these substances, thought to be uremic toxins and a cause of the above complications[9], may not be adequately removed satisfactorily by

conventional dialysis method with the present cellulosic dialysis membranes[10].

Elderly patients, especially, are more susceptible to these complications and are likely to develop secondary disease conditions.

Therefore, the basic strategy for chronic dialysis in the elderly is to develop the most adequate and cost effective system, including several alternative treatments (Table 2). When compared to the hemodialysis cost in a dialysis center, home dialysis is much less expensive because it does not require the involvement of a doctor or a nurse. There is no reason to hesitate to start self-care dialysis even in the elderly patient[11]. However, the number of patients who participate in home dialysis are appreciably lower than patients on center units[12]. Miniaturization of the device can make it easier to perform home dialysis and also improve the social activity of the patient. Continuous ambulatory peritoneal dialysis (CAPD) is the one modality that has been shown to stimulate home and self-care dialysis.

In order to establish a more safe treatment modality, the development of membranes with improved biocompatibility is important. Improved dialysis sterilization methods, dialysate composition and anticoagulant type used for extracorporeal circulation also are important from the safety point of view. Utilization of new treatment modality will improve the effectiveness of detoxification, provide for a safer treatment and possibly reduce the overall cost of therapy.

It has been possible to treat diseases associated with the imbalance of small molecules as is done by hemodialysis for renal failure but it is now possible to treat various diseases associated with the imbalance of macromolecules. The recent introduction of membrane plasmapheresis makes selective removal of pathological macromolecules possible. On-line plasmapheresis technologies that have been developed include double filtration, cryofiltration[13], thermofiltration[14], and immunoabsorption[15]. Utilizing these technologies, it is possible to treat autoimmune disease patients who have failed conventional drug therapies[16]. Successful applications have included the treatment of rheumatoid arthritis[17]. It is also documented that end-stage kidney disease and irreversible renal damage[18,19] can be prevented through various types of plasma treatment. Montoliu et al reported that three patients with mesangiocapillary glomerulonephritis treated by 4 liters of plasma exchange (10 to 16 times) showed improvements of renal function[18]. Three patients with myeloma kidney who initially received treatment including furosemide, sodium bicarbonate and peritoneal dialysis with no beneficial effect were treated by 3 to 5 liters of plasma exchange 2 to 3 times[19]. All the patients showed a marked improvement in renal function. The authors described that all therapeutic measures attempting to decrease serum light chain (Bence Jones) concentration may be of primary importance in management of acute renal failure in multiple myeloma. Since some of the chronic renal diseases that cause end-stage renal failures are of immunologic origin, it is

assumed that they can be prevented through this technology. If this is possible, plasmapheresis treatment will not be an end stage treatment like hemodialysis which is required until the patient dies or is successfully transplanted. As described above, a limited number of plasmapheresis treatments can reverse kidney failure, and it may be possible to reduce the number of patients requiring dialysis treatments. By applying this new technology, it is hoped that the number of new dialysis patients can be substantially reduced. At this time, there are over 80,000 dialysis patients in the U.S. alone. The annual increase in the number of dialysis patients is over 5,000. If the plasmapheresis technology can reduce this figure by even one-half, certainly the total medical costs will be substantially reduced[20].

This same type of treatment may be applied for the prevention of atherosclerosis. At this time, the pathogenesis of artherosclerosis is not clearly understood. However, the relationship of hyperlipidemia and artherosclerosis is well documented. The treatment of hyperlipidemia is possible, using this new membrane technology. Thermofiltration, by its selective removal of low density lipoproteins, is now possible as demonstrated experimentally and clinically in patients in which drug or diet therapies could not control their lipid levels[21,22]. As cardiovascular problems are among the most common in the elderly, the long-range impact of this treatment could be substantial.

The progression of end-stage atherosclerotic disease

including coronary heart disease (angina and myocardial infarction), peripheral vascular disease, cerebrovascular accidents and atherosclerotic senile dementia could be suppressed or reversed. If this is possible, the progression of cardiovascular disease, which requires vascular prosthesis implantation or coronary bypass surgery, can be reduced.

Currently, one of the major candidates for the artificial heart is the victim of end stage artherosclerosis or cardiomyopathy. If the origin of the disease is such that plasma treatment can be utilized, certainly the number of potential candidates for the artificial heart can be reduced quite substantially.

Malignant tumor growth is believed to be related to a disturbance in the immune system and the build up of suppressor factors in the body. Publications have reported cases of plasmapheresis treatment for patients with malignant tumors[23]. At this time, most reports are anecdotal. It is noteworthy that treatment periods were short, and there have been no long term treatment results reported. However, in combination with other traditional treatments such as immunologic, radiologic and drug therapies, the treatment of malignant tumors is more effective than without adjunct therapies. Reduction of mortality with this method of treatment has yet to be clearly documented.

In the past, the extracorporeal blood purification procedures were analogous to the artificial kidney treatment. However, the increased availability of more biocompatible and more porous membranes has expanded the capability of this method

of treatment to a wide range of disease states. The availability of this technology makes possible more extensive studies increasing the chances of understanding and treating the pathophysiology of various diseases which are more likely to be associated with the elderly patient population. If this proves possible, the expense of treating the senile patient who is incapacitated, bedridden and not contributing to society can be reduced and the patient returned to a more enjoyable, productive life. The basic research, applied research and device development in this field is beneficial to our society.

II. PRESENT STATUS

2-A. Artificial Kidney

Artificial kidney has several modalities to treat renal failure patients (Table 3).

Hemodialysis is the extracorporeal detoxification system to remove excess body water, to correct abnormal electrolyte levels and to remove small to middle molecular size uremic substances. It does this primarily by diffusive solute flux (solute removal is based on the concentration gradient of the solute and the membranes permeability). The system is a combination of dialyzer (dialysis membrane), dialysate delivery system, blood pump, extracorporeal circuit and monitor. Dialysis is most effective in the removal of small molecular substances.

Hemofiltration is an extracorporeal blood system using a

larger pore size, high flux membrane. Solute removal is by convective transport (bulk fluid removal). It requires dilution fluid rather than dialysate and is capable of removing more fluid and middle molecular uremic substances than in conventional dialysis.

Hemoperfusion is the extracorporeal detoxification system to remove toxic substances using absorbent. Blood is perfused over sorbents such as resins or activated charcoal.

Peritoneal dialysis is the system using the peritoneal membrane as a dialysis membrane by repeated infusion and drainage of dialysate to peritoneal cavity. The most commonly used scheme today is CAPD (continuous ambulatory peritoneal dialysis).

Also, combinations of different treatment modalities have been used to overcome the disadvantages of a single method. For example, hemodiafiltration (HDF) (convective and diffusive flux) can remove small and middle molecular substances with shorter treatment duration.

Miniaturization

Several methods have been developed to make dialysis systems more compact for the convenience of dialysis. Once uremia develops in citizens living in relative isolation, the options for life extension are reduced to self performed on-site regimens such as CAPD, home hemodialysis, or relocation of their home. Home dialysis can reduce the cost of hemodialysis and it is believed to be a better form of rehabilitation for the

patient. Also, portable systems provide for more mobility of the patients and permit travel. Several portable systems have been developed. Junken Co. (Japan) and the University of Utah group developed the wearable artificial kidneys, WAK-III, which is composed of a pumping section and reservoir (18L). Over 200 clinical treatments have been performed out by dialysate recirculating system[24]. The Univ. of Tokyo group has been working on the dialysate or hemofiltrate-regeneration system to develop really wearable artificial kidney using adsorbents with enzymes[25]. Activated charcoal, ammonium adsorbent (reformed zeolite) and a urease column (for breakdown of urea to ammonium and carbon dioxide) are the main part of this device[26]. Combined with pump sections, battery and reservoir, the total weight is 9 kg. The Univ. of Tokyo groups have also developed a urea adsorbent to reduce the weight of the WAK and simplify this system[27,28]. A total system weighing 5 kg. is composed of a urea adsorbent, charcoal, ion-exchanger and pump sections. It is a promising system for WAK but is still in the pre-clinical stage.

Adsorbent

Innovation of an adsorbent system is important as a supplemental therapy for daily dialysis and especially for compact artificial kidney system. Urea treatment is the key for development of a wearable artificial kidney because of the difficulty of removing urea using small amounts of dialysate. Adsorbents are used both in the dialysate delivery system for

regeneration of dialysate and in oral administration to patients as a supplemental therapy. The strategy of this therapy is to remove creatinine, uric acid and urea and the adjustment of electrolytes. Oral administration of newly developed oxystarch and activated charcoal is used effectively as a supplemental clinical therapy[29]. It is known that oxystarch (dialdehyde starch: (DAS), having an activated aldehyde group on its surface can form a Schiff's base complex with urea or ammonium, and activated charcoal can absorb creatinine, uric acid and other non-polar middle molecules. To reduce urea, creatinine and uric acid effectively, 30 to 40 g of DAS and 25-50 g of activated charcoal are required to be administered per day, depending on patient requirements. When these adsorbents are used orally, surface coating is necessary to prevent damage of intestinal mucosa and decrease efficiency due to competitive adsorption of lipophilic substances in the bowel tract.

As a dialysate regeneration and a hemofiltrate regeneration the Redy system has been commercially available and used in clinical treatments[30] (Figure 2). The principle of this adsorption system is enzymatic decomposition of urea by urease and adsorption of ammonium by zirconium phosphate. Creatinine uric acid and middle molecules are removed by activated charcoal. The Univ. of Tokyo groups have modified this regeneration system using reformed Zeolite mentioned previously[26].

The major problems accompanied with dialysis in the elderly patient are poor blood access and an unstable cardiovascular condition due to extracorporeal circulation. Oral

administration of adsorbents could be beneficial to the elderly because of no requirement of extracorporeal circulation and reduction of the frequency of hemodialysis. A miniaturization of the dialysis system with adsorbent allows for patient mobility during the procedures.

Continuous Ambulatory Peritoneal Dialysis (CAPD)

CAPD is a simple method using repeated infusion and drainage of dialysate using the peritoneal cavity (Figure 3). It utilizes the low dialysate flow rates and low volumes of dialysate. This allows portability, better creatinine dialysis than urea dialysis, and improved middle molecule clearances[31]. This method is particularly useful for those patients who are capable of and interested in self dialysis[32]. CAPD is reported to be as useful in the elderly as it is for the younger patient[11]. This modality is particularly prone to a high rate of technical failure such as by infection, sclerosing peritonitis and access problems[32,33]. Innovations to prevent these complications are being studied.

Membrane

Development of membranes of improved biocompatibility are needed (Table 4). Cellulosic membrane has a higher incidence of complement activation compared to synthetic polymer membranes[35]. Activation of complement in the circulation results in pulmonary leukostasis and peripheral granulocytopenia[36]. The impact of this effect is speculative but may be associated

with the high infection propensity seen with end stage renal disease patients treated by hemodialysis[37].

Considering the middle molecule hypothesis, the attempt to develop a membrane for dialysis that would afford higher permeability of middle molecules (giving a theoretical justification of the shortened dialysis time) may be a logical and challenging choice[38].

Polyacrylonitrile (PAN) membrane dialyzers and fluid balancing equipment were developed between 1970 and 1972. The principal innovation of this membrane is its greater permeability to middle molecules and consequently, an ultrafiltration of approximately ten times higher than that of Cuprophan membrane. Between 1975 and 1976, polymethylmethacrylate (PMMA) membrane dialyzers were developed that are suitable for hemodiafiltration[39]. Between 1977 and 1978, the cellulose acetate membrane gained a reputation for its excellent biocompatibility. Ethylenevinyl alcohol copolymer membrane (EVAL) was developed between 1978 and 1979. It showed a well balanced performance in removing low molecular weight and middle molecular weight substances and proved to be safer for the patient than the cellulosic membrane hemodialyzers. In general, these synthetics and modified cellulosics show improved biocompatibility (less reductions in blood cell counts, specifically, white blood cells and complement activation). Also, dialysis without anticoagulant infusion has been performed using synthetic EVAL membrane and improved blood lines[40]. The latest innovation is the development of the polysulfone membrane between

1981 and 1982. This membrane has a high protein permeability and has lessened the complications attendant with chronic dialysis[41].

Despite the numerous studies done in this field, exact parameters defining overall biocompatibility in blood purification systems have not been well established. Global understanding for biocompatibility including whole system of complement, kinin-kalliklein, coagulation, and fibrolytic system must be considered[42].

Reuse and Sterilants

Dialyzer reuse has been proposed to reduce cost. However, evaluation of the savings obtained by reuse is not easy. Cellulosic membrane has been used with the innovation of automated systems for reprocessing hemodialyzers. It has been reported that with dialyzers reused up to 30 times clearance were unchanged[43]. Also, hypersensitivity reactions so called "first use syndrome", occurs less often in re-use[44].

Ethylene oxide gas is recognized as one of the causes of hypersensitivity reactions[45]. Steam autoclaving and x-ray sterilization is reported to have better biocompatibility[46]. However, further examination in clinical study is required because high temperature and high energy may produce harmful degradation products.

Anticoagulant

Heparin is used as an anticoagulant even though it has an

effect on complement activation[47], platelet function change[48], lipid metabolism[49], and bone metabolism. These biological effects are critical for chronic dialysis patients because of repeated usage. Recently, in place of heparin many new anticoagulant drugs have been used in hemodialysis. Prostaglandin I_2 is used to diminish platelet adhesion and aggregation[50]. However, usage of PGI_2 is questionable in this stage due to its chemical instability and vasodilatory effect. PGI_2 analog (APS-306) is much more stable and has a lower vasodilatory effect than PGI_2. A highly selective synthetic thrombin inhibitor MD805[51], a new anticoagulant gabexate mesilate (FOY)[52] and a protease inhibitor 2-(6-Amidino) naphthyl 4-guanidino benzoate (FUT 175)[53] are being studied in order to control coagulability and platelet function except in those patients having bleeding diathesis. These new alternatives are to be used for the purpose of minimizing heparin dosage. Usage of these alternatives with biocompatible blood circuit and membranes may be feasible. Dialysis without anticoagulants has been tried[40].

Dialysate

multiple exposure to dialysate has problems in terms of biocompatibility during dialysis and chronic toxicity.

Dialysis using acetate as the dialysate buffer as opposed to a bicarbonate buffer[54] is reported to be associated with greater hemodynamic instability and various symptoms by means of metabolic changes and hypoxemia.

Quality control of dialysate for trace element is also important. Because the artificial kidney system cannot remove these trace elements combined with serum proteins, the toxicity due to these trace elements have to be removed by other means. Desferrioxamine (DFO), a chelating agent, is reported useful in the treatment of aluminum toxicity by mobilizing tissue aluminum stores in association with removal of diffusible aluminum in the dialysate[55]. Also, the levels of magnesium and zinc in dialysate must be limited to prevent increases in their blood level[56,57]. Dimethylnitrosamine, known as a precarcinogen, has been reported in dialysate water[58]. This and other dialysate or water borne agents may have a relationship to the increased incidence of malignant tumors in dialysis population.

The innovation of a dialysate delivery system including a decrease in the volume of dialysate by adsorbent is thought to be an important step in minimizing problems associated with the dialysate.

Continuous Arteriovenous Hemofiltration (CAVH)

CAVH is the method to remove excess fluids in acute renal failure (Figure 4). High water permeable membranes are utilized for CAVH (Table 5). To prevent overloading of cardiac function, a hemofilter with small surface area and primary volume and minimum circuit length are required. Hemofiltration may be performed using the patient's own blood pressure without any blood pump with an exchange rate of about 100 ml/hr. This modality allows for hemodynamically stable withdrawal of excess

fluid without the use of elaborate extracorporeal circuits[59]. This method can provide nutritional supports essential for the treatment of multi-organ failure[60]. It is especially good for elderly patients who are susceptible to developing multi-organ failure, and often present nutritional, metabolic, acid-base, electrolyte and hemodynamic abnormalities.

B. Plasmapheresis

The success of hemodialysis in the treatment of renal failure has promoted the development of extracorporeal technology for the therapy of other diseases. Diseases believed to be mediated by macromolecular weight substances such as circulating immune complexes, antibodies, low density lipoproteins, protein bound toxins, and others that accumulate in disease states have been treated by blood or plasma exchange since 1960.

Based upon early success in the treatment of various diseases by plasma exchange, its use in many diseases, and the use of the therapy for chronic treatment, the need for plasma products increases. Complications associated with their infusion, e.g. allergic reactions or infection, also increases. This stimulates the development of therapies that do not require plasma products. From the practical point of view, minimizing the need for plasma products can allow plasma treatments to be carried out more frequently, more extensively (processing larger volumes) and at lower costs. Because essential plasma components, as well as pathological ones, are removed during plasma exchange, techniques that are designed to remove only the

pathological components are highly desirable. Techniques that have been investigated include sorption, physicochemical treatment, and filtration.

Sorbents

Sorbents have been developed and used in direct hemoperfusion for drug overdose, uremia, and liver insufficiency[61]. Problems of biocompatibility and sorbent carry-over into the vascular system are overcome by means of on-line separation of plasma and plasma perfusion. Recently, several immunoabsorbents [Protein A[62], anti DNA antibody removal[63], heparin agarose LDL antibody[64], anti-A and anti-B antibody removal[65], polyvinyl alcohol gel[66], polymixin B fiber (endotoxin removal)[66], anti HBs antibody filter (Hepatitis B virus removal)[68]] have been developed for the treatment of immune disorders (Table 6).

Many kinds of charcoal and resin have been used for acute intoxication and liver failure including oral administration method[69].

Filtration

A simple treatment scheme, and one more universal in application, involves of the nonspecific removal of macromolecules in plasma. Membranes having a molecular cut-off of about 100,000 daltons allow the passage of albumin while retaining the macromolecular weight marker solutes. These

schemes include cascade filtration, cryofiltration and thermofiltration (Figure 5).

Cryofiltration is the on line plasma cooling system to remove cryogel - a mixture of various types of macromolecules including fibrinogen, globulin fraction, immune complexes, antibodies and albumin[13]. Clinical efficacy for rheumatoid arthritis and other autoimmune disease is reported[16,17].

Thermofiltration is the on-line filtration method kept near or above physiologic temperature to prevent cryogel formation[14]. This treatment for hypercholesterolemia involves the selective removal of low density lipoproteins, so-called "atherogenic cholesterol", that is related to the incidence of coronary heart disease, while retaining albumin and high density lipoproteins; as called "antiatherogenic cholesterol" that has negative correlation to coronary heart disease[21]. By means of modifying the abnormal lipid metabolism, this treatment modality may have impact on the progression and regression of artherosclerosis including coronary heart disease that is still the major cause of death and disability in the United States.

For cancer patients there are specific blocking factors or immunosuppressive substances for malignant tumors that exist in the patient's plasma[23]. Also non specific blocking factors are reported. Aiming for reduction of these blocking factors, patients are treated by plasma exchange, but still results are controversial.

III. STRATEGY

The objective is to reduce the numbers of end stage organ

failure patients through application of artificial organ technologies at much earlier stages in the disease process than has heretofore been possible. This will become more cost effective. The reduction in numbers of such patients will decrease the need for dialysis and transplantation. Reducing the incidence of end stage heart failure and occlusive arterial disease due to therosclerosis, vasculitis, or cardiomyopathy will lessen the need for artificial hearts and vascular or valve replacement. Preventing or slowing end stage bone and joint deterioration as related to long standing rheumatoid arthritis will decrease the need for artificial joints.

With the availability of artificial organ technologies, it is now possible to modulate the biochemical and immunological systems of the body. Chronic immunological diseases, including autoimmune diseases, atherosclerosis, cancer, and infection, can be treated by artificial organ technologies that regulate the body's bio-immunological chemicals, thereby halting and possibly reversing the disease process. While certain patients can be cured with or without the help of conventional medical or surgical therapy, in some groups of patients the number requiring treatment will certainly be reduced.

To reduce the cost of chronic dialysis, technological choices have to be made. Development of self-care systems including CAPD, more biocompatible materials (including membrane, dialysate, sterilant) and adsorbents and bioreactors (bacterial systems) as a supplemental therapy is thought to be an effective choice.

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LEGEND OF TABLES

1. Risk factor statistics (present at initiation of dialysis in all 157 patients[3].
2. Innovation in uremia treatment
3. Blood detoxification
4. Synthetic materials used for hemodializer and hemofilter
5. List of hemofilter for CAVH
6. Immunoadsorption systems described in the literature

TABLE 1

RISK FACTOR STATISTICS (PRESENT AT INITIATION OF DIALYSIS IN ALL 157 PATIENTS)[37]

Risk Factors Analyzed	Frequency	
Diabetes mellitis	17.2	
Arteriosclerotic heart disease (ASHD)	35.0	
Cerebrovascular accidents (CVA)	10.2	
Chronic obstructive pulmonary disease (COPD)	18.5	
Peripheral vascular disease (PVD)	22.2	
Nonskin malignancy (CA)	14.0	
In-center dialysis exposure time	79.9	
Home dialysis exposure time	17.2	100%
Satellite dialysis exposure time	2.9	
Program entry (patients entering prior to 1976)	19.7	
Sex (male)	52.5	

Mean entry year: 1978

Age: Mean 74.9 yrs Range: 70-87

TABLE 2

INNOVATION IN UREMIA TREATMENT

I.	**Apparatus**	
	1. Programable dialysis	
	2. Multipurpose system	HD, HDF, HF
	3. Miniaturization	portable, wearable, implantable
II.	**Dialyzer**	
	1. Shape	Hollow fiber
	2. Sterilization	Autoclave, - radiation
III.	**Membrane**	
	1. Materials	Cellulosic synthetic
	2. Structure	Thinner wall thickness
	3. Biocompatibility	Less complement activation
IV.	**Dialysate**	
	1. Alkalin agent	Bicarbonate dialysis
	2. Concentration	High sodium dialysis
	3. Regeneration	(ex. REDY SYSTEM)
V.	**Anticoagulant**	
	1. New anticoagulants	FOY, FUT, prostaglandins
	2. Non-anticoagulation	(ex. Kuraray's EVAL Dialyser)

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TABLE 3

BLOOD DETOXIFICATION

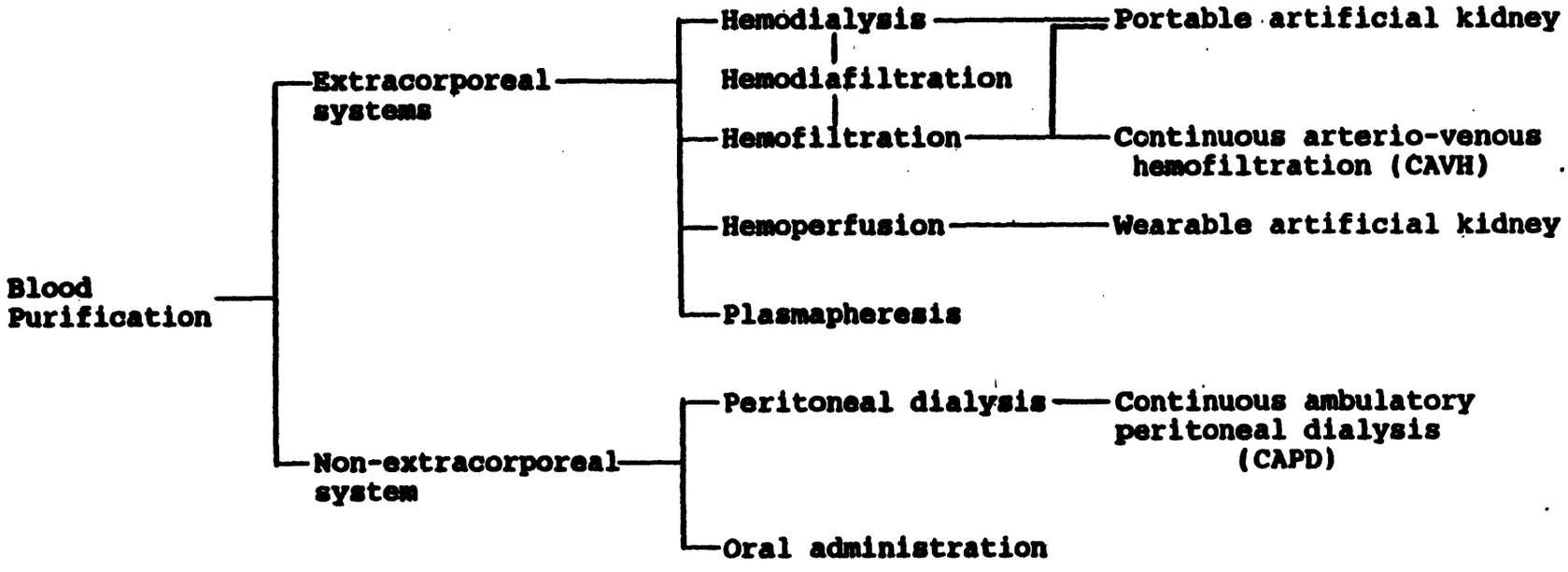

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TABLE 4

SYNTHETIC MATERIALS USED FOR HEMODIALIZER AND HEMOFILTER

Material	Manufacturer
Polyacrylonitrile	Rhone-Poulanc (France)
Polymethylmethacrylate	Toray Ind. (Japan)
Ethylenvinyl alcohol	Kuraray Co. (Japan)
Polysulphon	Amicon Co. (USA)
Cellulose 2.5 acetate	Enku (FRG)

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TABLE 5

LIST OF HEMOFILTER FOR CAVH

	Amicon	Asahi		Gambro		Toray	Renal system	
	Diafilter-20	PAN50P	PAN60A	FH55	FH77	TK601		
Material	Polysulfone	PAN		Polyamide		PMMA	Polysulfone	
Module	HFAK	HFAK		HFAK		FHAK	HFAK	
Surface area (M^2)	0.25	0.5	0.6	0.6	1.4	0.3	0.25	0.5
Priming volume (ml)	20	42	50	43	90	26	25	50
Maximum TMP (mmHg)	500	500	500	600	600	500	500	500
Sterilization	EOG	EOG		EOG			EOG	

TABLE 6

IMMUNOADSORPTION SYSTEMS DESCRIBED IN THE LITERATURE

Immunoadsorbent	Substance Removed	Application	Author
Protein A	IgG IgG immune complexes	In Vitro	Rawer et al
Synthetic blood group B antigenic determinants	Anti-B antibodies	In Vitro	Chang
Glomerular basement membrane antigen	Anti-GBM antibodies	Dogs	Terman et al
Bovine serum albumin	Anti-BSA antibodies	Dogs	Terman
Protein A	IgG	Dogs	Terman et al
Heparin agarose	LDL	Dogs	Burgstaler et al
Anti-LDL antibodies	LDL	Pigs	Stoffel et al
Glutaraldehyde treated human erythrocytes	Complement components	Sheep	Schmer et al
Heparin agarose	LDL	Sheep	Schmer et al
Staphylococcus aureus Cowan I	IgG	Human	Bansal et al
DNA	Anti-DNA antibodies	Human	Terman et al
Staphylococcus aureus Cowan I	IgG	Human	Ray et al
Blood group A and B antigen	ABO antibodies	Human	Bensinger et al
Anti-LDL antibodies	LDL	Human	Borberg et al
Protein A	IgG	Human	Terman

LEGENDS OF FIGURES

1. Factors involved in the development of cerebral and cardiovascular disease in uremic patients and patients on dialysis.
2. Schematics of dialysate regeneration system (REDY).
3. Schematic of continuous ambulatory peritoneal dialysis.
4. Schematic of continous arteriovenous hemofiltration.
5. Schematic fo on-line plasma treatment.

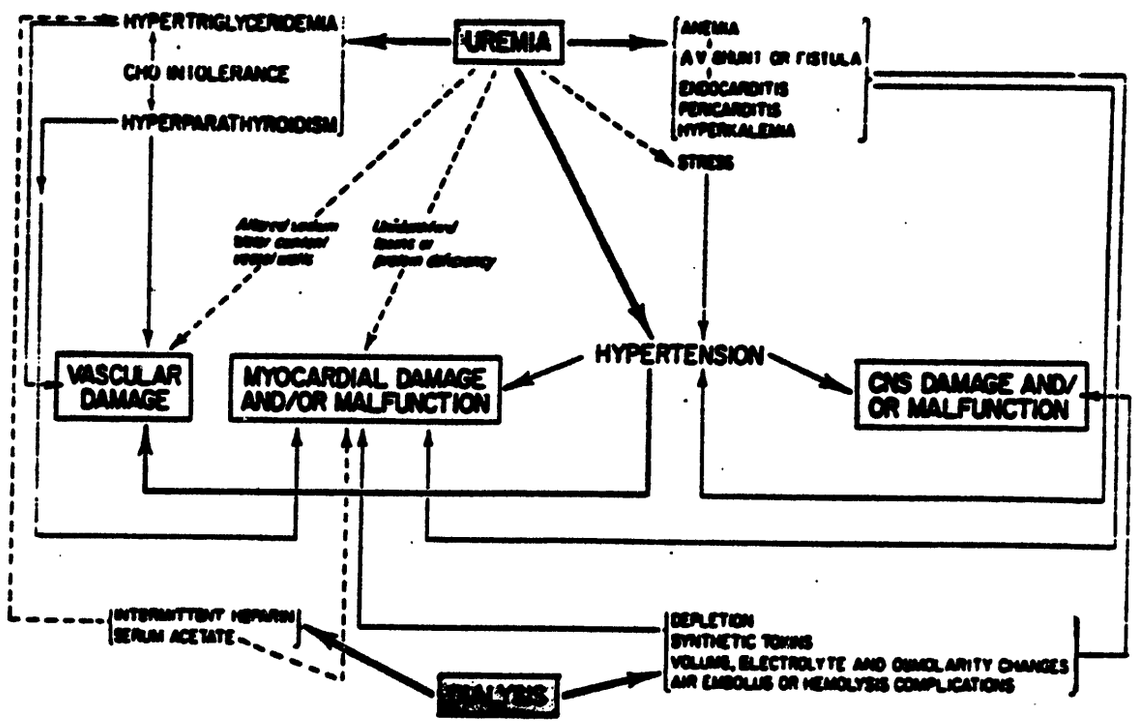

Figure 1

Factors involved in the development of cerebral and cardiovascular disease in uremic patients and patients on dialysis.

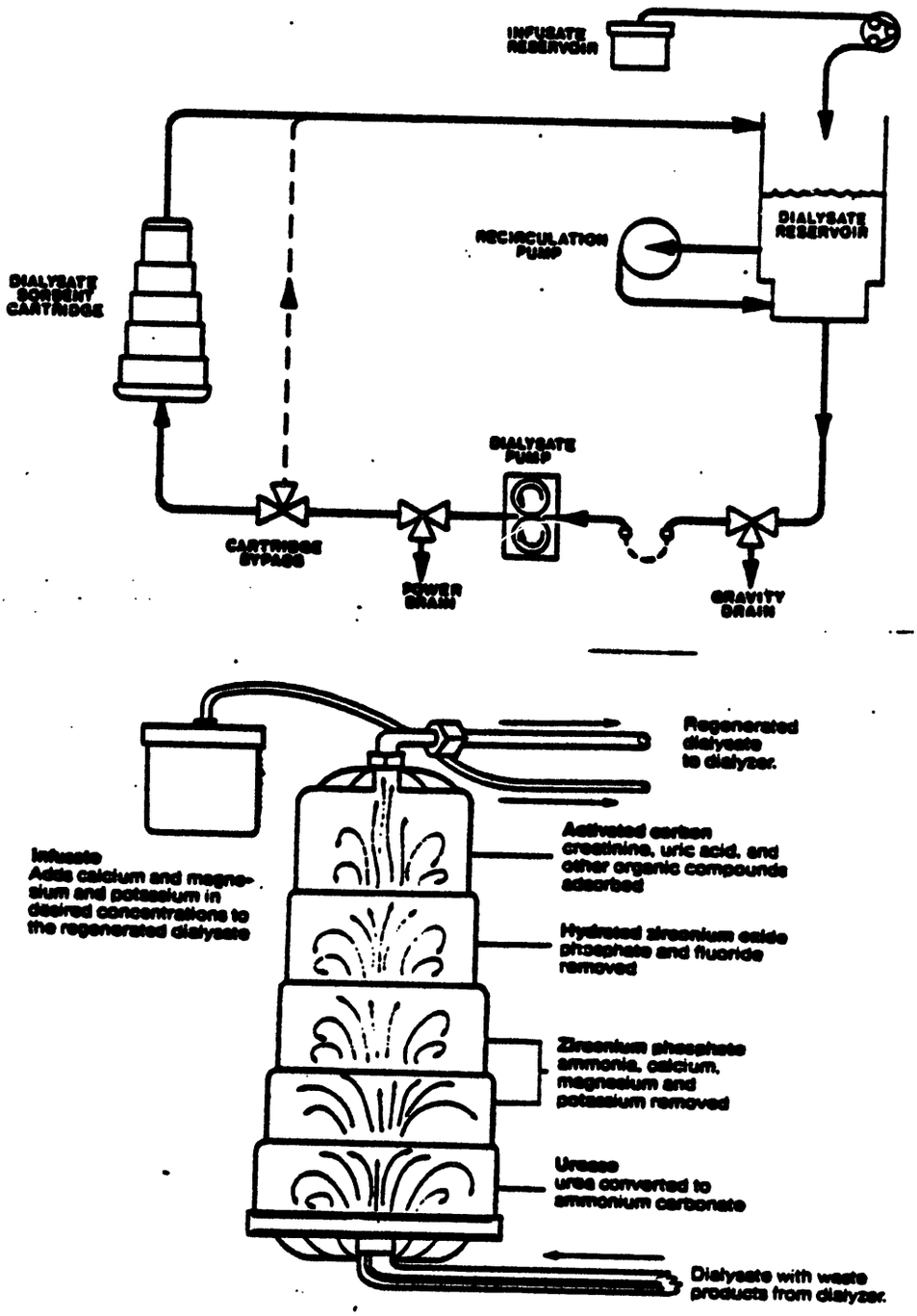

Figure 2

Schematics of dialysate regeneration system (REDY)

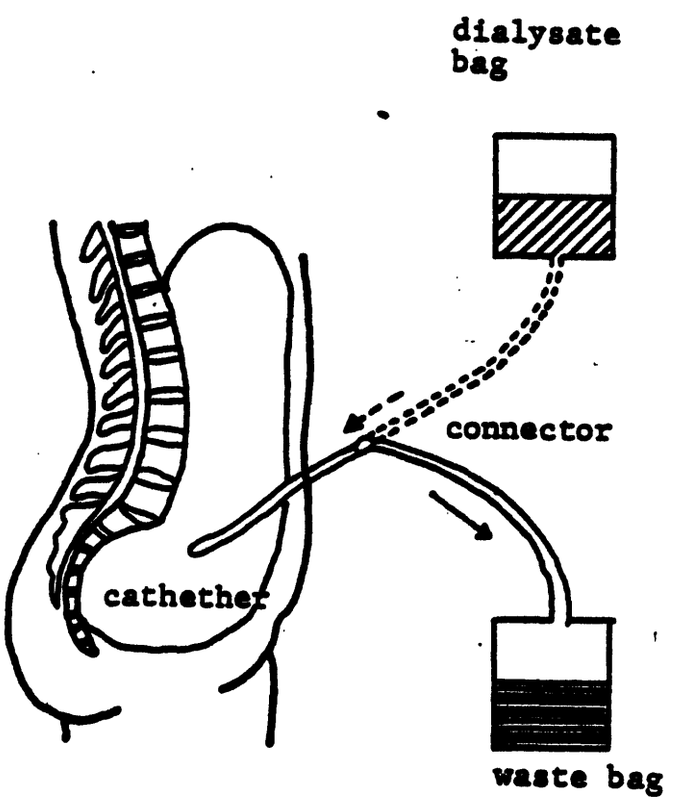

Figure 3

Schematic of continuous ambulatory peritoneal dialysis

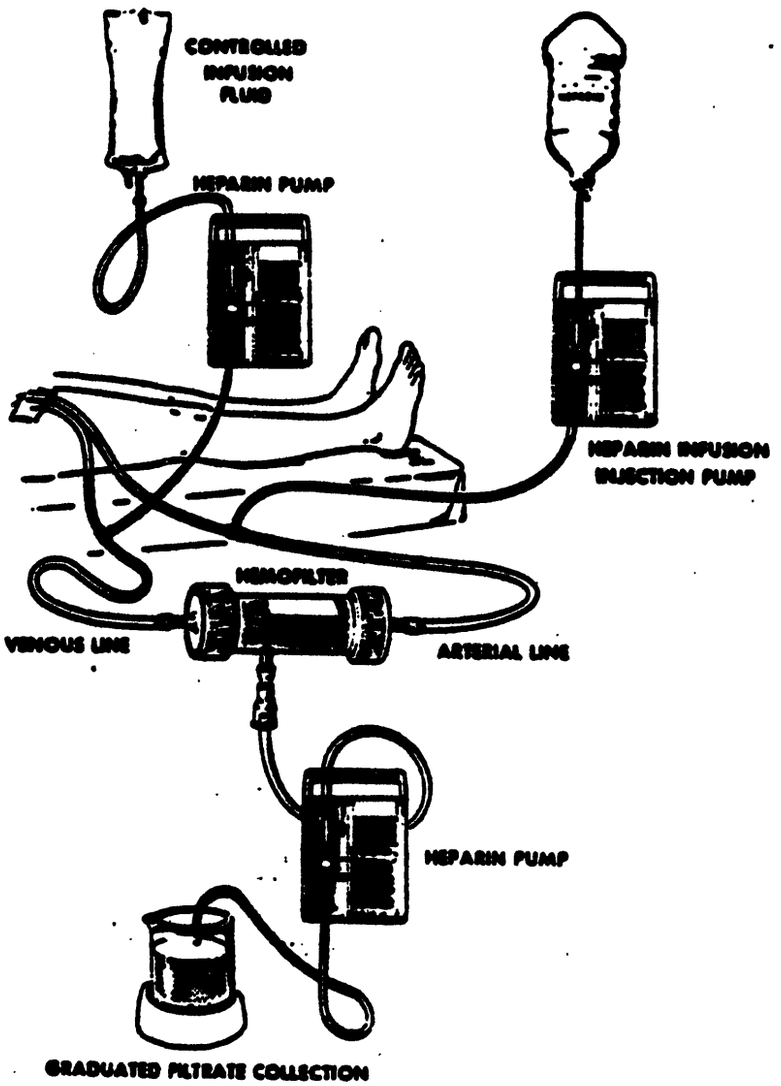

Figure 4

Schematic of continuous arteriovenous hemofiltration

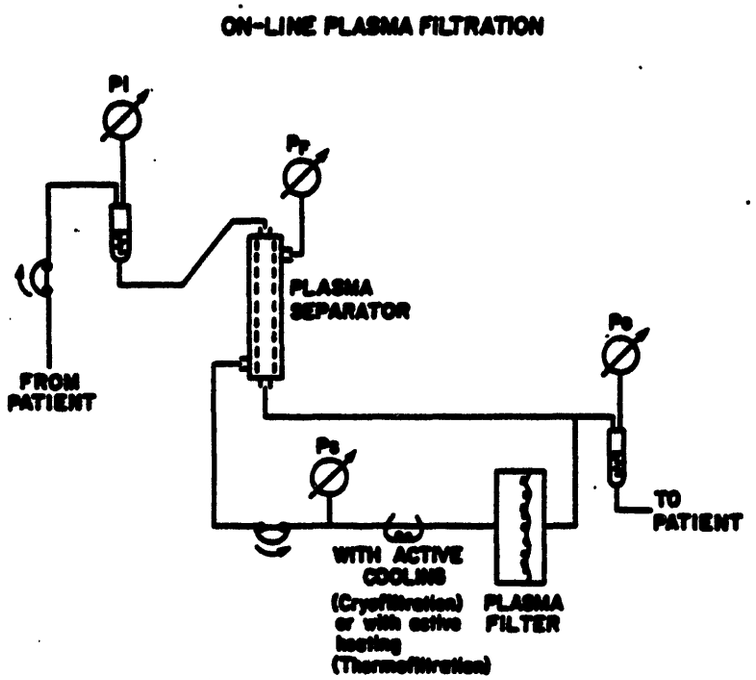

Figure 5

Schematic of on-line plasma treatment

TASK II: ADVANCES IN MECHANICAL VENTILATION TECHNIQUES

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TABLE OF CONTENTS

I. Overview

The recent advancement in ventilatory technologies has introduced various types of reliable, effective simple to use respirators not only for hospital use but also for home use. Traditionally, the volume cycled ventilator is the main tool for this application. However, many other respiratory assist devices have recently been introduced. These include not only devices specifically developed for respiratory assist, but also other biomedical gas delivery devices that are available can also be utilized for this application.

Currently, portable pneumatic cardiac prosthesis actuators weighing less than 3 Kg are becoming available, and at least three such devices are available worldwide. One of the systems has been used successfully in five total artificial heart patients. It turns out that the gas delivery requirements for the portable pneumatic heart actuator and the portable respirator are similar, hence the requirement of lower pressures for the respirator enables developers to design a much more reliable and smaller portable respirator without the necessity of major technological innovations.

The recent introduction of jet ventilators, which can be made smaller and simpler, has the potential application for not only long-term ambulatory respiratory support, but also for left ventricular assistance if the ventilatory cycle is properly

synchronized with ventricular diastole. A simple home use cardiopulmonary support system could be assembled in this fashion.

The recent advances ECMO (extracorporeal membrane blood oxygenation) technology imply that large portions of the respiratory failure patient population can be salvaged, as evidenced by the recent European group's studies. This technology enables the diseased lung to rest for a few weeks. Further development of the membrane oxygenator specially designed for ECMO purpose period much longer.

Recently, oxygenator technologies are switching from the traditional bubble device to the membrane oxygenator. The availability of more blood compatible gas permeable membranes guarantees longer and safer extracorporeal membrane oxygenation. Since the elderly population is more infection prone and more macromolecular abnormality oriented, improved blood compatibility of the system will be particularly beneficial in this group of patients. Another interesting technology introduced recently is total respiratory support using hemodialyzers rather than oxygenators. With several technical considerations, it is now possible to remove total adult body production of carbon dioxide from the blood employing a standard hemodialyzer. Consequently together with a hemodialyzer, total respiratory support can be established by only priming the alveoli with oxygen without respiratory movement.

Certainly these extracorporeal blood gas exchange systems will allow the respiratory systems to rest in order to heal some of the disease processes in the lung.

II. Available Mechanical Ventilation Technologies

Mechanical ventilation technologies have advanced such that chronic ventilatory support is a routine medical treatment. Both in the hospital and in the home the feasibility of assisted mechanical ventilation for the treatment of chronic respiratory insufficiency has been reported (1-8). The specific physiological benefits of long-term ventilatory assistance have also been documented (9-13). Patients with neuromuscular or musculoskeletal disease may often benefit substantially from such therapy and may thereby be permitted to live with a significantly improved quality of life, avoiding many of the prolonged hospital stays they might otherwise be required.

Several options are available to maintain adequate ventilation in the home. These include: a) volume-cycled ventilators; b) positive pressure breathing apparatus; c) oscillating beds; d) body respirators ("iron lung"); e) plastic wrap ventilation; f) chest-abdomen cuirass respirators; g) pneumobelts; and h) electrophrenic respiration.

a) The volume-cycled ventilator is particularly successful in patients with compromised respiratory mechanics. Sivak et al (1) recommended either the LP-4 ventilator (Life Products, Boulder, Colorado) or the PVV portable volume ventilator (Life Care Services, Boulder, Colorado) because of their portability (27 pounds each) and ease of operation. Currently, portable

pneumatic cardiac prosthesis actuators weighing less than 3 kg are becoming available. One of these systems has been used successfully in five total artificial heart recipients. The gas delivery requirement for the portable pneumatic heart actuator and the portable respirator are similar, but the requirements of lower pressure for the respirator enables researchers to develop a much more reliable, smaller, portable respirator without any major technological innovations necessary.

b) The positive pressure breathing unit is an effective means of facilitating carbon dioxide elimination and preserving lung compliance. The pump is small and mobile and can be easily operated by a battery or house current and on room air by another person at home. It can be cycled automatically or by active inspiration. During waking hours it can be used intermittently or continuously, as needed. Humidified air is desirable if it is used more than 10 to 15 minutes at a time. In patients who require almost continuous mechanical ventilatory assistance during the waking day, a slower respiratory rate, a longer expiratory time interval in the respiratory cycle, and a positive pressure not exceeding 20 cm H_2O will minimize the undesirable reduced venous return to the heart associated with the application of positive pressure (3).

c) An oscillating bed provides ventilatory assistance by moving the diaphragm with gravity-induced abdominal visceral movements. Instead of reduced venous return to the heart, circulation is enhanced by the oscillation of the bed. The oscillating bed can ventilate the patient awake or asleep without

any body encumberances. It provides a greater sense of personal freedom and is more physiologic. However, it may be most useful for patients with abnormal control of ventilation rather than compromised respiratory mechanics. Joos et al (14) reported improved ventilatory efficiency with the upper part of the rocking bed elevated 15^{o} to 30^{o}. Inkeley et al (15) pointed out that some diaphragmatic function is preserved in patients with late stage Duchenne dystrophy. Alexander et al (3) reported that effectiveness of the oscillating bed depended on the patient's ability to adapt his rate of ventilation to the oscillations of the bed.

d) Prolonged intermittent use of body respirators, such as the "iron lung", is beneficial for patients with progressively severe hypercapnia secondary to obstructive lung disease, Kyphoscoliosis or poliomyelitis (5,6). In contrast, intermittent positive pressure breathing (IPPB) has little effect on chronic respiratory failure in obstructive lung disease (2,3,4). Rochester et al (13) pointed out that body respirators diminish inspiratory muscle electrical activity and indicated that these respirators assume the work of breathing and provide a rest for the overburdened inspiratory muscles. The immediate benefit is a relief of dyspnea. It is also possible that the reduction of inspiratory muscle energy expenditure which results from body respiratory therapy improves the function of these muscles and thus contributes to clinical improvement in patients with chronic progressive respiratory failure (3).

e) Plastic wrap ventilation is similar to ventilation with body respirators or the "iron lung". The patient, lying in bed, is placed in a polyurethane wrap which completely envelopes the body except for the head. A pump connected to the wrap intermittently creates negative pressure inside the wrap. An arched, metal screen support rests on the bed, inside the wrap and over the thorax and prevents the plastic from lying directly on the patient's chest and allows freedom of respiratory expansion. Like the oscillating bed, the plastic wrap respirator affords continuous ventilatory support and limits mobility. Patients find it functional and comfortable for sleeping and resting (3).

f) The chest-abdomen cuirass works on the same principle as the plastic wrap ventilator. It creates a negative ambient (extrathoracic) pressure and acts as a bellows mechanism. The unit allows mobility, as it can be operated from a wheelchair-mounted battery or from an electrically-powered wheelchair (3).

g) The pneumobelt (intermittent abdominal pressure respirator) is another means of providing mechanical ventilatory aid. It produces increased external abdominal pressure which cause active expiration and augments passive inspiration. An elastic expandable, flat bladder incorporated within an abdominal corset is inflated with 50 cm H_2O positive pressure. The corset compresses the abdominal wall and causes the diaphragm to rise and forced exhalation to occur. Inspiration follows with deflation of the bladder and descent of the abdominal viscera. To

be maximally effective, the patient must be in a sitting position of at least 75° (16). The unit also allows a good deal of mobility, as it, like the chest abdomen cuirass, can be operated from a separate battery carried on a wheelchair or from the battery of an electrically-powered wheelchair (3).

h) Electrophrenic respiration is an effective form of long-term management in primary alveolar hypoventilation (11, 17-21). Glenn et al (18,22,23) have reported their experiences with electrophrenic respiration, with a total of 53 patients, thirty-seven of whom were quadriplegic. The longest duration of continuous support by electrophrenic respiration was 5 years. Hyland et al (11) reported that one phrenic nerve stimulation allowed to maintain adequate ventilation with normal ventilation-perfusion rate. Electrophrenic respiration can provide effective long-term treatment of alveolar hypoventilation of both the central and primary types with proper selection of patients and careful placement of the phrenic electrode.

The application of mechanical ventilation in the home care setting can be traced as an evolutionary process. It should be emphasized that not all patients are suited for long term support (8,24). Although Sivak, et al have demonstrated that home care is less expensive (25), some consideration must be given to the long term goals of home care. The clinical course of respiratory deterioration usually dictates either that mechanical ventilation will be rehabilitative, (that is, provide the hope of rehabilitation and a returning to a previous life style) or that it will be only supportive and preserve intellectual function and

physiological well being (1,26). As emphasized by Sivak, careful preparation for home care (27) and proper patient classification (28) is necessary for proper technological application of mechanical ventilation in the home.

III. New Types of Mechanical Ventilatory Assist Technologies

In spite of the striking efficacy and safety of mechanical ventilation, the method involves considerable deviation from the normal physiological mechanism of respiration (29). When used improperly or on patients incapable of compensating for the almost inevitable though usually minor disturbances which result from interference with normal bodily processes, mechanical ventilation may become harmful to a significant degree, resulting in: a) harmful cardiovascular effects (30-43), b) damage to the lungs (44-48), c) uneven ventilation (49-50), d) disturbances of acid-base balance, e) cerebral vasoconstriction (51-59) and f) renal, hepatic effects (60). Minimizing these harmful effects is absolutely necessary in order to advance the state of the art in mechanical ventilation.

Inspired gas reaches the alveoli by a combination of convection and diffusion. Gas transport is classically approached in terms of cyclic ventilation where most of the transport of fresh gas is achieved by bulk flow through the airways, with mixing throughout the large alveolar compartment by diffusion (61). Conventional ventilators have tended to mimic this pattern of respiration by using normal breathing frequencies and applying either positive pressure at the airway or negative

pressure around the thorax to induce the convective transport of fresh gas into the lungs (61). The conventional management of patients in respiratory failure is to enhance convective flow. However a conventional ventilator does nothing to enhance diffusion (62). Furthermore, application of high pressure to a lung with nonuniform distribution of time constants may damage the lung, especially in elderly patients who have chronic obstructive lung disease. For example, pneumothorax, pneumomediastinum or subcutaneous emphysema may occur in the elderly patients' lung.

Recently, high-frequency ventilation (HFV) has appeared based on the concept that oscillatory flow can accelerate diffusion and is adequate for gas transport (62). HFV is a form of mechanical ventilatory support that differs from conventional modes of ventilation in both its relative tidal volume (Vt) and respiratory rate (63). HFV uses tidal volumes less than anatomic dead space at frequencies considerably greater than normal (up to 40 Hz).

A number of investigators have offered definitions of HFV based on respiratory rates.

1) high-frequency positive-pressure ventilation:
   respiratory rate = 60 - 110 breath/min
2) high-frequency jet ventilation:
   respiratory rate = 110 - 400 breath/min:
3) high-frequency oscillation:
   respiratory rate = 400 - 240 breath/min

This HFV has relevance for elderly patients based on the following experimental and clinical results.

1) During conventional mechanical ventilation, the distribution of ventilation is governed mainly by the regional lung compliances. However during HFV, the lung compliances become relatively unimportant (63). Elderly patients usually have problems in lung compliances.

2) For the same mean airway pressure, the degree of barotrauma in the lung might be less during HFV than conventional mechanical ventilation because of a decrease in both peak pressure and phasic lung distension (64).

3) In several patients there was an improvement in gas exchange during HFV as compared with their standard form of mechanical ventilation (62).

4) Large tidal volumes by conventional mechanical ventilation deplete the surfactant in the lung faster than small tidal volumes by HFV (65). HFV may augment lung stability at least in diseased elderly patient's lungs by preventing atelectasis and minimizing changes in tissue and surface forces.

There are three kinds of systems used in HFV delivery 1) open system 2) closed system 3) pleural surface system (63).

1) Open System

Open ventilator systems are those in which there is a port left open to the atmosphere at all times to allow the escape of respired gases. The advantage of this system is that they require no pneumatic seal at the airway opening. However the disadvantage of this system is that the gas pressures and flows

achieved in the airway may be dramatically altered by interventions that alter pulmonary impedance (63). Currently there are three major types of open-system devices: a) jet ventilators, b) flow interrupters c) oscillators. In both a) and b), gas from a high-pressure source is allowed to flow into the airway for a given length of time. Oscillator-type ventilators consist of a piston driven by a motor, which creates a to and fro movement of gas within the airway.

2) Closed Systems

The airway in the closed system differs from that in the open system in that it is isolated from atmosphere during the inspiratory phase of the ventilator cycle, thus assuring that the total tidal volume generated by the ventilator enters the respiratory system (63). There are two major types of these closed systems: a) valved ventilation and b) oscillator type ventilation. Solenoids or rotating valves are used in valved ventilation. Electric motors or high air pressure source are used in oscillator type ventilators. Recently, Ngeow and Mitzner (66) have developed a new type of closed oscillator type ventilator that is completely sealed and thus has the advantage that oscillatory volume cannot leak from the system. A portable HFV system has been developed at NU-TECH Industries, Inc. using miniature brushless DC motors under a NIH grant. A improved respirator system with a portable configuration, high reliability and simple control features could treat patients at home on a long term and unsupervised basis without the sacrifice of their mobility. The unit will provide the chronic obstructive

pulmonary diseased elderly patients with 5 to 10 L/min of extra ventilation without increasing the work of breathing on the part of the patient.

3) Pleural Surface System

This system employs oscillations that are used at the chest wall rather than at the airway. This has the advantage of not requiring airway access but the disadvantage that the transfer of oscillatory energy to the lung may be technically difficult. This technique may ultimately prove to be valuable in applying ventilatory assistance in elderly patients with incipient respiratory failure.

IV. ECMO (Extracorporeal Membrane Lung Oxygenation)

Life threatening pulmonary failure not responsive to conservative therapy is routinely treated with mechanical ventilation. However this method has its limitations.

ECMO is a treatment for pulmonary failure considered irreversible by current medical treatment using an extracorporeal membrane lung oxygenator. Oxygenation to, and CO_2 removal from the blood are achieved via passive diffusion in a membrane similar to that used in hemodialysis. By preventing hypoxia and hypercapnea, the membrane lung can maintain life while otherwise intolerable pulmonary damage heals. Repair may be possible because appropriate levels of extracorporeal support can relieve the patients lung of their primary burden of respiratory gas exchange and of the handicaps of conventional therapy: high airway pressures and high oxygen concentrations.

ECMO enables elderly patients to create a better environment in which the diseased lung can recover. The lungs are now free to be treated directly with bronchoscopy, pulmonary lobe irrigation and locally applied antibiotics, steroids or detergents, rather than just waiting for the diseased lung to recover. Many kinds of membrane are used experimentally aiming for improved ECMO system. These are shown in Table I.

Historically Willem Kolff first described blood oxygenating across the cellophane membrane of his artificial kidney (67) in 1944. Since then, the development of the gas exchange device has undergone a rapid evolution in search of an efficient, safe, simple to use and economical device that would accomplish the needs of extracorporeal oxygenation during open heart surgery. In 1983, 75% of the marketplace used bubble oxygenators, 25% used membranes. A dramatic shift has occurred in the last two years. Currently, 56% of the market place uses bubble oxygenators, while 44% use membrane oxygenators. Today, we are in the age of the membrane oxygenator. Currently, there are ten membrane oxygenators available in the market and there are only four bubble oxygenators still in commercial use (Table II).

In 1956, Dr. Kolff and Effler (68) developed a coil type membrane oxygenator, using the technology Kolff described in the cellophane membrane of his artificial kidney. This ciol type membrane is a predecessor of the Sci-Med or coil membrane (69), although modified, but still clinically available today.

In 1969, Lande made a commercially available plate type membrane. The plate technology is still used in membranes today.

This plate technology continued through the mid 1970's on the Travenol membrane oxygenator when it became a clinical reality. The Travenol membrane and the Kolobow Sci-Med membrane are the last survivors so called the "first generations of membranes".

As we entered a "second generation" of the membrane oxygenator, two types are currently available namely the hollow fiber and flat sheet type (71).

As early as 1968 there is a design described from a parallel bundle of capillaries were surrounded by a central oxygenating mannifold. Gas circled among these fibers as blood went through the fibers. However, the high cost, blood flow limitations, poor CO_2 transfer and large surface area has precluded the clinical use of such a device. It was not until Suma and Associates (72,73) in Japan reported a newly developed polypropylene hollow fiber oxygenator (Figure 1) made by Terumo in 1981 (74). Another example of a hollow fiber device is the one with an external blood flow. What that means is that the blood flow around the fibers and gas flows through the fibers. This is a Maxima hollow fiber oxygenator made by Extracorporeal. The fiber bundle is composed of polypropylene hollow fiber wound around a core, encases in a polycarbonate shell. The effective membrane surface area is approximately $2m^2$. The advantage of such a device is that it has a reduced priming volume of 480 ml and basically one size fits all patients. This device was used for patients with recommended flow rates of 1-7 liters per minute.

The Bard membrane is another example of an external blood flow hollow fiber. This device has integrated heat exchanger, a

coiled type, as well as a built-in collapsible venous reservoir, which is a closed system.

The flat plate technology is made up of either porous or non-porous material. The Sci-Med oxygenator is of a non-porous, coil type membrane. The true example of a flat plate membrane is the Travenol membrane lung or TMO, as mentioned earlier. The TMO became a reality in the mid 1970's and there are some institutions still using the device today. However, it does not seem that simple to use. Travenol, realizing that the TMO's limitations, complexness, because of its external heat exchanger, two pump system, developed the LPM-50. The Low Pressure Membrane 50 uses the parallel plate configuration of its father, the TMO. Another example of a flat plate membrane is the Cobe membrane lung, CML. The Cobe membrane oxygenator has a $2.25m^2$ surface area of polypropylene. This oxygenator has an integral, coil type heat exchanger.

The Interpulse membrane oxygenator by Extracorporeal requires a large piece of permanent equipment called "the pulser". The Interpulse is equipped with a pulsing device that augments secondary flow in the blood path and thus enables the manufacturer to utilize only $0.8m^2$ surface area of a teflon-like material as a membrane. The pulsing effect of the oxygenator is used to expose the blood elements to the minimal oxygenating surface. The Extracorporeal "shake and bake", as it was called, was short lived in the clinical arena. Much of the attention of Extracorporeal came to develop their hollow fiber Maxima, which was described previously. The Shiley oxygenator is a rectangular

shaped membrane, with an integral heat exchanger. It has a surface area of approximately 2.3m^2. The sheet is folded in about 60 blood flow and 61 gas flow channels, separated by a non-woven screen spacer. As blood enters the flow channels, it encounters innerdigitalization of the blood and the gas screen spacers. This creates a passive secondary flow pattern and causes an intermixing of the blood layers and greater exposure of the blood elements to the surface of the membrane. This is the last participant of the flat plate membranes.

All of these membrane oxygenators have been designed and developed mainly for the short-term usage during open heart surgery. As compared to the bubble oxygenators, the membrane lungs have been shown to elicit less trauma to the blood elements and thus made extracorporeal circulation safe for more than several hours. However, the interaction of blood with an artificial sruface used in a membrane oxygenator inevitably causes various adverse effects including complement activation with subsequent platelets and leukocytes sequestration in major internal organs. Biological substances released from these cells are believed to constrict and/or obstruct the regional blood vessels, change their permeability, and cause damages in tissues including the lung. Most of all, extracorporeal circulation with oxygenators requires heavy systemic anticoagulation of patients, which is responsible for bleeding complication in approximately 50% of patients receiving ECMO. The patient is required to be hospitalized, and the procedure is carried on for maximum of weeks in the intensive care unit requiring extensive monitoring

and continuous supervision. Therefore, this technique is currently applied only to a patient group with reversible acute respiratory failure, and has little therapeutic value for home-stay patients with chronic progressively deteriorating respiratory insufficiency. In light of a steady increase in death rate due to the progressive obstructive pulmonary disease among the elderly in the United States, a development of an ECMO system aimed for this latter group of patients appears to be mandatory.

In spite of the striking efficacy of ECMO in oxygenation and CO_2 removal, veno-arterial ECMO associated with continuous positive pressure ventilation has failed to improve survival in severe acute respiratory failure patients (75). There were two factors in this ECMO failure; 1) the use of veno-arterial bypass with proportional decreases in pulmonary perfusion, 2) the use of high pressure continuous positive pressure ventilation resulting in focal pulmonary alkalosis and barotrauma in the underperfused diseased lung (76).

Gattinoni et al (76-78) has applied a new approach to the treatment of acute respiratory failure by dissociating the two main respiratory functions, i.e. CO_2 removal and oxygen transport. CO_2 extraction was assured by use of an extracorporeal membrane lung through a low flow veno-venous bypass, thus preserving pulmonary blood flow. Oxygen transport was provided by diffusion through the diseased natural lungs ventilated 2 to 3 times/min to preserve pulmonary mechanics and volumes (Low Frequency Positive Pressure Ventilation with

Extracorporeal CO_2 removal, LFPPV-ECCO$_2$R, Figure 2). The goal of this technique is to prevent ventilation-perfusion mismatching in nonhomogeneous lungs through lung static inflation and to avoid the local and systemic complication of continuous positive pressure ventilation, while providing a better environment for lung healing.

The combination of high frequency ventilation (HFV) and ECMO enable us to establish a new concept; one in which CO_2 removal and oxygen transport will be achieved by HFV, and additional oxygenation and CO_2 removal are accomplished by a low flow veno-venous gas exchange system. It has been also recognized that oxygenation of blood occurs somewhat during hemodialysis, but hemodialyzers are quite effective for the removal of CO_2. With the blood flow of 400 cc/min, it is possible to remove as much as 50% of CO_2 production. Using a hemodialysis membrane for this method enables us to perform the serial exchange of O_2/CO_2 and solutes/water respectively in elderly patients. Management of elderly patients will be simplified by this technique, and cost-performance will be enhanced. In order to avoid lung edema, continuous arterio-venous slow ultrafiltration is proven to be effective. Small effective ultrafilters are currently available. Currently, an ideal oxygenator for ECMO purpose is not available. They are functionable but it is only less than 30 hours. In order to develop an oxygenatior for this application following criteria should be applied.

1. Gas exchange capability lasting more than 1 week and easily replaceable.

2. Small surface area with more biocompatible membrane.
3. Development of simple, small atraumatic pump applicable for one month.
4. Simple and small priming volume system.

Ideally this system can be operated with minimum or no anticoagulating agent. The development of a portable,simple to use ECMO system, which requires no or little anticoagulation, would make it possible to treat many patients with chronic progressive respiratory failure at home. Synonymous to this would be the prevalence of home dialysis. Currently 14 to 18% of patients with end stage renal disease are treated with this remedy with less cost and more acceptable quality of life.

V. Peritoneal oxygenation and CO_2 removal

Theoretically, peritoneal gas exchange of O_2/CO_2 is possible like that in peritoneal dialysis. Although oxygen transport characteristics of the peritoneal membrane is known to be small, augmentation can be expected by utilizing artificial blood with high oxygen carrying capacity. Artificial blood is saturated with oxygen and pumped into the peritoneal cavity. Oxygen then diffuses down a concentration gradient into the tissues and blood supply of the peritoneum (79). Recently a hemoglobin conjugate has been developed as an oxygen carrying blood substitute at Ajinomoto CO, Japan (80). Now in-vivo studies of this artificial blood are being performed with excellent results at the Department of Artificial Organs, Cleveland Clinic. This artificial blood may be applicable for peritoneal oxygenation.

On the other hand, it is well known that substantial carbon dioxide can be removed during a standard hemodialysis as described previously. In a recent study it is also suggested that hypercapnia can be corrected by closed loop, re-circulation peritoneal dialysis with chemical extraction of CO_2. This simple paracoporeal technique is able to remove at least 33-50% of re. ting human CO_2-production (81). For respiratory assistance purposes, artificial blood can be utilized instead of conventional dialysate. The artificial blood has certainly a higher CO_2 affinity than dialysate, and oxygen supply to the peritoneal cavity is accomplished simultaneously. This peritoneal oxygenation and CO_2 removal could enhance the weaning of elderly patients from mechanical ventilators and could be used in non-hospital settings similar to that of peritoneal dialysis. These methods can enhance the quality of an elderly patients' life because they could be free from trachial intubation.

VI. Implantable Artificial Lung

There are three broad classes of membrane lungs, based on the resistance they offer to blood flow: the first is high flow resistance (more than 200 mmHg at 4 L/min blood flow rate) and is used only with a pump on bypass; the second is moderate flow resistance (up to 100 mmHg at 5 L/min blood flow rate) and is used with a pump on V-A bypass, or can be used with or without a pump on A-V bypass; and the third is low flow resistance (less than 20 mmHg at 2 L/min blood flow) which could be considered for use as a booster lung as a unilateral implant in parallel with

the natural lung, with the blood flow driven by the pressure generated by the right ventricle.

Six aspects of design for implantable lungs should be considered (82). The first aspect is the provision for adequate gas transport. The second is avoidance of thrombus formation. The third is the prevention of tissue disposition or overgrowth on the membrane. The fourth provision concerns ventilation. This need not be made via a connection to the bronchi or trachea but could be done via a stoma in the chest wall. The fifth is drainage of fluids from the gas space. An implanted artificial lung would not have cilia to move material towards the trachea, nor would it have the ready capability for absorbing fluids. However, a drainage system could be incorporated fairly easily. The sixth is removal of airway particulates by facilitating lavage (82).

Recently the extracapillary flow type hollow fiber membrane oxygenator in which blood flows outside and gas passes inside of hollow fibers has been developed. Since this type of hollow fiber has low flow resistance, pumpless ECMO for total right ventricle to left atrium bypass could be done (83). At this stage, no existing membrane lung is suitable for this purpose. Collaboration among many disciplines is required for the development of an implantable artificial lung. Blood compatible biomaterials, which necessitates no or little anti-coagulation under a low blood velocity, is to be developed. The materials should be strong enough without rupture when made in a very thin structure, should be moldable to yield fine cappillary

structures, and above all, should be quite permeable to oxygen and carbon dioxide but not to water. This artificial lung would require an implantable ventilator, which facilitates gas movement in and out from the device, since respiratory muscles may not be usable for this purpose.

The heart and lung frequently fail simultaneously due to the extensive interaction of these closely related organs. It seems reasonable to consider the design of a combined artificial heart and lung prosthesis (85). We are at the stage where we can envisage reasonably that an implantable total artificial heart could be available in the early 1990's. The NIH has just recently issued Request for Proposal to develop completely implantable total replacement and biventricular bypass systems. Accomplishment of this program will certainly facilitate the development of an implantable artificial heart and lung system.

Recent progress in organ transplantation technology has enable to bring lung transplantation into clinical reality. Although short term clinical results appear to be promising, only few facilities in the the United States are currently performing this procedure. Similarly to cardiac transplantation, absolute lack in donor population is the major drawback in this modality, together with problems in rejection and infection. Increase in aged population is a common feature in every developed country in the western world. Death rate from chronic lung disease has been steadily increasing. Unfortunately pathology of the lung in the most of this population appears not to be reversible. There is an urgent need to develop a total replacement device of lung

function, which is preferably implantable. The criteria for an artificial implantable heart and lung are: 1) capability of physiologically adequate blood pumping and gas exchange, 2) provision for maintaining membrane surfaces free of deposits; and 3) damage to blood components should not exceed the capacity of the body to dispose of and renew them.

(a)

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LEGEND OF TABLES

Table I Currently available membranes for ECMO.

Table II Membrane and bubble oxygenators currently in commercial use.

TABLE I

1. Dense membrane
   a) Silicon rubber
      i) Polydimethylsiloxane
      ii) Dimethylsiloxane-carbon block copolymer
      iii) Polyfluorosiloxane
      IV) Polydiphenylsiloxane
   b) Polyalkylsulfone
2. Microporous membrane
   a) Polytetrafluoroethylene
   b) Polypropylene
   c) Polysulfone
3. Combined membrane

   Polypropylene + silicone/polyalkylsulfone

TABLE II

OXYGENATOR	MANUFACTURER	PRICE ($)	MEMBRANE MATERIAL	CONFIGURATION
TRAVENOL TMO	BAXTER/TRAVENOL	405	POLYPROPYLENE	FLAT-PLATE, ACCORDIAN PLEATED *
TRAVENOL LPM-50	BAXTER/TRAVENOL	434	POLYPROPYLENE	FLAT-PLATE, ACCORDIAN PLEATED *
SARNS/OMNIS HF	OMNIS (SARNS)	N.A.	POLYPROPYLENE	HOLLOW-FIBER (EXTERNAL BLOOD PATH)*
CAPIOX 11	TERUMO	419	" "	HOLLOW-FIBER (INTERNAL BLOOD PATH)*
INTERPULSE	J&J	395	" "	FLAT-PLATE, PARALLEL SHEET, SEPARATE*
MAXIMA	J&J	395	" "	HOLLOW-FIBER (EXTERNAL BLOOD PATH)*
H-4000	BARD	425	" "	HOLLOW-FIBER (EXTERNAL BLOOD PATH)*
BOS-CM	BENTLEY	464	" "	HOLLOW-FIBER (INTERNAL BLOOD PATH)*
M-2000	SHILEY	415	" "	FLAT-PLATE, ACCORDIAN PLEATED *
CML	COBE	410	" "	FLAT-PLATE, ACCORDIAN PLEATED *
SCI-MED 1	SCI-MED	435	SILICONE RUBBER	SPIRAL-COILED, CONTINUOUS SHEET **
SCI-MED 11	SCI-MED	N.A.	" "	SPIRAL-COILED, CONTINUOUS SHEET **

* MICROPOROUS
** NON-MICROPOROUS

LEGEND OF FIGURES

Figure 1 Hollow-fiber membrane oxygenator. Gas exchange area, $5.4m^2$ peociws vy 60×10^3 fibers of polypropylene.

Figure 2 LEPPV-ECCO$_2$R Technique (from Pesenti A, et al. Trans Am Soc Artif Intern Organs 1980;26:550).

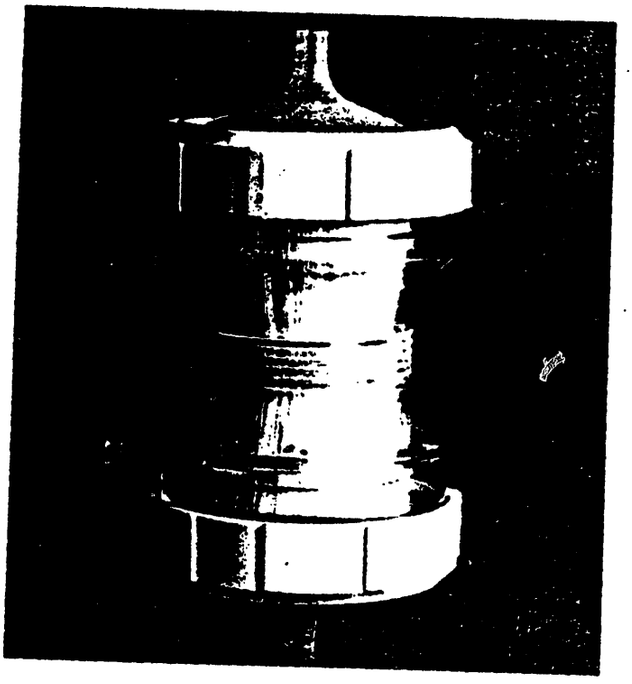
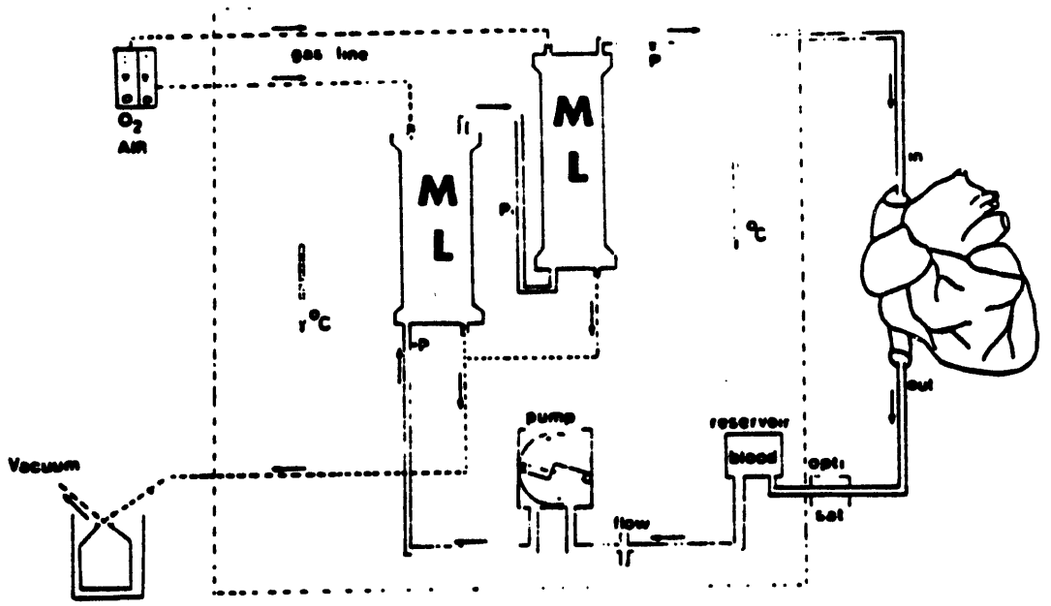


Figure 1 Hollow-fiber membrane oxygenator. Gas exchange area, 5.4m^2 peocisws vy 60 x 10^3 fibers of polypropylene.



MONITORING

VENOUS DRAINAGE SATURATION

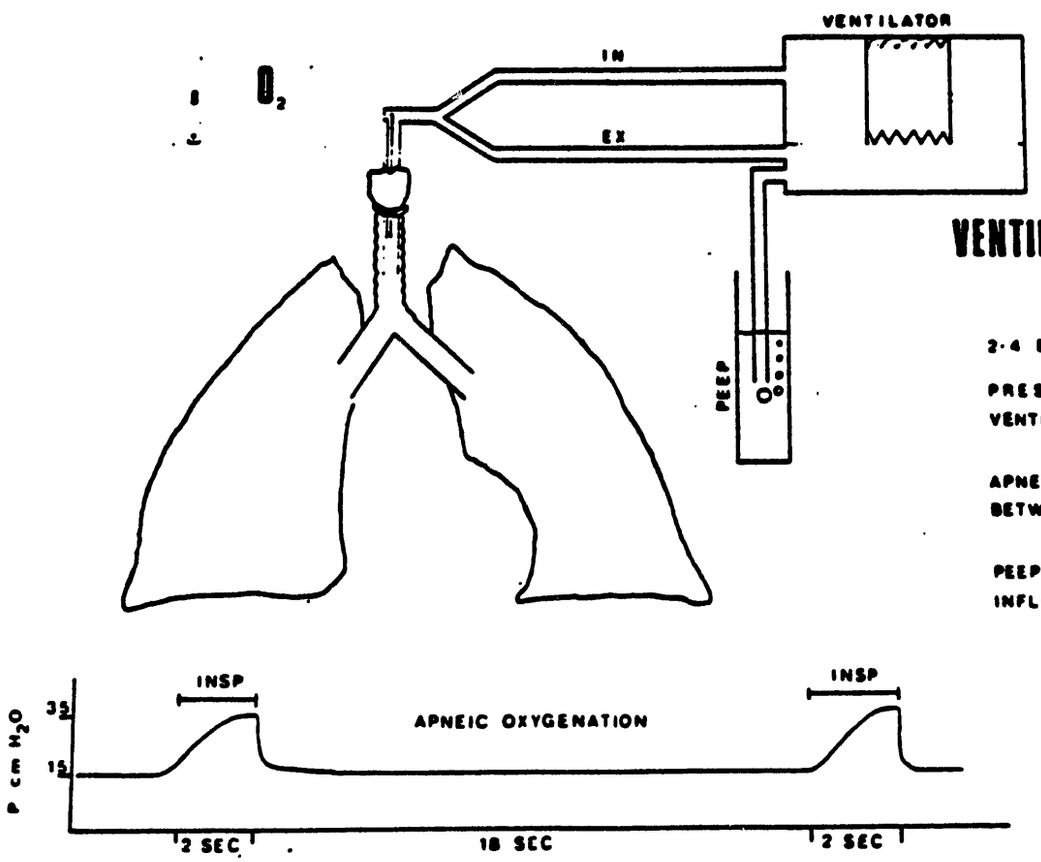
BLOOD FLOW

TEMPERATURE

ΔP IN OUT ML

EXTRACORPOREAL CIRCUIT

The extracorporeal circuit for LFPPV-ECCO$_2$R.



VENTILATORY MANAGEMENT

2-4 BPM

PRESSURE LIMITED VENTILATION (35 - 40 cm H_2O)

APNEIC OXYGENATION BETWEEN BREATHS

PEEP TO MAINTAIN LUNG INFLATION

Essentials of ventilatory management during LFPPV-ECCO$_2$R.

Figure 2 LFPPV-ECCO$_2$R Technique (From Pesenti A, et al. Trans Am Soc Artif Intern Organs 1980;26:550).

TASK III ADVANCES IN RESUSCITATION SUPPORT SYSTEMS

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I. Introduction and Cardiopulmonary Resuscitation

It is estimated that one third of all deaths in the U.S.A. are due to ischemic heart disease. One half of these are attributable to acute myocardial infarction (AMI). One half of AMI die suddenly (within one hour of onset), and most of the remainder (annually approximately one half million patients) are admitted to the hospital with AMI.

The mortality rate during hospitalization and during the year following myocardial infarction are approximately 15 and 10 percent respectively, with at least half of the post-hospitalization deaths occurring suddenly before the victim can be returned to the hospital. Thus, sudden death from ischemic heart disease is the most important medical emergency today.

It seems probable that a large number of these deaths can be prevented by prompt, appropriate treatment, which may provide either entry into the emergency medical services (EMS) system or cardiopulmonary support using cardiopulmonary resuscitation (CPR).

The National Conference on Cardiopulmonary Resuscitation (CPR) and Emergency Cardiac Care (ECC) held in September 1979 developed standards and guidelines for CPR and ECC as a revision of the 1973 meeting (1). They describe the life support principles and techniques as basic cardiac life support (BCLS) and advanced cardiac life support (ACLS) (2).

Concerning the survivors of out-of hospital cardiac arrest, it was reported that the survival relates to four factors (3): (1) whether cardiac arrest was witnessed, (2) the cardiac rhythm

at the time of arrest, (3) whether or not cardiopulmonary resuscitation (CPR) was initiated by lay bystanders, and (4) speed in arrival time of paramedic unit. In 611 patients with out-of-hospital cardiac arrest, these variables were predictive of outcome (Table 1). Among 22 patients with favorable findings on all four predictive factors, 15 (70%) were discharged alive. This contrasts with only one survivor among 97 patients with all four unfavorable findings. Myerberg et al (4) has also described critical importance of the cardiac arrest rhythm. Among 352 consecutive victims of out-of-hospital cardiac arrest, of 24 patients presenting with ventricular tachycardia (VT), 16 (67%) were discharged alive. When the arrhythmia was ventricular fibrillation (Vf), 55 (23%) recovered. However, when a bradyarrhythmia was the initial mechanism, of 108 patients 9 (8%) were resuscitated and none survived. Another helpful predictor is the heart rate immediately after defibrillation. Only 5% survived when the rate was less than 60 beats/min, and 17% when it ranged from 60 to 100 beats/min; of these 43% were long-term survivors (4).

Improvement in results of resuscitation following out-of-hospital cardiac arrest has been progressive. In the period from 1971 to 1973, overall survival was 14%, whereas from 1973 to 1978, it had increased to 23% (4). At present, the hospital discharge rate from out-of-hospital ventricular fibrillation is up to 30% (5). However, long-range survival has been poor. In a prospective follow-up of 276 resuscitated patients who were

discharged alive from the hospital, the probability of remaining alive at 4 years was only 49% (6).

New techniques for CPR included multiple transthoracic pacing devices(8), transesophageal cardiac pacing, and retrograde coronary perfusion.

(1) Multipurpose transthoracic pacing device in emergency (8). This device enables: 1) intracardiac epinephrine or other drug injection, 2) the obtaining of a blood sample for arterial blood gases, and 3) the rapid transthoracic insertion of a temporary pacemaker electrode, all simultaneously via a single myocardial needle insertion. This device has been used clinically in ten patients for the emergency treatment of bradycardia or asystole with hypotension. The results were not satisfying but this technique is expected to be useful if it is combined with cardioverter-defibrillators in the future.

(2) Transesophageal cardiac (atrial) pacing (9).
This technique is still in the research phase. If this is mounted on an esophageal obturator airway (EOA) or esophageal gastric tube airway (EGTA), it will be useful for CPR.

(3) Retrograde coronary venous perfusion.
This is achieved by using a balloon-tipped catheter and roller pump for the resuscitation of acute myocardial infarction.

II. Surgical innovation for cardiopulmonary failure

Introduction of coronary arterial surgeries such as bypass surgery improve substantially the outcome of the coronary arterial disease. Autologous saphenous vein graft or internal mammary arterial graft implantation revolutionalized the treatment of coronary arterial disease and prevented the premature sudden death of patients due to the myocardial infarct. Even though the benefits of this surgery are still discussed among medical colleagues, the contributions of this procedures for heart diseases are difficult to negate. Noninvasive balloon angioplastic procedures are also gaining its popularity. If catastrophic cardiopulmonary failure and diseases lead to this failure can be predictable, certainly preventive surgical procedures will be the most ideal resuscitation support we can provide. Some new surgical procedures which might be beneficial from this point of view will be discussed in this section.

(A) Total reversal of pulmonary circulation

Although primary pulmonary hypertension (PPH) is thought to result from increased resistance to pulmonary blood flow occurring at the level of the small pulmonary arteries and arterioles, the actual cause still remains obscure. Since the pulmonary circulation possesses no valves and the direction of flow is determined by the pressure gradient, blood in the pulmonary circulation theoretically could flow in either direction. If the blood could be made to flow into the pulmonary veins and return to pulmonary arteries, the inflow resistance (pulmonary vein resistance) should be less than usual because the cross sectional area of the veins exceeds that of the arteries.

In the literature, Houle (10) established that gas exchange was possible with reversal of the pulmonary circulation to one lobe of the canine lung. All published reports since that time (11-15) have described reversal of flow performed at the level of either one lobe or else a unilateral lung, with survival times of the animal extending over one year, even though the survival rate was low. The lungs can oxygenate venous blood just as well reversed pulmonary circulation as in normal circulation, the resistance to reversed flow being very similar to that of forward flow. There is, however, controversy regarding the long-term effects on the vasculature, in histology for retrograde pulmonary circulation.

Totally reversed pulmonary circulation technique is also still in the research phase (16). Several approaches that have been tried are discussed below.

1. When the heart of the patient is intact, an intra-atrial septation technique have been utilized that is similar to the Mustard operation in TGA (Transposition of Great Arteries) (Figure 1). In this case the left atrium is divided into two chambers (anterior and posterior) by a baffle. The venous blood is pumped out from the right ventricle into the left atrial posterior chamber via an interposed graft, then retrograde into the pulmonary veins. After oxygenated blood returns to the pulmonary artery, it flows into the left atrial anterior chamber, left ventricle, and finally into the ascending aorta.

2. When the heart has severe damage, a single artificial heart could be utilized combined with totally reversed pulmonary flow (16) (Figure 2). After the left and right ventricles are resected at the atrio-ventricular groove, the remnant left and right atria are sutured to make a common atrial chamber. A blood pump is connected to aorta and pulmonary artery. Venous blood from the venae cavae enters a common atrial chamber and then into the pulmonary veins. After oxygenation, the blood returns to the pulmonary artery, blood pump, and finally ascending aorta. With this technique, various kinds of blood pumps (pulsatile or nonpulsatile) could be used. Since heart-lung transplantation is not indicated for elderly patients over 55 years old, the techniques mentioned above could be applicable to elderly patients in the future.

B. Reversal of the Coronary Flow

The theoretical concept of delivering oxygenated blood to an ischemic myocardium by way of the coronary venous system antedated by many decades (17-18) the present widespread utilization of coronary artery bypass grafting. In earlier studies, coronary sinus retrograde perfusion was performed in order to reverse the coronary flow totally. The results achieved by this procedure were summarized by Beck (17-20) as the Beck II operation, which was applied to 186 patients and was approved to be efficacious in selected patients. However, it has been discarded because of a high mortality rate even by Beck himself

and due to the advent of aorto-coronary bypass (direct coronary artery revascularization). The retrograde coronary perfusion technique is currently used as a method of myocardial protection during cardiac operations. Coronary artery bypass grafting is now the procedure of choice as a means of myocardial revascularization, but a group of patients remain who are not candidates for this approach.

These are patients who have:

1) Diffuse atherosclerotic disease and poor run-off,
2) Persistently severe angina pectoris following unsuccessful coronary artery bypass operation.
3) Small coronary arteries found at operation with little likelihood of long-term coronary artery bypass graft patency.

Approximately 12 to 30% of the revascularization candidates fall into this group (21-23).

In elderly patients, calcification of the ascending aorta or coronary atheroma is frequently seen. This fact affects selection of the operative procedure. For example, the proximal anastomosis must then be performed in an unusually high aortic positions or even on the innominate artery and endarterectomies have a tendency to be necessary. Since the venous system is not affected by atheromatous changes, there has been renewed interest in reversing flow in the coronary venous system in order to deliver oxygen and substrate to poorly perfused or ischemic heart muscle selectively. This selective retrograde coronary venous perfusion (SRCVP) has been applied to patients who have the above

mentioned diseases, using internal mammary artery-coronary vein anastomosis or saphenous vein bypass grafts from aorta to cardiac vein (24-26). The results seemed to be acceptable and encouraging because symptoms such as anginal pain were relieved and tolerance to physical activity improved. However, long-term observation is needed concerning patency of the anastomosis and graft. This technique would be adopted for elderly patients from the indicative disease, since most of the candidates reported were over 50 years old. Recently SRCVP has been studied by providing temporary support to ischemic myocardium in animal experiments. This assist system consists of a balloon-tipped catheter and pump system (such as a roller pump) (27-28) (Figure 3). Moreover, if this system could be used in conjunction with artificial blood (29-31) and a certain kinds of nutritional solutions, many ischemic disease patients could be saved.

III. Mechanical circulatory assistance

Recent advancements of pump technology are such that it is possible to resuscitate circulatory or cardiopulmonary failure patients by utilizing various types of circulatory assistance.

Depending on the intended function, there are many types of cardiac prostheses available.

Types of cardiac prostheses

(1) Transient cardiac prosthesis

This group of prosthesis is used to support the temporarily failing natural heart and includes intraoartic balloon pumping, cardiopulmonary bypass, and temporary left ventricular assist or biventricular bypass devices. It is

expected in these applications that the failing natural heart will recover within several days to several weeks, after which time the assist device can be removed and the patient's heart would resume its normal function. Since emergency applications of these devices is required, simple implantation and removal is necessary. This group of prostheses is available and routinely used on clinical patients.

(2) Interim cardiac prosthesis

This category of cardiac prosthesis is used on patients waiting for a suitable donor heart for transplantation and contains left, right, biventricular assist devices and the total artificial heart (Figure 4). This device can also be applied to the recipient during the possible rejection crisis of the transplanted heart. It is not necessary that this type of prosthesis be totally implantable since its use is intended for only up to one month. Hence pneumatically actuated devices are suitable for this application.

Currently at least seven implantations of such devices have been performed since the mechanical total artificial heart was implanted in a 47 year-old male patient as a bridge procedure to heart transplantation in 1969 (32-33). The pneumatically driven total artificial heart was implanted in a 61 year-old man for permanent use in 1982 (34-36); five implantations have been performed with three patients still alive (37), and one of these three patients has survived for over one year.

The limiting factor in these applications, however, may be infection, as indicated to date by heart transplantation

experiences. Two recent developments perhaps will have an impact on this problem: (1) the availability of cyclosporine A as an immunosuppressive agent, which reduces the necessary dosage of steroids and (2) the introduction of plasmapheresis technology as a means of combating infections. Leukopheresis allows for massive leukocyte infusion for the prevention and treatment of infection in addition to the currently available antibiotic regimens. Other possibilities are also offered by plasmapheresis, since antibodies can be removed quite effectively and hence the presently employed immunosuppressive therapy could be reduced or even eliminated.

(3) Permanent cardiac prosthesis

This group of devices is intended to be totally implantable for up to two years and is still under development.

Development of a totally implantable electrically actuated left ventricular assist device system (LVAS) is now in the preclinical evaluation phase. At least six groups (Table 2) in the world are trying to develop this system. The LVAS consists of a blood pump, energy converter, variable volume compensation device, internal battery, transcutaneous energy transmission system, external battery and a diagnostic system (Figure 5,6,7). System reliability has been assured in animal experiment for up to seven months. Some of these will be available by the end of 1987 (38). After that, clinical trials will be initiated.

As another totally implantable LVAS, thermal engine ventricular assist programs (39) are currently being pursued by two groups in the USA and one group in the USSR. This system is

driven by a Stirling cycle engine and uses electrically heated, morten salt as a source of energy. Utilization of plutonium 238 as a power source would make a system operative for at least 10 years, but the current social climate in the western hemisphere is not in favor of such an atomic energy application. In vivo animal experiments have been continuing to evaluate the system performance (Figure 8).

The development of a variable volume compensation device (compliance chamber) (40) is essential for both the electrical and thermal LVAS. Durability of this device has been demonstrated for up to 2 years in animal experiments. Prevention of gas leakage and improved gas refill methods are problems that remain to be solved.

A completely implantable total artificial heart (Figure 9,10) will be available for temporary application by 1991 and permanently by 1995 on the basis of the techniques and components learned from the totally implantable LVAS development (38). Currently at least six groups in the world are working toward this goal (41).

These cardiac prostheses are particularly useful for the elderly, since patients 55 years and older are excluded as candidates for heart transplantation.

IV. New Therapy for Malignant Tachyarrhythmias

There are three currently available techniques for the purpose of terminating ventricular tachycardia and fibrillation. They are as follows (42):

1. high energy defibrillation

2. antitachycardial pacing

3. low energy cardioversion

The three techniques have many advantages in that these devices can be implanted by relatively minor surgical procedures, can control ventricular tachyarrhythmia resistant to usual drug treatment, and can eliminate the side effects of drugs. These techniques are more suitable for the elderly patients who are suffering from recurrent life-threatening ventricular tachycardia (VT) and fibrillation (VF).

1. Defibrillators

Implantation of a defibrillator has become a routine procedure to treat malignant ventricular tachyarrhythmias. Since the first automatic defibrillator was implanted in a 57 year-old-woman suffering from recurrent life-threatening ventricular arrhythmias unresponsive to conventional drug therapy in February 1980 (43), over 500 defibrillators have been implanted. The automatic implantable defibrillator (AID) (manufactured by INTEC Systems, Inc., Pittsburgh, PA., USA) is an electronic device designed to monitor cardiac rhythm continuously, to identify ventricular tachycardia and fibrillation accurately, and then to deliver high energies in the range of 25 to 30 joules promptly when such arrhythmias occur (Figure 11).

Results of clinical trials demonstrated that this device was suitable for successful arrhythmia termination in a great majority of patients at risk for sustained ventricular tachycardia and fibrillation. Echt (44) reported that the AID

could reduce the one year sudden death rate from 25 to 30% to as low as 1.8% in patients who have already experienced episodes of sustained ventricular tachycardia and fibrillation. The majority of recipients of an AID have coronary artery disease or a myocardiopathy as a basic disease (Table 3) and have poor left ventricular function (ejection fraction below 30% and average age around 55 years old). Although endocardial mapping and use of excision or cryoablation can achieve control of ventricular tachycardia in selected patients, the procedure has a high operative mortality in the range of 9 to 20%) and is not well suited to patients with polymorphic VT or Vf, multiple morphologies at VT and/or poor left ventricular function (45).

It is probable that defibrillator implantation will be the primary therapy for VT and VF in place of drug therapy. Since the surgical risk and incidence of the side effects of antiarrhythmic drugs are much higher in elderly patients than in younger patients, defibrillator implantation seems to be the primary therapy of choice.

2. Antitachycardia pacemaker

Several kinds of antitachycardia pacemakers have been developed for automatic termination of ventricular tachycardia and fibrillation and have undergone clinical trails (46-50). Currently available devices are shown in Table 4. Most of the patients implanted with these antitachycardia pacemakers are 50+ years old. Ventricular tachycardia termination may be accomplished by single, double or triple extrastimuli, burst, or overdrive suppression. The antitachycardia pacemaker has the

advantage that low energy consumption is required to terminate VT, and therefore the generator can be considerably smaller than those required for low energy cardioversion and defibrillation. The termination of the ventricular tachycardia can be achieved with no discomfort to the patient. An other advantage is that only minor surgical procedures are required for insertion.

3. Low energy cardioverter

One other available technique for automatic termination of ventricular tachyarrhythmias is low energy cardioversion (less than 5 joules). A low energy cardioverter consists of a smaller generator (Figure 12) and a fully transvenous lead system that can be inserted with a relatively minor surgical procedure. This device (Medtronic Model 7210) has been applied to seven patients to date (mean 64 years old mean, range 56-68 years) (51).

The antitachycardia pacemaker and cardioverter needs a defibrillator as a back up system to prevent several harmful complications such as acceleration. On the other hand the high energy produced by the defibrillator is not always necessary to terminate defibrillation. Therefore, an ideal automatic electronic tachycardia terminating device should combine antitachycardia pacemaking, low energy cardioversion, and backup higher energy defibrillation. It should be fully programmable between these three modes of tachyarrhythmia termination and use various combinations of these technologies. The ideal system should use transvenous electrode system and the automatic arrhythmia detection algorithms based not only on a patient's

rhythm but also on the physiological consequences of the arrhythmia.

V. Implantable cardiac pacemaker

A permanent pacemaker implantation is the routine treatment for arrhythmias. The implantable pacing system consists of a generator and the flexible conductive lead (electrode).

1. Generator (battery)

The life span of the generator has been extended for up to 10 years by improvements in the energy source from a zinc-mercuric oxide electrochemical cell to a lithium iodide cell (Figure 13). However, replacement of the battery still cannot be avoided. A telemetrically rechargeable generator is expected to be developed for this purpose by modifying a transcutaneous energy transmission system which is one of the main components of totally implantable LVAS funded by the NIH. All transcutaneous energy transformers utilize a magnetic flux linkage between a primary and a secondary coil to transmit power: they have the primary transformer outside of the body while the secondary is totally implanted (52-53).

A different approach solving this problem is nuclear pacing which is powered by the isotope plutonium 238 (Table 5). Parsonnet (54) reported higher reliability, superior performance and safety of a

nuclear pacing system. Actual survival at 10 years was 92%, meeting the expected performance goal of 90% (Fig 13). The common cause of replacement was an inappropriate pacing mode (fixed rate pacing mode). The causes of death of 25 of the 131 patients was not attributable to failure of the pacing system. This successful result suggests that the combination of a radioisotopic power source with a multiprogrammable dual-chamber pacemaker could at least provide a physiologic pacing system that would last the lifetime of virtually every patient. Its use is not permitted now due to sociological reasons.

2. Lead (electrode) system

Breaking and dislodgement of the lead wire and tip are the usual cause of the pacing or sensing failure. Silicone was the main material used for the pacing lead, but recently polyurethane or Biomer-like segmented polyether polyurethane leads have been utilized clinically or studied in animal experiments. To prevent dislodgement of the lead, the shape of the lead tip has been designed to anchor well into the trabeculation of the ventricle and atrial appendage.

An implantable leadless pacing system has been developed to eliminate lead-related complications, however these are still in the research phase. A leadless pacemaker consists of completely separate transmitter and receiver modules. The transmitter

contains a battery, a pulse timing circuit and a oscillator driving a tuned circular coil. The receiver module contains a second tuned circular coil and a peak-to-peak detector circuit connected across the bipolar screw-in electrode on which the module is built. This system uses electromagnetic induction to transmit electrical impulses to the heart in place of the flexible lead. An asynchronous mode, leadless pacemaker and leadless ventricular inhibitory pacemaker have been designed and tested in animal experiments.

3. Multiprogrammable pacemaker (physiological pacing)

"Pacemaker Syndrome", which was first described by Mitsui (55), is characterized by palpitations, a feeling of malaise, vasomotor problems, and sometimes anginal pain. These symptoms may be attributed to poor circulatory adaptation to the pacing rate, but the essential element of the syndrome is the interruption of atrio-ventricular sequence (A-V synchrony) in the demand type VVI pacemaker, resulting in AV valve dysfunction and drop in cardiac output. Recently physiologic pacing systems that can activate the atrium, reestablish AV synchrony, and result in better patient comfort and exercise tolerance have been developed as a DVI (A-V sequential) pacemaker or a dual chamber (VDD, DDD) pacemaker (Table 6). Since A-V synchrony can increase cardiac output by 20% these pacemakers are very effective in patients with normal

sinus node function during daily activity and exercise. However these are contraindicated in patients with sinus node dysfunction, especially with sinus bradycardia or atrial fibrillation.

In an attempt to find a method of providing rate-responsive pacing to those patients with sinus node dysfunction, some investigators have turned to other indicators of physiologic demand beside the atrium. This physiological responsive pacing can be defined as pacing to optimize cardiac output to meet metabolic needs in the absence of normal physiological control. Control is achieved by sensing some physiological variables that are correlated to actual physiologic need, hence increasing (or decreasing) paced heart rate and cardiac output.

a) Temperature (56, 57) - A thermister is mounted on a lead in the right ventricle to measure mixed venous blood temperature. Temperature increases during exercise because of the exercising muscles and the concomitant body core temperature increase. Increasing temperature produces a higher paced rate. This is in the research phase (Figure 14).

b) QT interval (58) - A right ventricular unipolar-like electrode is used to detect the repolarization, (T-wave) subsequent to the pacemaker stimulus. QT interval normally shortens

due to changing sympathetic tone and circulating catecholamines. A shorter QT interval produces a higher paced rate.

This development was realized with the TX_1 pacemaker, which is based on the Vitatron DPG generator (Vitatron Medical BV, Dieren, The Netherlands), and three patients have received the TX_1 pacemaker.

c) Respiratory rate (59,60) - A separate lead subcutaneously transversing the thorax is used to measure electrical impedance changes due to changing lung volume. The average sensed respiratory rate is used to control the heart rate. Higher respiratory rates produce a higher pacing rate.

This rate responsive respiratory-dependent pacemaker (Biotec S.P.A., Bologna, Italy) was implanted in 22 patients: mean age 65, range 22-88 years. Nineteen of these patients received respiratory-dependent ventricular pacing (VVI-RD) and 3 patients received respiratory-dependent atrial pacing (AAI-RD) (Figure 15).

d) Oxygen saturation (61) - An optical detector on a lead (fiber optic catheter) in the right ventricle measures the mixed venous oxygen saturation (Figure 16). As mixed venous oxygen saturation diminishes, the pacing rate increases.

This technique is also being evaluated in

patients implanted with permanent pacemakers.

e) pH (62) - A membrane pH electrode near the distal end of the right ventricle lead senses the pH which is proportional to the concentration of carbon dioxide generated by exercising. As the pH diminishes, the pacing rate increases.

Seven devices were implanted in patients from 1977 to 1979. The resultant potential problems derived from biocompatibility of the electrode and tissue growth around the electrode tip.

f) Body activity (63) - An accelerometer-like sensor in the pacemaker senses whole body motion and some secondary local muscle motion. As body activity increases, the sensor signal likewise increases, and the pacing rate.

g) Stroke volume (64) - By measuring changes in intracavitary impedance, this sensor is capable of detecting relatively small changes in stroke volume.

h) Preload (end-diastolic pressure) and contractility (dpldt) (65) - An intracardiac pressure transducer could be used to assess alterations in preload and contractility. Such data could be employed by a rate responsive pacemaker. These are still in the research phase.

VI. Implantable Sensors

The development of various implantable devices such as cardiac prostheses, pacemakers, cardioverters, and defibrillators have created an increasing need for implantable sensors (65) that could be incorporated into such systems to control them more physiologically.

1. Physical transducers

Physical transducers may be used to measure pressure, flow, acceleration, velocity, position etc. Implantable ultrasonic and electromagentic flow transducers have been developed over the last twenty years. These have been implanted for various periods of time and are commercially available. Both piezoresistive and capacitive sensors have been studied for implantation purposes as pressure transducers. Although packaging techniques to protect the lead wires still remains a problem, both sensors can be implanted in the body with relatively good stability. Since the maximum measurable pressure of these sensors depend on the diaphragm thickness, a silicon diaphragm sensor could be used to measure force, stress, strain, sound and vibration with some modification of the diaphragm. Miniature silicon acceleration devices have been developed. Integration of the acceleration could yield velocity information, and then with a second integration, obtain an indication of position.

Several miniaturized solid state flow sensors used temperature gradients and thermal loss as a measure of flow velocity.

2. Chemical Sensors

Ion selective electrodes have been used for many years. There are two important new developments in this field. One is an ion sensitive field effect transistor (ISFET) and the other is a fiber optic sensor. The ISFET is made basically for pH measurement, but can also be used as a specific ion sensor, for K+, Na+, Ca++, etc, when combined with a special ion selective membrane. The ISFET can also be used to measure glucose, lactate, urea, etc. by immobilizing enzymes onto the membrane.

The fiber optic sensor is a device which utilizes the difference in absorption of the light wavelength, by the use of certain dye. pH, pO2, pCO_2, alcohol, and lactate sensors are reported in the literature.

In spite of many efforts devoted for the development of reliable sensors, currently it is quite a disappointment for the availability of clinically reliable sensors. Many years effort are necessary to achieve this goal.

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LEGEND OF TABLES

Table 1 Outcome among 611 patients with out-of-hospital cardiac arrest.

Table 2 Long-term electric left ventricular assist systems under development in the United States.

Table 3 Characteristics of 78 consecutive patients selected for AICD implantation.

Table 4 Currently available antitachycardia pacemaker.

Table 5 List of pacemakers implanted, inclusive dates of implants (first and last of series), number out of service and deaths, percent of original implants still in service, and age of the oldest still in service.

Table 6 Available DDD pacemakers

Table 1 Outcome Among 611 Patients With Out-of-Hospital Cardiac Arrest

Event Witnessed	Number of Patients	Discharged Alive(%)
+	380	28*
-	231	3
Arrythmia of cardiac arrest		
VT or VF	389	28*
Asystole	222	3
Bystander-Initiated CPR		
+	168	32*
-	443	14
Response Time (min)		
4.0	39	56
4.0-8.0	139	35
8.0	186	17

*p 0.01

(From: Eisenberg M., et al. JAMA 1981;246:50)

Table 2 *Long-term electric left ventricular assist systems under development in the United States*

Institution	Corporation	Type/description energy converter	Blood contacting surface	Valve type	Pump location
The Pennsylvania State University	Sarns, Inc.	*Electromechanical*/low-speed reversing motor drives cam or high-speed reversing motor drives roller screw	Smooth Biomer	Bjork-Shiley	Subdiaphragmatic
Children's Hospital Medical Center (Boston)	Thermedics, Inc.	*Electromechanical*/low-speed motor drives cam	Textured Biomer diaphragm within a powered titanium surface	Bovine pericardium	Subdiaphragmatic
Texas Heart Institute (Houston)	Gould, Inc.	*Electromechanical*/high-speed motor and gears drive cam	Textured Biomer diaphragm within a powered titanium surface	Porcine xenograft	Subdiaphragmatic
Stanford University	Novacor Medical	*Electromechanical*/solenoid energizes two opposite pusher-plates	Smooth Biomer	Porcine xenograft	Subdiaphragmatic
Massachusetts General Hospital (Boston)	Abiomed	*Electrohydraulic*/motor-driven turbine pressurizes silicone fluid that compresses blood sac	Smooth Angioflex	Human Dura mater	Intrathoracic
Cleveland Clinic Foundation	Nimbus, Inc.	*Electrohydraulic*/motor-driven gear pump pressurizes silicone fluid that moves pusher-plate	Biolized gelatin		

(From: Gaines W.E., et al. Heart Transplantation 1984;3:323-328.)

Table 3 Characteristics of 78 Consecutive Patients Selected for AICD Implantation

Males/Females: Mean Age (range):	60/18 54 yrs. (16-74)
Primary Cardiovascular Diagnoses	
coronary artery disease:	59 (76%)
primary cardiomyopathy:	18 (23%)
prolonged QT syndrome:	1 (1%)
Ejection Fraction (mean):	.32
Previously Failed Antiarrhythmia Drugs (mean):	4.5
Previous Episodes of Sudden Cardiac Death (mean):	3.5
Previous Cardiovascular Surgery	
coronary artery bypass:	13
myectomy:	1
pacemakers:	10

(From: Reid, P.R., et al. PACE 1984;7:1338-1344).

Table 4 Currently Available Antitachycardia Pacemaker

MANUFACTURER/MODEL	MODE
Telectronics/Pasar	Extrastimuli, Burst
Telectronics (Optima-MP)	Dual Demand
Intermedics (Cybertach)	Burst
Medtronic (Symbios)	Burst, Dual Demand
Medtronics (5998)	Burst (Externally triggered)
MSiemens-Elema (668)	Dual Demand
Cordia (Omni-Orthocor)	Burst, Extrastimuli (externally triggered)

Table 5

List of pacemakers implanted, inclusive dates of implants (first and last of series), number out of service and deaths, percent of original implants still in service, and age of the oldest unit still in service.

Model	Number Implanted	Dates of Inclusive Implant	Out of Service (Deaths)	% in Service (Excluding Deaths)	Oldest Unit (Months)
Cordis 184 A, B	58	10/29/74 to 1/1/83	15 (8)	86% (43/50)	91
Medtronic 9000A	37	8/3/73 to 12/8/76	21 (8)	55% (16/29)	114
Numec/Arco	36	4/9/73 to 1/27/75	17 (7)	65% (19/29)	120
Coratomic C-100	20	11/7/74 to 11/19/80	8 (2)	67% (12/18)	100
Totals	151	4/9/73 to 1/1/83	61 (25)	71% (90/126)	

(From: Parsonnet V., et al: PACE 1984;7:90-95).

TABLE 6 AVAILABLE DDD PACEMAKERS

MANUFACTURER/MODEL	PACING MODE			
MEDTRONIC/VERSATRAX 7000	DDD	DVI	VVI	
MEDTRONIC/VERSATRAX 7000A-235	DDD	DVI	VVI	
MEDTRONIC/SYMBIOS 7007/7008	DDD	DDO	DVI	
INTERMEDICS/COSMOS 283-01	DDD	VVT	OOO	
	VDD	VPP	DVO	
	AOO	AAI	DOO	AAT
TELECTRONICS/AUTIMA 2251	DDD	DOO	DVI	VOO
	VDD	VVI		
TELECTRONICS/AUTIMA II 2291	DDD	DOO	DVI	VOO
	VDD	VVI		
PACESETTER AFP	DDD	VVT	DDI	DVI
	AOO	DDX	VDD	AAI
	OFF	VVI	AAT	VOO
	DOO			
	(DDD with PVC detector on)			
CPI/DELTA	DDD	DOO	ATT	
	VDD	VVT	AAI	
	VAT	VVI	AOO	
	DVI	VOO		
CORDIS/GEMINI 415-A	DDD	VVT	VVI	
	VDD	AAI		
CORDIS/SEQUICOR 233F	DDD	VDD	DVI	VVI

(pacing mode is described according to three-letter code).

LEGEND OF FIGURES

Figure 1a Intra-atrial septation technique to reverse the pulmonary circulation.

Figure 2b Intra-atrial septation technique to reverse the pulmonary circulation.

Figure 2 One pump TAH with reversed pulmonary flow.

Figure 3 Schematic diagram of the diastolic synchronized retroperfusion experimental system. Arterial blood is shunted from a peripheral artery to the diastolic synchronized retroperfusion (D.S.R.) catheter located in the coronary (C) sinus. Diastolic synchronized retroperfusion is achieved by means of an air-blood unit, which is actuated by an electropneumatic console.

Figure 4a (Jarvik 7) Diaphragm type total artificial heart.

Figure 4b Dual pusher-plate type total artificial heart (Cleveland Clinic).

Figure 5a Proposed anatomical locations of E3C implantable components of Nimbus-Cleveland Clinic ventricular assist system.

Figure 5b Pump-actuator components of the above mentioned system.

Figure 6 Schematic representation, showing the complete Novacor-Stanford VAS, and the anatomic location and relationship of subsystems.

Figure 7 Dual chamber pump. The cylinder tucked under the pumping chambers houses the hydraulic drive unit. (Abiomed, Danvers, Mass.).

Figure 8 Locations of the pump-actuator and the engine module. System 8 developed by Cleveland Clinic, University of Washington and Whalen Biomedical.

Figure 9 Completely implantable TAH system proposed by Cleveland Clinic and Nimbus, Inc.

Figure 10 The Pennsylvania State University roller screw drive total artificial heart.

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Figure 13 Acturial survival of pulse generators as a function of power soruce. Note the 80 percent survival of lithium batteries at 90 months compared with the previously used mercury-zinc batteries.

Figure 14 The implantable temperature-controlled pacemaker system. The microcomputer-based pulse generator measures temperature from a thermistor in the lead and delivers stimuli through the pacing electrode. Whlie exercise is detected from right ventricular temperature, the microcontroller increases the ventricular pacing rate. The percutaneous connector allows direct recording of the ventricular electrogram and temperature.

Figure 15 Diagram of followup. Nineteen patients received rate responsive respiratory-dependent ventricular pacing (VVI-RD) and 3 patients received rate responsive respiratory-dependent atrial pacing (AAI-RD).

Figure 16 Cross-section through the S -sensor.

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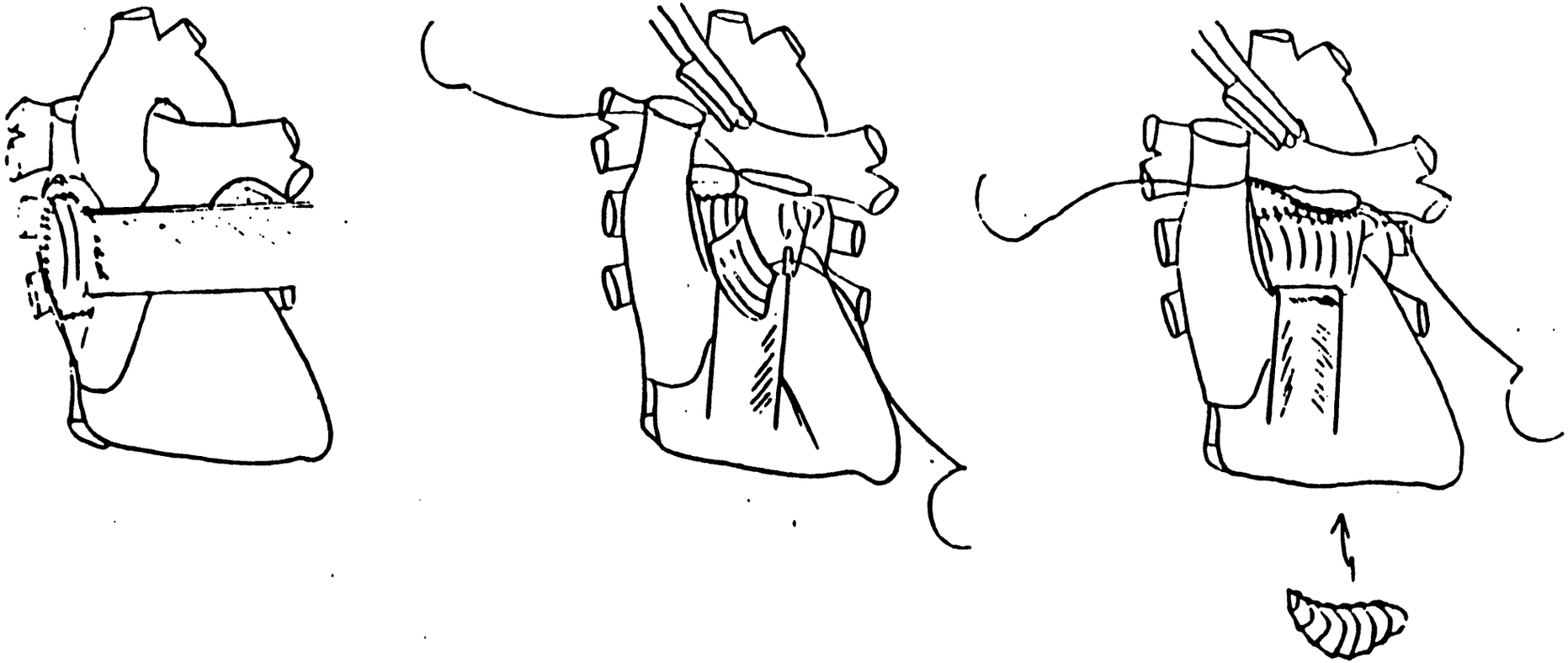
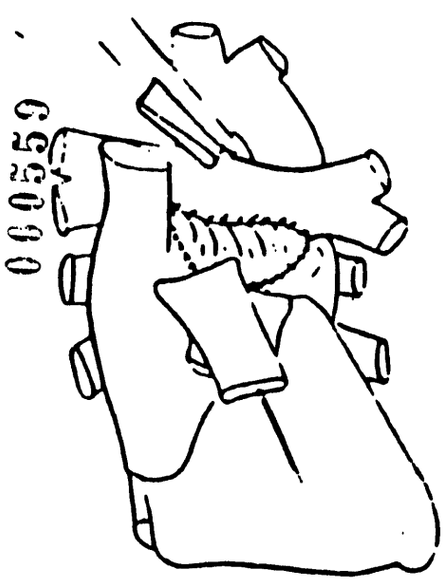


1. Left atrium is opened and a Dacron baffle is sutured over the orifices of pulmonary veins.

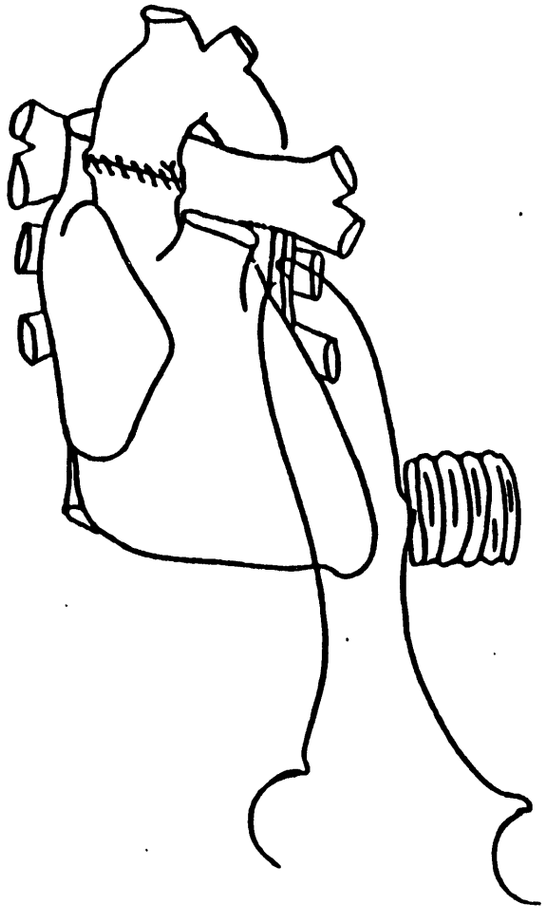
2. After division of aorta and pulmonary artery, left atrial roof is opened and suturing of the baffle is completed. Now, both the orifices of all pulmonary veins and the aperture of the left atrial appendage are excluded from the functional left atrium.

3. After extending the opening in the pulmonary artery bifurcation the back wall of the pulmonary artery is sutured to the inferior edge of the roof of the left atrium. A patch of Dacron is required anteriorly.

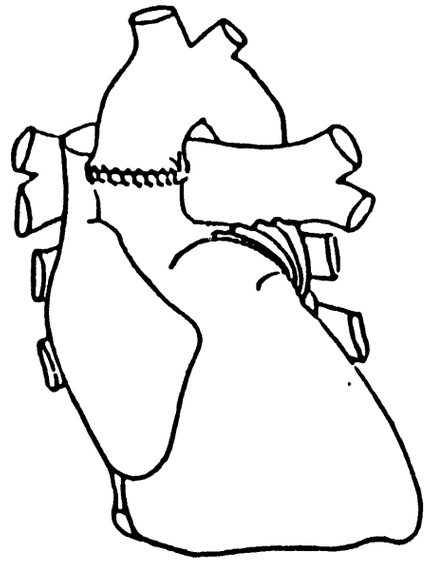
Fig 1(a) Intra-atrial septation technique to reverse the pulmonary circulation.



4. The pulmonary artery-to-left atrial connection is now completed.



5. Following repair of the aorta, the left atrial appendage is anastomosed to a Dacron graft.



6. The proximal end of the graft is anastomosed to the stump of the pulmonary artery, permitting blood to flow into the pulmonary veins, under the baffle. Return from the lungs is via the pulmonary artery then into the left atrium under the patch.

Figure 1(b) Intra-atrial septation technique to reverse the pulmonary circulation

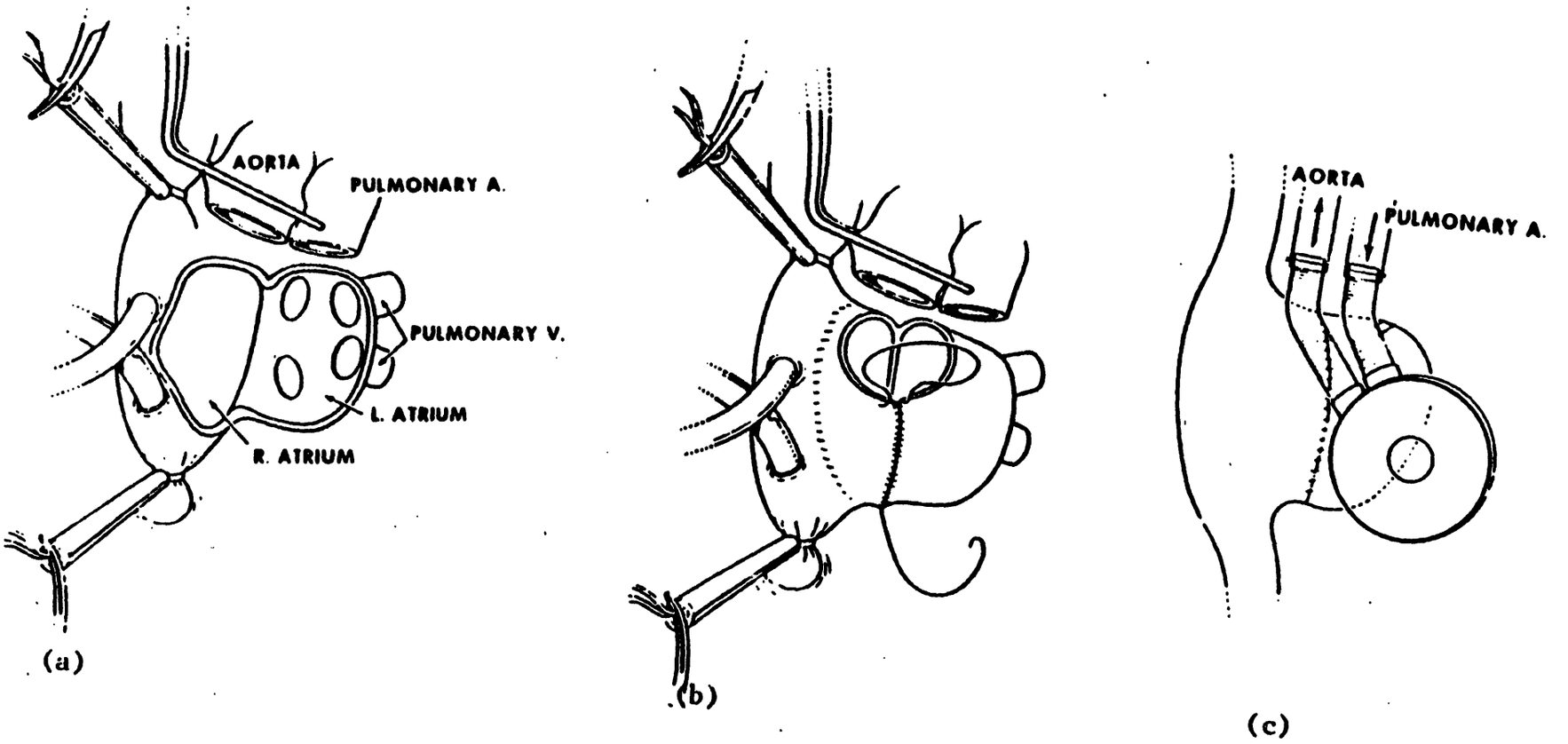


Figure 2 One pump TAH with reversed pulmonary flow

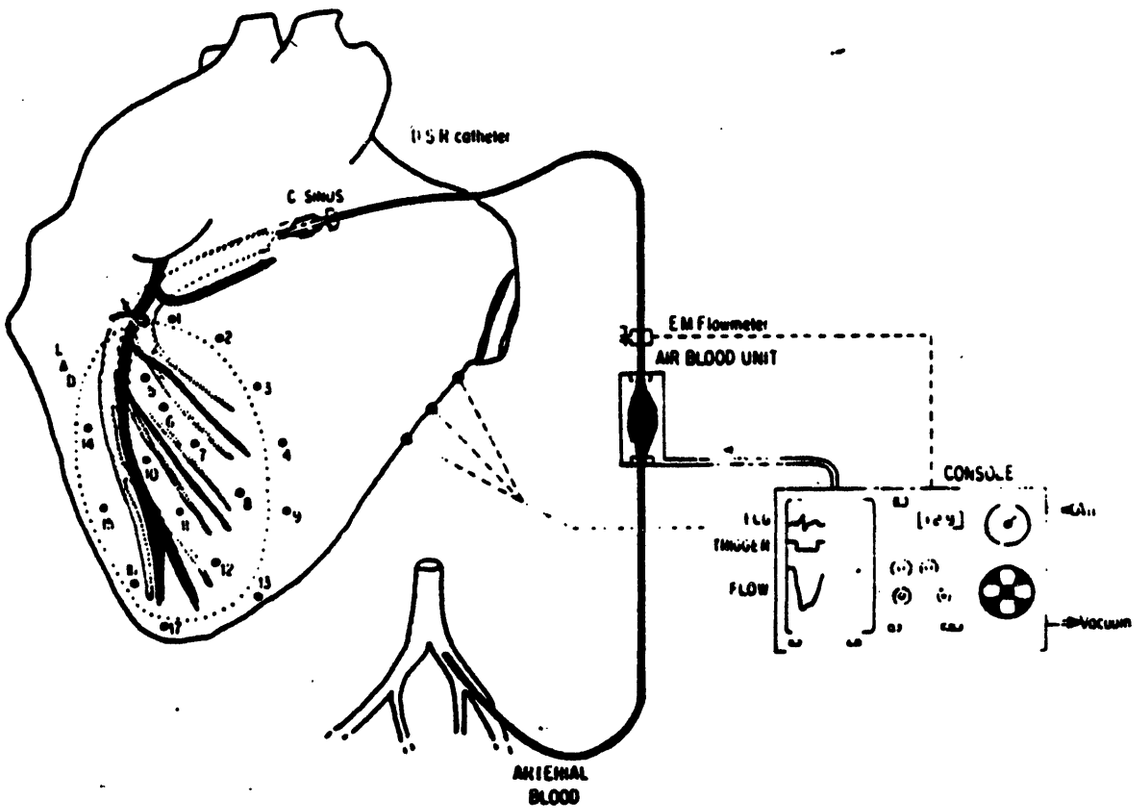


Figure 3 Schematic diagram of the diastolic synchronized retroperfusion experimental system. Arterial blood is shunted from a peripheral artery to the diastolic synchronized retroperfusion (D.S.R.) catheter located in the coronary (C) sinus. Diastolic synchronized retroperfusion is achieved by means of an air-blood unit, which is actuated by an electropneumatic console.

(From Berdeaux A., et al. Am J Cardiol 1981;47:1033-1040).

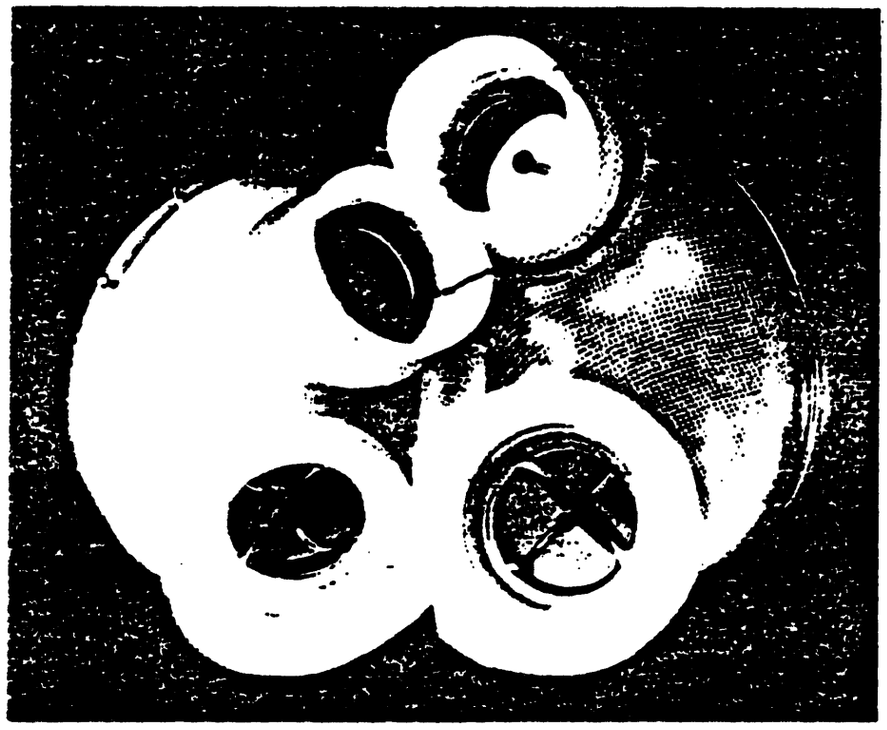


Figure 4(a) (Jarvick 7) Diaphragm type total artificial heart

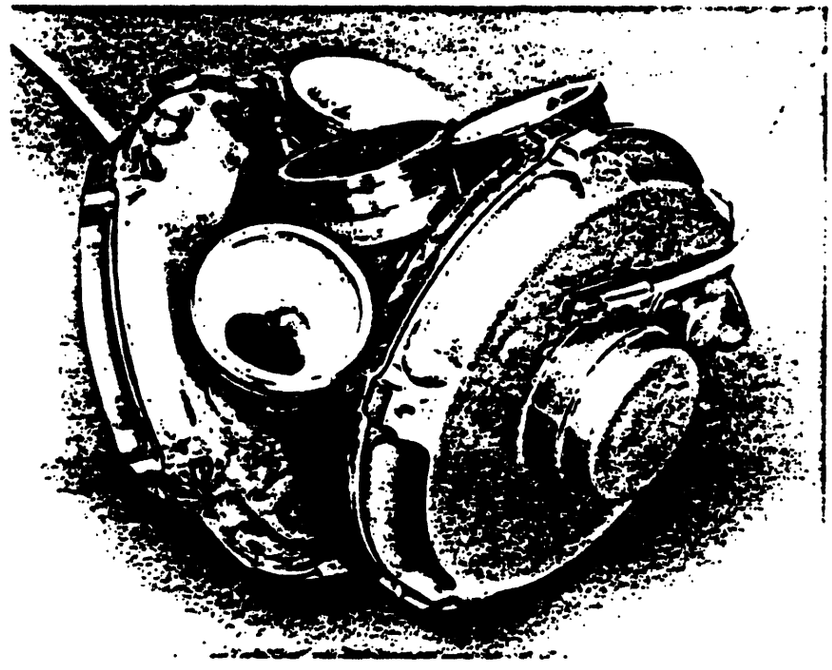


Figure 4(b) Dual Pusher-Plate type Total Artificial Heart (Cleveland Clinic)

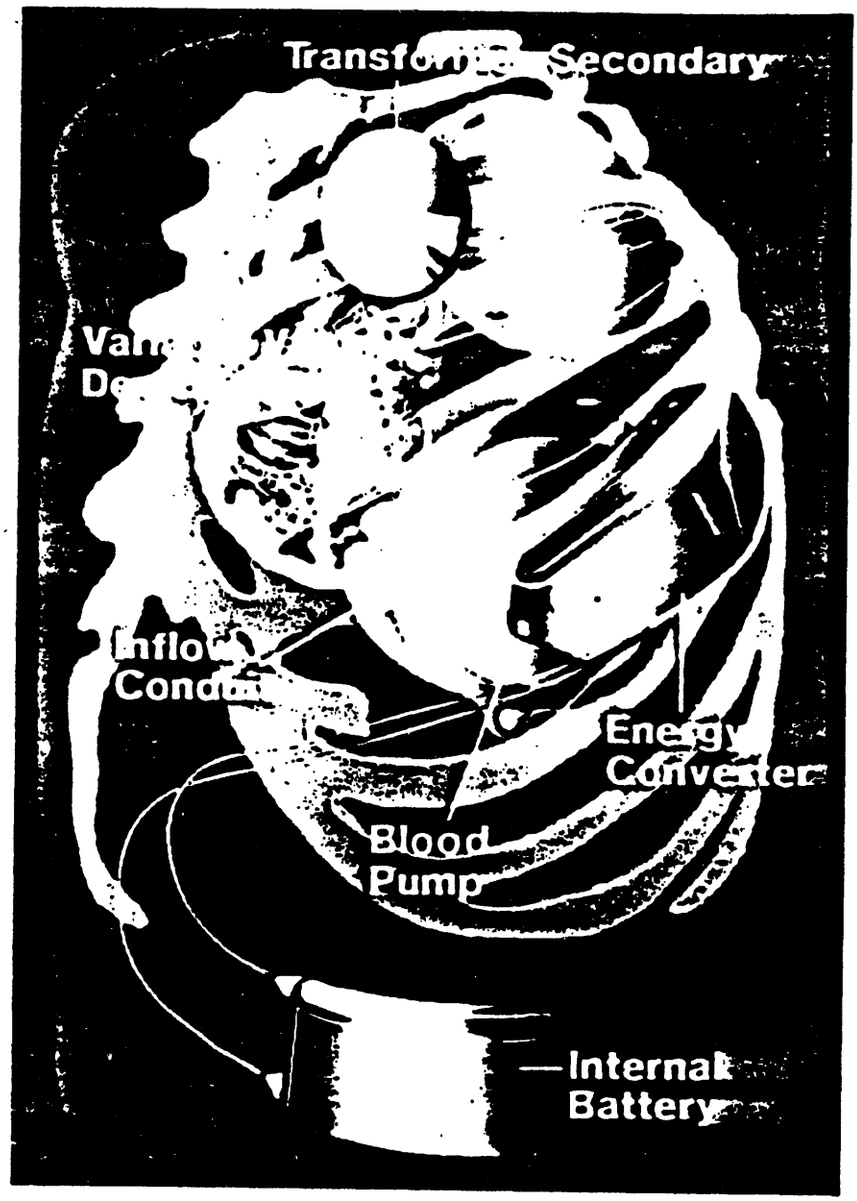


Figure 5(a)

Proposed anatomical locations of E3C implantable components of Nimbus-Cleveland Clinic ventricular assist system.

Figure 5(b) Pump-actuator components of the above mentioned system.

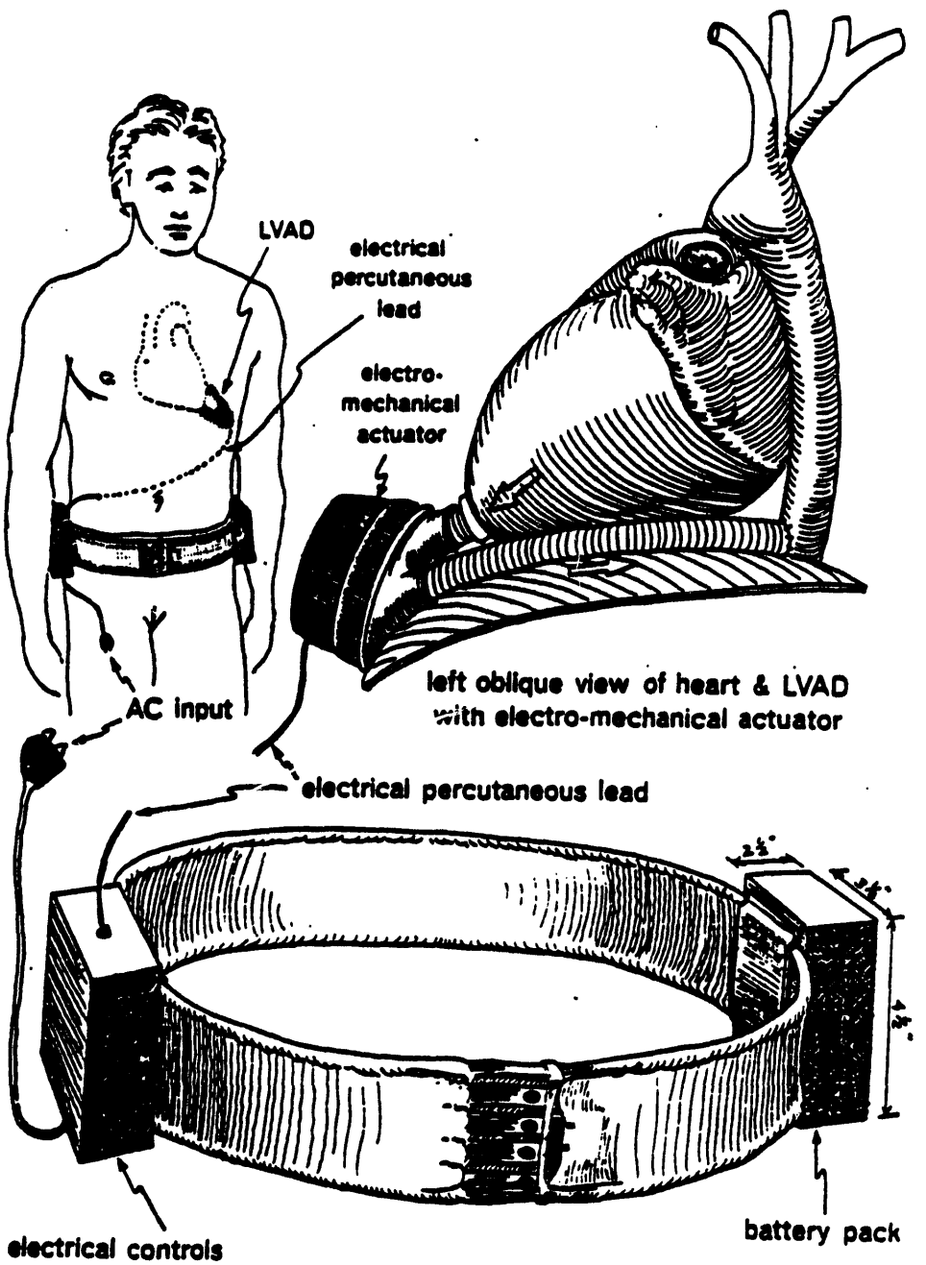


Figure 6 Schematic representation, showing the complete Novacor-Stanford VAS, and the anatomic location and relationship of subsystems.

(From Altieri F.D. Artif Organs 1983;7:5-20).

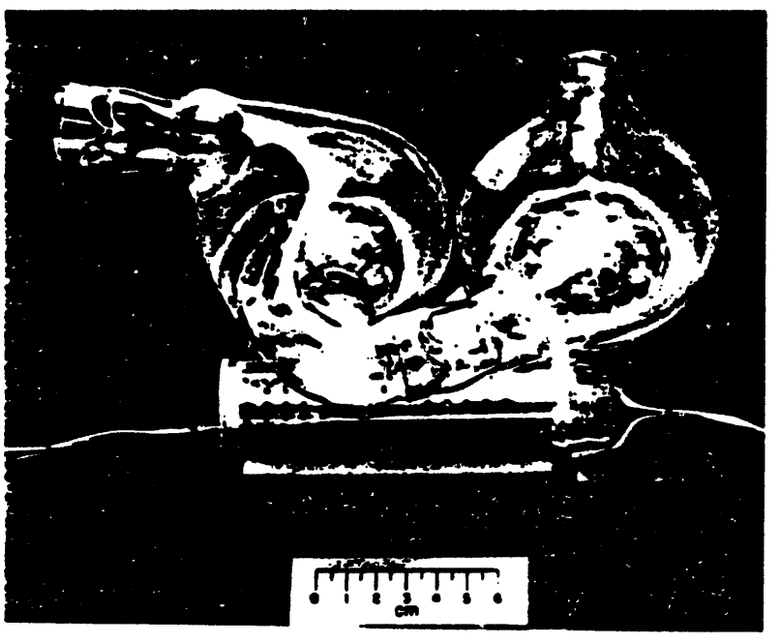
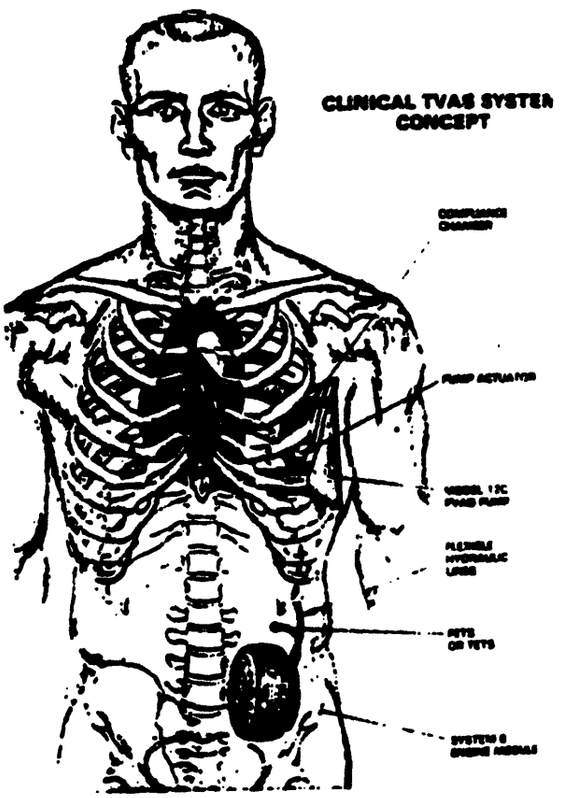


Figure 7 Dual chamber pump. The cylinder tucked under the pumping chambers houses the hydraulic drive unit. (Abiomed, Danvers, Mass.)

(From Singh P.I., et al. Trans Am Soc Artif Intern Organs 1982;28:117-122).



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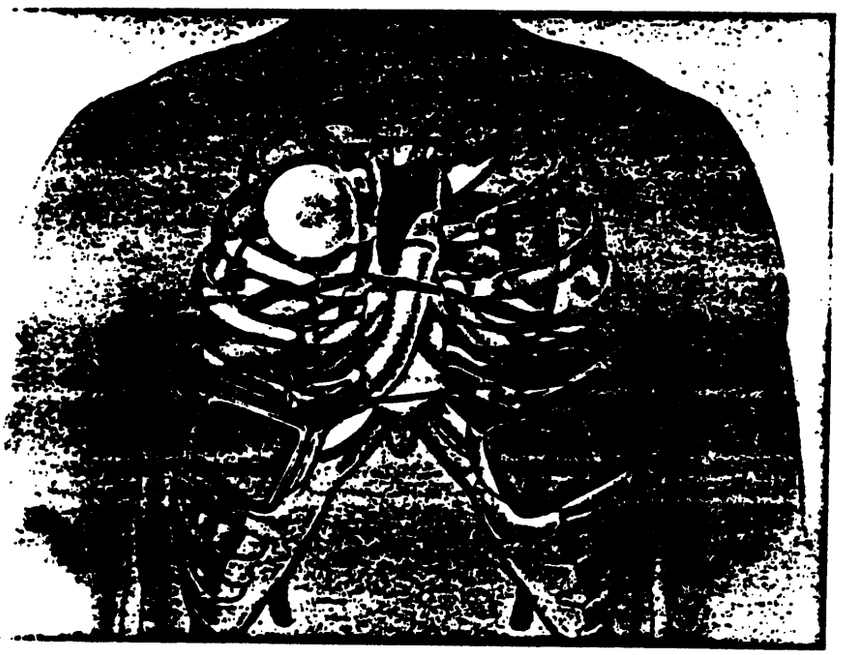


Figure 9 Completely implantable TAH system proposed by Cleveland Clinic and Nimbus, Inc.

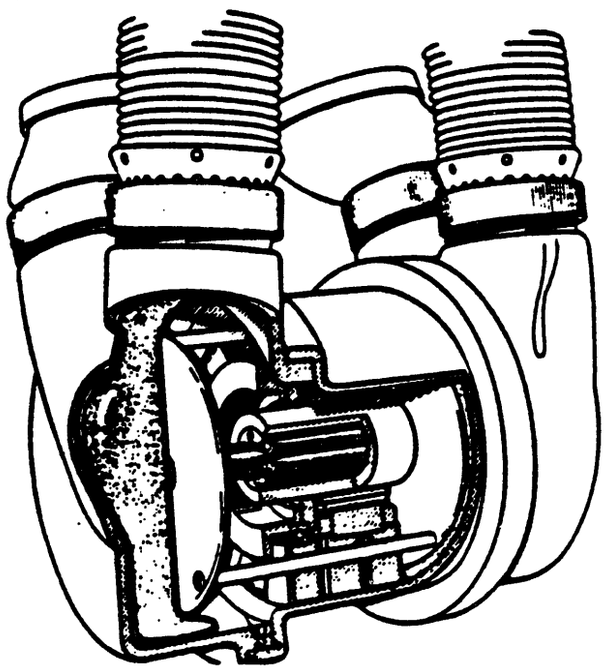


Figure 10 The Pennsylvania State University roller screw drive total artificial heart.

(From Rosenberg G., et al: Trans Am Soc Artif Intern Organs 1982;28:123-126.

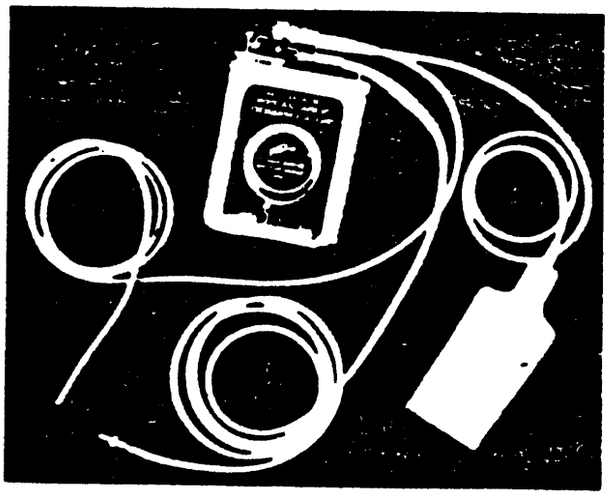


Figure 11 The automatic implantable cardioverter-defibrillator with, left to right, its superior vena cava, bipolar right ventricular, and apical patch electrodes.

(From Mirowski M., et al. PACE 1984;7:534-540).

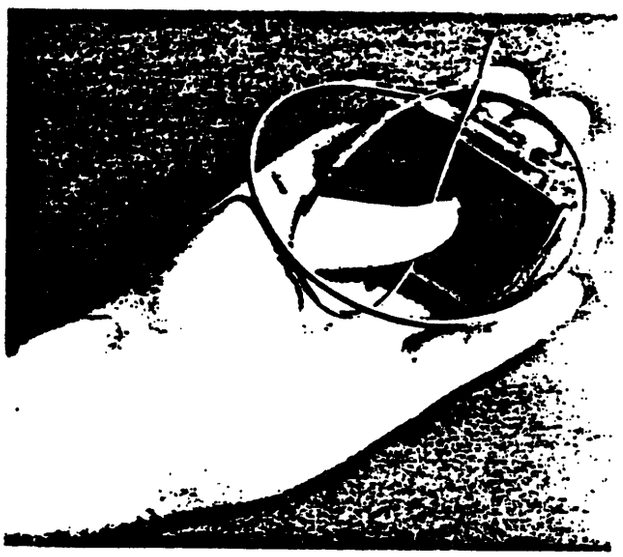


Figure 12 Picture of cardioverter and lead in surgeon's gloved hand.

(From Zipes D.P., et al. PACE 1984;7:1325-1330).

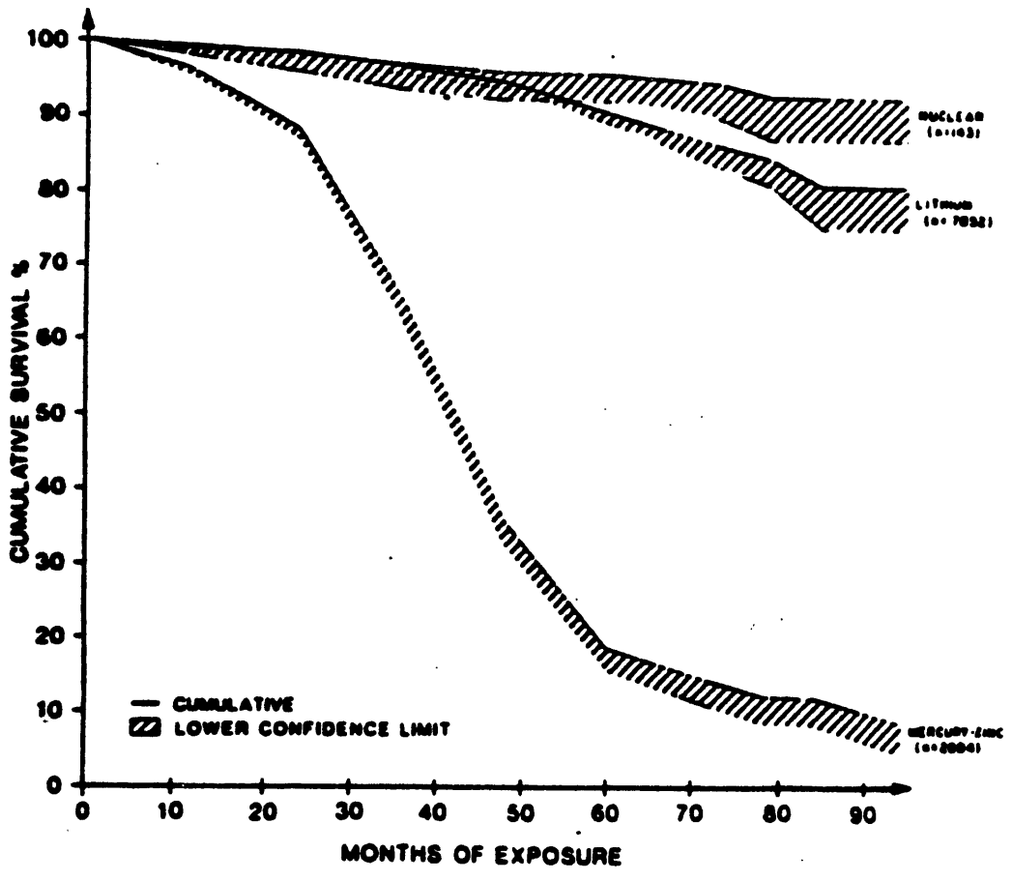


Figure 13 Acturial survival of pulse generators as a function of power source. Note the 80 percent survival of lithium batteries at 90 months compared with the previously used mercury-zinc batteries.

(From Personnet V., et al. PACE 1984;7:90-95).

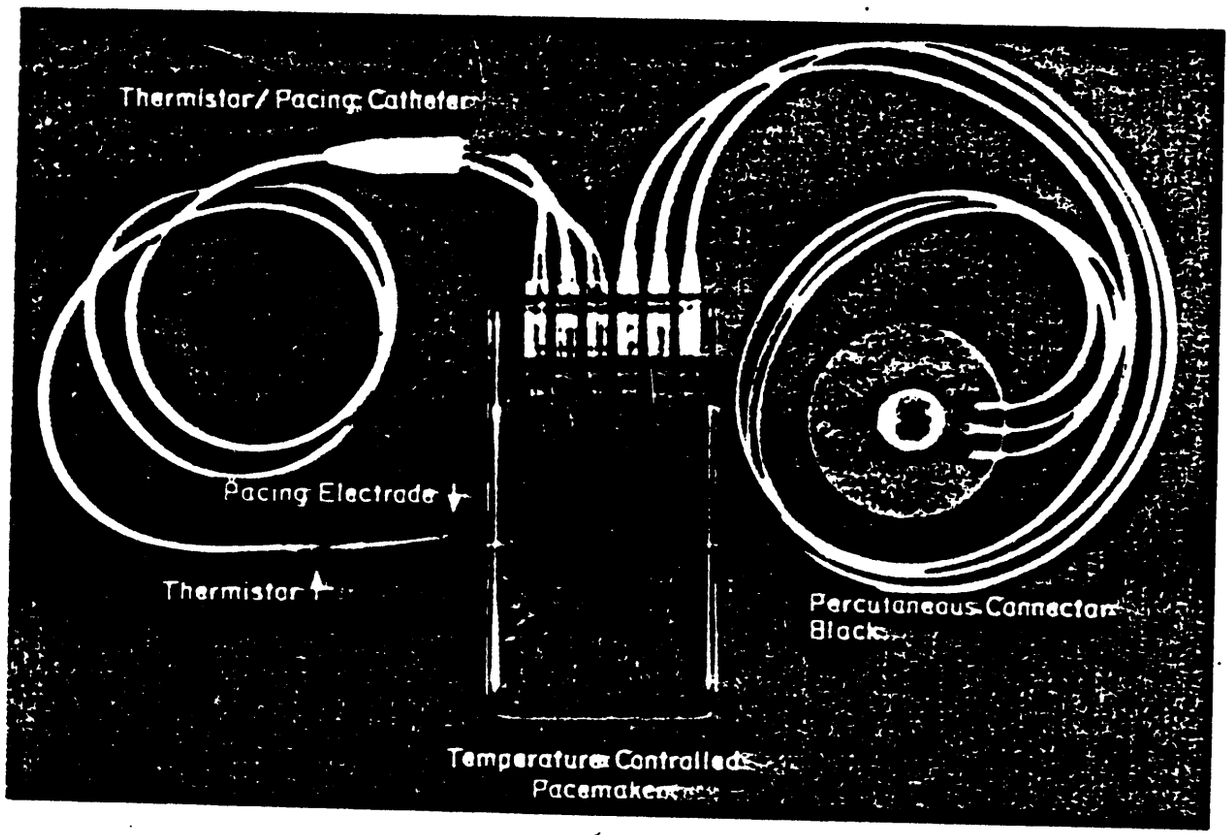
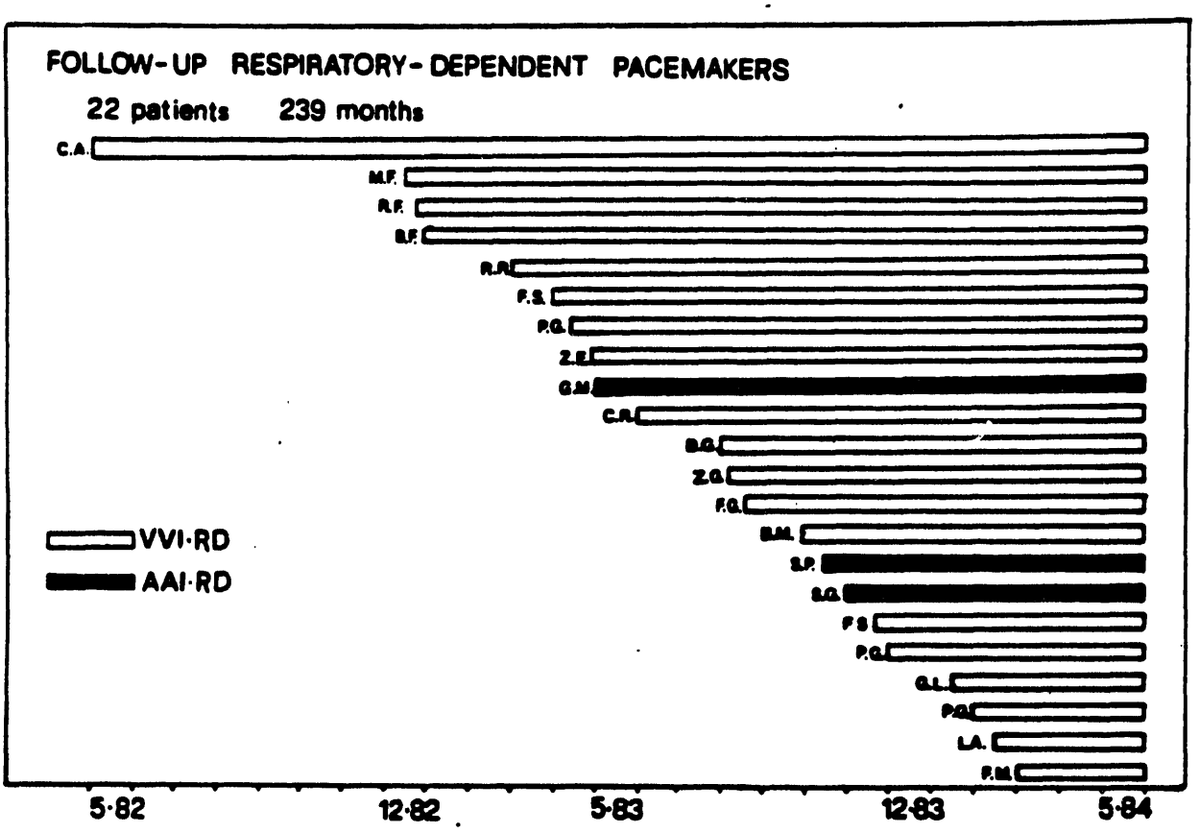


Figure 14 The implantable temperature-controlled pacemaker system. The microcomputer-based pulse generator measures temperature from a thermistor in the lead and delivers stimuli through the pacing electrode. While exercise is detected from right ventricular temperature, the microcontroller increases the ventricular pacing rate. The percutaneous connector allows direct recording of the ventricular electrogram and temperature.

(From Fearnot N.E., et al. PACE 1984;7:1240-1245).



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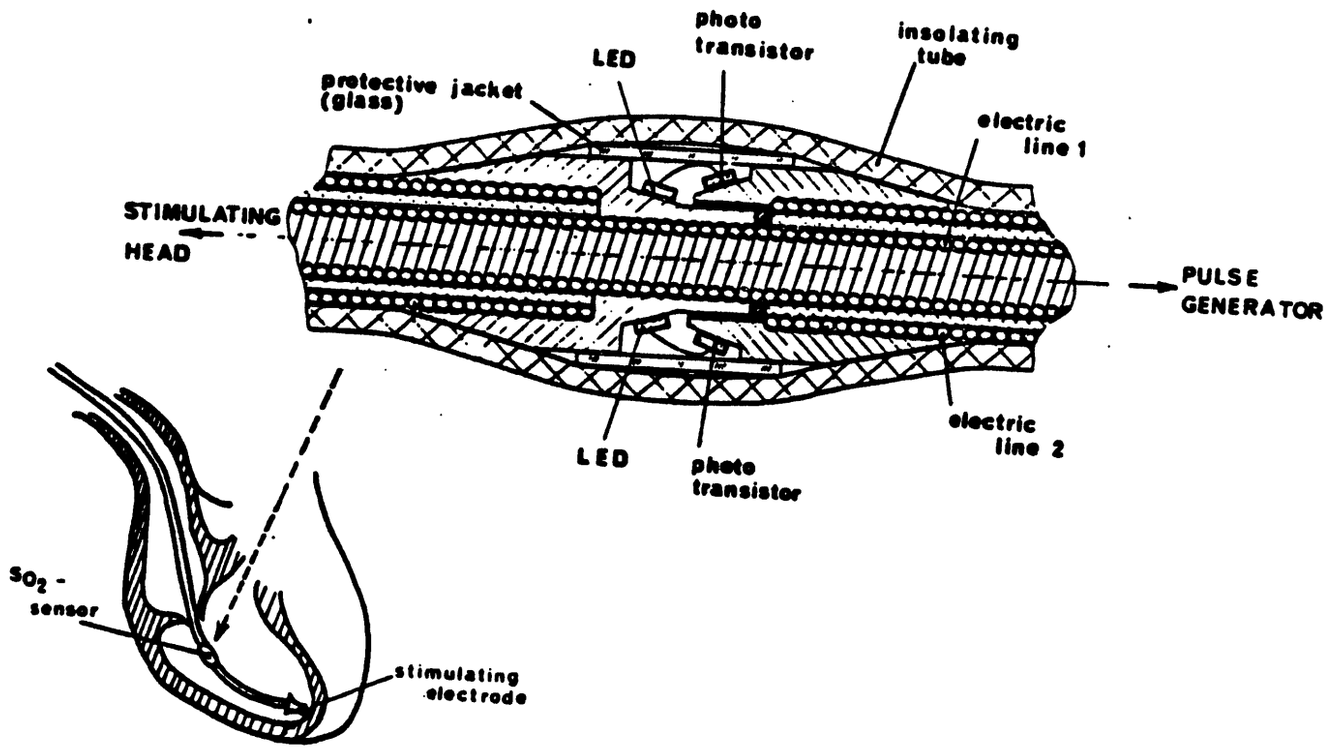

Figure 16 Cross-section through the $S0_2$-sensor.

(From Wirtzfeld A., et al. PACE 1983;6:494-497).

TASK IV: ADVANCES IN NUTRITIONAL SUPPORT TECHNOLOGY

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TASK IV: ADVANCES IN NUTRITIONAL SUPPORT TECHNOLOGY

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TASK IV: ADVANCES IN NUTRITIONAL SUPPORT TECHNOLOGY

I. INTRODUCTION

From the report of the Bureau of Census in 1984, the population and ratio of the elderly in the United States has been increasing[1]. In 1960, the population of the elderly over 65 years old was 16.5 million and the ratio was 8.0% of the total population. In 1982, however, the population and the ratio had increased to 25.2 million and 11.2%, respectively. With the increase of the elderly, the number of deaths by diseases, as well as by malnutrition, have also been increasing. More than 50,000 hospitalized patients die in the United States yearly because of nutritional deficiency. Furthermore, it is estimated that nutritional deficiency affects more or less 500,000 yearly in their struggle to recover from a malnutritional state. Recently, the rate of malnutrition has risen to 56% - 85% at various nursing homes. Recent progress, however, in nutritional supporting technologies has provided the improvement of the nutritional state of patients with critical states such as a serious burns, cancer, pre and post major surgery and sepsis. For the treatment of the elderly, however, special considerations have to be paid to their underlying metabolic and immunologic disorders. For example, even with a human considered to be healthy, normal values of plasma fibrinogen levels increase with age (Table I)[2]. In addition, the common diseases in the elderly such as cardiovascular disease, diabetes mellitus, cancer and chronic liver disease are greatly related to the malfunction of the immmuno-metabolic system.

Thus, conditions of the elderly or of their nutritional state are

referable to the changes in metabolism that occurs with aging. In other words, the correction of abnormal metabolism of the elderly, whether it be of normal or of disease state, is thought to produce good results for the elderly.

Further development of nutritional support can improve and maintain the nutritional state of the elderly satisfactorily, and innovative technologies which are mostly based on extracorporeal circulation techniques, can provide not only the method of treatment, but also the method of prevention of the diseases which plague the elderly.

The purpose of this section is to address the advances in the technologies for nutritional support, those being parenteral and enteral feeding; and immunometabolic support.

II. NUTRITIONAL SUPPORT

The method of nutritional support can be divided into two classes, the first being parenteral nutrition, and the other enteral nutrition. In parenteral nutrition, artificially-made nutritional solution is administered intravenously. In enteral nutrition, various nutritious substances are infused into the gastro-intestinal tract. Strategies and details of advances in these technologies are described in the following paragraphs.

A. Marketing strategies

The purpose of applying nutritional support technology is to provide the elderly who are in a malnutritonal state with sufficient nutrients which will support, fully or partially, the life of the

elderly well. As a matter of fact, among nursing home residents, 85% of the patients are showing various degrees of protein-caloric malnutrition[3] and 56% of the patients are suffering from severe malnutrition[4]. It is thought that the population of the elderly who need nutritional support is quite high.

To further develop reliable technologies for nutritional support would decrease the rate of the malnutritioned elderly and by doing so decrease the number of hospitalized elderly. Also, reducing the number of hospitalized elderly would lessen the need for full medical care which would subsequently lead to cost-effectiveness.

Further developments of technologies for nutritional suppport promise to abolish any complications of devices and warrant the patient being ambulatory without any uncomfortably heavy devices. This would provide the elderly with the chance of a better quality of life.

B. Parental nutrition

The integrated laboratory and clinical investigations which have culminated directly in the development of intravenous hyperalimentation (IVH) started in 1962[5]. Thereafter, continuous intense efforts had been made for the completion of total parenteral nutrition (TPN) therapy. The first successful clinical TPN therapy was initiated by Dudrick's group in 1968[6]. A 36-year-old woman, with incomplete mechanical small bowel obstruction and ileus secondary to extensive intraperitoneal metastatic ovarian carcinoma, was fed entirely by IVH and was discharged from the hospital to her home. During the last six

months of her life, it was possible to maintain her nutrition intravenously at home with a large and heavy hospital apparatus. This apparatus, however, allowed her to be ambulatory and to live with her family. Since this successful clinical application, this technique has become an invaluable tool in the management of certain complicated nutritional problems. With the development of TPN technology, the indications for and the applications of ambulatory home TPN have increased greatly. Indeed, it is estimated that more than 3,000 patients are receiving home TPN currently[7]. Furthermore, it is predicted that this number will multiply significantly each year as awareness of the safety and efficacy of home TPN grows, as scientific and technological advances in parenteral feeding techniques and substrates are extended, and as emphasis on cost-effective home health care programs is accentuated[8].

The TPN device consists of five basic components: 1) an implantable catheter for central venous access; 2) bags of nutrient solution which can be prepared by the patient or a family member; 3) an infusion pump to deliver the infusate at a constant rate; 4) a portable stand which serves as an intravenous pole with or without a monitoring device to warn the patient when the infusion is almost completed; and 5) an infusion line with an in-line 0.22-micron filter which moderates transmission of microbes from solution to patient.

Blood access to the patient's central venous system is

extremely important for long-term TPN therapy. Due to its hyperosmolarity, TPN requires infusion through a central venous catheter which is usually placed via the subclavian route. The catheter is inserted either by puncture of the subclavian or external jugular vein, or under direct vision by exposure of the cephalic or other similar superficial vein. The catheter tip is advanced until it lies in the superior vena cava at its junction with the right atrium (Fig. 1). The distal end of the catheter is run in a subcutaneous tunnel to emerge through the skin of the chest wall near one of the nipples at a site where the patient can clearly see it. In between infusions the patient fills the catheter with 1.5 ml of heparin solution(1,000 units/ml), a so-called "heparin lock" to prevent clotting within the catheter and to allow mobility[9]. As materials for the TPN catheter, polyethylene and silicone rubber (Hickman or Broviac) have been widely used[8,10]. It is acknowledged that successful management of the catheter commences with insertion under sterile conditions after meticulous skin preparation. With the use of a standard polyethylene or silicone catheter, however, this procedure has been associated with a 33% incidence of clinically occult subclavian vein thrombosis detectable on a radionuclide venogram[11,12]. The requirement for the development of a non-thrombotic catheter lies in the investigation of a more biocompatible material for the catheter. Polyurethane is a promising material and is currently under clinical investigation[12,13]. Linden and his colleagues reported that the incidence of clinical thrombophlebitis was less with a polyurethane

catheter than with a silicone rubber catheter[12]. Also, Fabri and his colleagues reported in their radiographic study that the use of polyurethane catheters in 20 patients showed no evidence of venous thrombosis up to a period of 820 days without the administration of any heparin as an anticoagulant[13]. Those studies show that polyurethane is expected to be a suitable material for TPN catheters. Further clinical evaluations by other institutes need to determine its usefulness for TPN. Although care of the catheter is meticulously made, catheter complications with TPN include structural failure, migration, sepsis and thrombosis. To minimize these complications, continuous efforts have been made to develop the implanted vascular access device which consists of a self-sealing silicone rubber septum encased in a port made of metal or plastic attached to a silicone catheter. Currently, several of these devices are under investigation for clinical use (Table II)[14]. Fluids, drugs and blood can be administered into this port system by a simple needle puncture through the skin into the port. These systems will minimize the potential for infection and be more cosmetically acceptable to the patient. The need for dressing changes is completely abolished by these systems. Another attempt at trying to avoid indwelling catheter troubles such as thrombosis and infection, has been made by Havil and his colleagues[15]. Their basic idea is to create an arterial-venous (A-V) shunt in the arm or leg as a vascular access for the administration of nutrient solutions. Hypertonic solutions fed into such a vein are rapidly diluted and hence relatively nonirritative. By this

means a patient can be treated at home without the necessity of hospitalization. For the creation of an A-V fistula, a natural vein graft of a patient or a synthetic graft such as Gore-Tex (W.L.Gore, Inc., USA) is used. This method for home TPN is awaiting further clinical evaluation.

Ingredients of TPN include essential and non-essential amino acids as nitrogen sources, carbohydrates in the form of dextrose and fat as energy sources, various electrolytes, water-soluble and fat-soluble vitamins, essential fatty acids, and trace elements which are especially required in long-term feeding. Typical adult and pediatric home TPN regimens are listed in Table III and Table IV[7]. Adjustments in these basic formulations are necessary for each patient depending upon individual requirements, tolerances, body chemistries, and disease process. For home TPN, pre-mixed solutions are supplied by vendors, but solution compounding can be made by a patient himself or by a member of the family without any serious trouble. The self-mix option is among the most difficult of home care techniques, however, no higher risk of infectious complications in mixers has been reported recently[16], not only because of the hypertonic resistance of the solution to microbial growth but also because of the meticulous preparation and adequate sanitary facilities in the home. For the preparation of nutritional formulas for the elderly however, particular considerations must be paid. First, many physiological functions decline progressively throughout adult life. In most cases there is uncertainty about the significance of nutrition in altering the process of these

changes. The other issue is that food intake in general diminishes with age, but there is very little solid knowledge on which to base recommendations for the optimum intake of individual nutrients by older people. Because of these reasons, special nutritional formulas for the elderly have not yet been developed. Lack of adequate fundamental data regarding geriatric nutrition has caused emphasis to be placed upon the investigation of the requirements for energy[17,18], protein[19,20] and vitamins[21]. Definite data about nutritional requirements for the elderly has not been provided yet. Although there is limited information for the elderly, "recommended dietary allowances" in the USA are available at this time[22].

Realizing that manual flow clamps on gravity-flow systems cannot always maintain the flow rates and the necessity of total volume accuracy required for the infusion of parenteral nutrition solution has led to the development of computerized infusion pumps. Currently, available infusion pumps are listed in Table V. The introduction of infusion pumps has greatly increased the accuracy of the infusion volume intended to infuse in comparison to the conventional gravity-flow system. At this time, however, pumps listed in Table V as general pupose do not satisfy all the aspects of the evaluations[23]. These evaluations are made by the following assessments which are: range and accuracy, flow rate continuity, flow rate error change after 24-48 hours operation, accuracy with elevated blood pressures, maximum occlusion pressure, effects of bottle height, operation during transport, drop sensor mispositioning, pump set mispositioning, fluid

depletion and air in line, volume counter, keep vein open (KVO) rate, resistance to tampering and accidents, memory functions, alarm disable, battery life, electrical safety, electromagnetic interference (EMI), interference with other equipment, line voltage variation, effects of fluids, quiet operation, ease of use, and servicing[23]. Further developments satisfying these aspects are necessary for the success of the infusion pump.

By using these intravenous hyperalimentation technologies, appropriate nutritional conditions can be achieved and maintained for those who are in malnutritional states. These malnutritional states include inflammatory bowel diseases, short-bowel syndrome, certain congenital malabsorption syndromes, pseudo-obstructive syndromes, acute renal failure, acute hepatic failure, the operative malnourished patients, and the complicated post operative or post-trauma patients. Small bowel resection culmunating in short-bowel syndrome is among the most frequent indications for TPN. Necessities such as extended resective procedures arise from bowel infarction, malrotation, gangrenous volvulus, radiation enteritis, unrelenting inflammatory bowel disease such as Crohn's disease and extensive abdominal trauma. Acute flare-ups of inflammatory bowel disease and acute pancreatitis may be treated with periodic TPN therapy, since bowel rest tends to shorten the duration of the acute attack.

Congenital malabsorption syndromes, such as cystic fibrosis and developmental failure of villi, might be a candidate of TPN. Additionally, TPN is indicated in those patients afflicted with various pseudo-obstructive syndromes, such as scleroderma.

Because of the fact that TPN might hasten the ultimate demise of the patient with metastatic cancer disease, full-scale TPN may not be indicated or ethical in the near-terminal cancer patient[16].

These TPN technologies have contributed not only in the improvement of malnutrition caused by inadequate food supply, but also in the therapy of metabolic malnutrition.

One of the serious disorders to plague the elderly is diabetes mellitus. Someone who is suffering from this disease is at a high risk for ischemic heart disease, renal failure, degenerative peripheral neuropathy and retinopathy. Despite intensive efforts with a proper diet, many diabetics need insulin injection therapy to maintain an adequate nutritional state and prevent disastrous vascular disorders. The improvement of insulin therapy can be achieved in many cases when single injections are replaced by continuous insulin infusions. For accurate insulin therapy of a patient, continuous infusion pumps have been developed (Table VI)[24]. Further innovation includes an implantable computerized programmable microinfusion pump and a closed loop infusion pump. The implantable open loop insulin pump, which can inject continuously the proper amount of insulin to a diabetic based upon the analysis of blood glucose profiles of a patient, is under clinical investigation[25]. This system, however, is not suitable for variations in changeable daily glucose levels of a patient. The closed loop system, which is the glucose-controlled insulin infusion system, is being widely investigated by many laboratories[26,27].

Furthermore, current infusion pump technology could provide the opportunity for the treatment of severe left ventricular dysfunction by strong inotropic agent[28], for controlling chronic severe pain of cancer patients[29], and in treating advanced malignant neoplasma by escalating in doses of chemotherapeutic agents[30,31].

B. Enteral Nutrition

The development of total parenteral nutrition has been a major breakthrough in nutritional technology. In many patients, however, adequate nutritional support can be given with specially formulated liquid diets administered by the enteral route. Enteral nutritional support avoids the potential technical, metabolic, and septic complications of parenteral nutrition. However, it is rather difficult to provide more than 3,000 calories per day by this means.

Patients who benefit from enteral alimentation via a nasogastric feeding tube are those with a normal gastrointestinal tract function who refuse or are not able to take adequate oral alimentation. Those patients include, for example, geriatric, senile dementia and anorexia nervosa patients. In addition, enteral feeding benefits the patients with neurologic or muscular diseases who are unwilling or unable to swallow effectively, such as stroke patients, postoperative neurosurgical patients, and those with multiple sclerosis, myasthenia gravis, and dermatomyositis. Also, patients with obstructing lesions of the proximal gastrointestinal tract may receive benefit from this

nutritional support. Those patients include head and neck tumors, esophageal carcinoma, benign esophageal stricture, gastric carcinoma, and gastric outlet obstruction due to chronic duodenal ulcer disease. Such patients usually are fed liquid diets through an enterostomy tube placed distal to the obstructing lesion. In this way, significant malnutrition may be corrected prior to surgical treatment[32].

Enteral feeding tubes are now generally made of silicone rubber or polyurethane(Table VII). Such tubes are expected not to crack or stiffen after prolonged exposure to gastric secretions, a problem that was common with polyvinylchloride. Use of the smallest tube that will allow for passage of the formula is essential to maximize patient comfort and tolerance. The most popular nasoenteric feeding tubes are weighted with elemental mercury or tungsten, which facilitates passage of a small-bore tube into the stomach and when necessary to the duodenum or jejunum through the pyloric sphincter.

When proximal gastrointestinal tract function or continuity is impaired, enterostomy tubes can be surgically placed directly into the stomach or jejunum. Such tubes inserted into the jejunum should be placed as proximally as possible, so that maximal digestion and absorption will minimize the risk of diarrhea[33].

For continuous or scheduled enteral feeding, several enteral pumps are currently available. It is estimated that, at this time, 35,000 enteral pumps have been used at hospitals and nursing homes in the United States for enteral feeding. Such

pumps include the Kangaroo pump (Chesebrough-Ponds, Inc.), Dobbhoff pump (Biosearch Medical Products, Inc.), Keofeed pump (IVAC Co.), Rateminder-II pump (Anatros Co.), and Flexiflo-III pump (Ross lab). These electromechanical pumps have recently become available and have been used both for maintaining an accurate infusion rate and in facilitating delivery of the viscous solution through a small-bore tube by application of continuous positive pressure. In addition, usage of such pumps has decreased the likelihood of diarrhea and has permitted more careful assessment of patient tolerance of the enteral formula.

Currently, numerous enteral formulations are available. They differ in osmolarity, digestibility, caloric density, lactose content, viscosity, residue, fat content, taste, and expense. There are several commercially prepared homogenates of selected food items (Table VIII-1.2). When these diets are administered in adequate amounts, these preparations can fully satisfy an individual's caloric and nutritional need. However, a specific nutritional formula for the elderly has not been developed yet.

The major complications of these diets are diarrhea and crampy abdominal pain secondary to the high osmotic load or, occasionally, to an extensively rapid infusion rate.

Further investigations regarding these nutritional technologies include innovating the nutritional formula which can easily be modified to the condition of each individual, and developing the method of assessment of the effectiveness of nutritional support for the individual nutritional state.

III. THERAPEUTIC APHERESIS

As mentioned before, nutritional states of the elderly are greatly related to the malfunction of the immuno-metabolic system, which is common in geriatric people. So, it is considered important to correct the abnormalities of metabolism which increase with aging. In this aspect, therapeutic apheresis, especially on-line plasma treatment with returning essential nutrients, is an approach to preserving nutritional and immunological homeostasis.

Therapeutic apheresis is the use of a procedure to separate components of the blood followed by removal of one or more of these components. This procedure is used therapeutically to remove cells or solutes which are thought to be harmful[34]. The idea of therapeutic apheresis is over 3,000 years old. People who were performing the role of medical doctors today had been cleansing the body of sick patients by blood letting to get rid of the foul and noxious matters[35]. Recent successes of extracorporeal technique, blood access, membrane technology and centrifugal technology have turned this old dream into the reality of a scientific realization.

Blood is divided into two components which are plasma and cell components. In cell components, three basic cell types exist; red blood cells, white blood cells and platelets. There are several modalities which deal with the subject of plasma or of some solutes in plasma. In such modalities, there are therapeutical plasmapheresis (plasma exchange), thermofiltration and cryofiltration. Cytapheresis is intended to remove certain cell components from the whole blood.

Details of these modalities are to be described in the following paragraphs.

IV. METHODS OF PLASMA SEPARATION

For the separation of the plasma in the blood, there are two basic approaches. One is membrane plasma separation and the other is centrifugal plasma separation (Fig. 2)[36].

The principle of plasma separation by membrane separators is to separate the noncellular components of the blood from the cellular components of the blood by using porous membranes (Fig. 3). Several materials for the porous membrane have been developed for clinical use (Table IX), those being cellulose diacetate (Asahi Medical Co., Teijin Co., Terumo Co., Japan), polyvinyl alcohol (Kuraray Industrial Co., Japan), polymethylmethacrylate (PMMA) (Toray Industries, Inc., Japan), polyethylene (Mitsubishi Rayon Co., Japan), polypropylene (Fresenius Co., West Germany, Takeda Medical, Japan, Travenol Co., USA), polyvinyl chloride (Cobe Co., USA). These membranes are made with a porosity ranging from 0.2 - 0.6 um (Fig. 4).

There are two types of housing for these membranes, with one being a hollow fiber type (Fig. 5) and the other being a plate type (Fig. 6). As a membrane plasma separator, the hollow fiber type is very common. The outlook of the hollow fiber type is very similar to the hemodialyzer; however, operation of a membrane plasma separator is quite different. Dialyzers for hemodialysis and hemofilters for hemofiltration require high transmembrane pressure, while for sufficient operation of a membrane plasma separator, particular considerations must be paid, those being: a) high plasma separation rates with

high sieving are possible at low transmembrane pressure, generally below 50mmHg[37]; b) increasing transmembrane pressure leads to deterioration of plasma flux, sieving and hemolysis[38]; c) the nature of the blood and its cellular and macromolecular concentrations will greatly dictate operation limits[39] (Fig.7). Generally, plasma is separated easily at a rate of 30ml/min with a blood flow of 100ml/min.

For the centrifugal separation, several varieties of centrifugal apparatus are available, including intermittent flow and continuous flow instruments (Table X). The process of the intermittent separation is drawing the blood by pump, separating the blood into components by centrifugation and then reinfusing cellular components, discarding, or treating the plasma. In continuous separation, these processes are performed successively. Centrifugal machines have been made by three manufacturers; IBM (USA) and Fenwell (USA) are making continuous centrifugal apparatus and Hemonetics (USA) is making intermittent centrifugal machines.

By centrifugal separation, plasma is separated at 15-25ml/min with the blood flow being 40-60ml/min. Disadvantages of this procedure are: a) plasma may not be separated completely from the cellular components of the blood and platelets can be removed in the plasma[40]; b) the apparatus is so big and heavy that the transportation is not very easy.

Separated plasma includes all kinds of soluble substances in the blood, which are albumin, globulin, immune complexes, electrolyte and so on. Pathological macromolecules which are distinct in some diseases are the subject of plasma treatment, but in diseases where

pathological macromolecules are not determined, plasma exchange has a potential modality for clinical therapy.

V. THERAPEUTIC PLASMAPHERESIS (Plasma Exchange)

Plasma exchange is a method by discarding separated plasma to remove pathologic macromolecules which are not excluded by conventional hemodialysis and hemofiltration. By using this technology, many diseases which are considered difficult to treat by conventional therapy have become possible to be treated effectively. These diseases include rheumatilogic, hematologic, neurologic, and other immuno-metabolic disorders (Table XI).

All of these diseases however, which have been treated by plasmapheresis, are not always the object of plasmapheresis. This is because this method has limitations, such as (a) the requirement of plasma products (albumin solution, fresh frozen plasma, plasma protein fraction), (b) loss of essential plasma solutes creating possible immunologic and nutritional deficiencies and (c) potential contamination by plasma substitutes[41].

In spite of these limitations, the use in numbers of plasmapheresis is increasing year by year[42]. With the increase in the number of plasmapheresis procedures, the quantity of plasma products which are purchased for this therapy has been increasing remarkably. This increase in the demand of plasma products is envoking a big ripple, to the blood business, which in turn, is falling into a chronic shortage of blood donations[43]. Recently, however a technology for the selective removal of pathogenic macromolecules has been developed and is under clinical investigation. None or little plasma

products are required by this technology, which would therefore reduce the tendency of an increase in the demand for plasma products.

Further, on-line plasma treatment by its selective separation of the pathological macromolecules eliminates the need for supplements that would normally be lost by plasma exchange. Such technologies prevent further nutritient depletion in such patients who may already have a compromised nutritional status.

In the case of acute hepatic liver failure, however, the pathogenic substances responsible have not been clearly determined yet, and the prognosis by conventional therapy is extremely poor. Plasmapheresis is thus a good modality of treatment at this moment. As a matter of fact, the recent positive prognosis for acute liver failure with the use of fresh frozen plasma has been increasing from 15% by conventional therapy to 35% by plasmapheresis therapy[44]. Thus, plasma exchange may have a high probability for effective therapeutic treatment of metabolic disorders, but this method must be considered for proper application and practice.

VI. PLASMA TREATMENT

Plasma treatment is the method intended to remove pathological molecules selectively. By this method, loss of essential plasma, the requirement of plasma products which are observed in plasmapheresis, can be reduced effectively. On-line plasmapheresis provides a suitable methodology for this plasma treatment. Plasma separated by a membrane separator is processed for cryofiltration, thermofiltration, cascade membrane filtration (Fig. 8) or sorbent treatment. Treated

plasma is then returned to the patient with its cellular components (Fig. 9)[45]. These current technologies are reviewed briefly.

A. Cascade Membrane Filtration

Once plasma is separated from the cellular components, it is easy to remove certain toxic substances, as well as to add to this system. If we know certain macromolecules should be removed, we can use cascade membrane technology[46] to selectively remove molecules of a few million daltons molecular weight (e.g., immune complexes), or below 100,000 daltons molecular weight (e.g., albumin fractions) (Fig. 10)[47]. For this purpose, several secondary filters have been developed by several industries (Table XII). Clinical application of this procedure is under investigation, however, autoimmune diseases such as systemic lupus erythematosus and thromboangitis obliterans, which are difficult to treat by conventional therapy, have shown remarkable improvements by this method. Also, it has been possible to treat arteriosclerotic obliterans which is common in old age and in which in its progressive stage, amputation of the leg is often its final treatment[48].

Thus, this technology is promissing as a therapeutic modality in clinical application, but further effort to develop filters which have a property corresponding to molecular abnormalities of various immuno-metabolic diseases must be performed continuously.

B. Cryofiltration

Cryofiltration is a form of plasma therapy that consists

of the on-line plasma cooling and filtration of plasma for the removal of macromolecular plasma solutes from patients with immune-mediated diseases (Fig. 9 middle).

Immune complexes are formed in the body of autoimmune diseases and are found in the circulation. They are pathologic molecules with molecular weights of greater than 100,000 daltons, but because of the physiochemical properties of the molecules and the membrane properties, it is difficult to use a simple membrane filtration system effectively to separate those macromolecules from albumin or small molecules. From the finding that white turbid cryoprotein is very often present in refrigerated plasma which was taken by plasmapheresis from the autoimmune disease state, an attempt was made to utilize the phenomenon of cold separation to accelerate the effective separation of albumin and cryoproteins. Cryofiltration was developed by Malchesky and Nose' in 1980[47,49]. This process involves rapid cooling of the plasma in an on-line system to form cryogel, which is then filtrated under cold conditions. The cryogel is retained on the filter and lower molecular weight solutes are returned to the patients. This cryogel contains a number of substances found in plasma, such as immune complexes, Rheumatoid factor, immunoglobulins and fibrinogen (Table XIII)[50,51]. This system has been used to treat several immune mediated diseases including rheumatoid arthritis, rheumatoid vasculitis, systemic lupus erythematosus, cryoglobulinemia and cold-agglutinin hemolytic anemia. The patients over 60 years old who did not respond to conventional therapies showed 80% good or excellent

responses[52]. Remarkable decreases in immune complexes and immunoglobulins by cryofiltration are noted in rheumatoid arthritis patients, with clinical improvements such as Ritchie index, grip strength, 50 feet walking time and duration of morning stiffness[50,53].

Cryogel, which is removed with cryofiltration, is formed continuously from heparinized plasma in relatively short time (10-20 minutes) at near freezing temperatures[54,55]. Cryoprecipitate is similar to cryogel but several distinctions can be made between them, because cryoprecipitate is formed from serum during three to five days at 4°C environmental temperature. From the observation that cryogel contains many immune related substances and that reduction of cryogel accompanies the clinical improvements, cryofiltration possesses great possibilites in the treatment of a variety of autoimmune mediated diseases[45].

C. Thermofiltration

In cryofiltration, the regulation of the plasma temperature has a certain effect on the selection of macromolecules which aggregate in the cold. An in vitro attempt to study selective removal of several solutes in plasma at varying temperatures up to 37°C, was made in 1983[55]. By using Kuraray EVAL-4A filter (Kuraray Industrial Co. Japan), successful in vitro separation of high density lipoproteins (HDL) from low density lipoproteins (LDL) was noted at a physiological temperature[56,57]. LDL cholesterol levels have been shown to have a high correlation with the risk of coronary heart disease, while HDL cholesterol shows a strong inverse correlation[60]. The idea

of thermofiltration, which is the plasma treatment procedure with plasma filtration at near or above normal physiologic temperature, was contrived and named by Nose' in 1984[59]. The first clinical application of this method was made in 1985 for a 39 year old patient that had sclerosing cholangitis, with a high concentration of cholesterol (210-450mg/dl) and a very high LDL/HDL cholesterol ratio (8.61)[60]. The patient tolerated this procedure well. Results showed that the LDL/HDL cholesterol ratio decreased to 6.96, with the reduction of the LDL-VLDL cholesterol level by 33.3%. In the performance of thermofiltration, plasma substitute is not required. From these observations, by using this technology it has become possible to reduce abnormal plasma LDL cholesterol levels. In addition, this methodology has great possibilities, not only in treating the end stage of artheriosclerosis, but also in preventing the disease in the elderly. This technology can also be applied to other diseases which contain within the patient's plasma, some cellular toxic or inhibitory factors which can be destroyed by heat exposure, as in cancer or hepatic failure patients[61].

D. Sorbent Treatment

Since 1963, metabolic assist systems for the support of hepatic failure patients have been developed in conjunction with membrane plasma separation. Noble initial trials, however, did not result in good responses, because of the immature technology of plasma separation at that time[62]. Meanwhile, numerous techniques have been used for solute removal for hepatic support, including hemodialysis[63], hemofiltration[64,65], direct

hemoperfusion of activated charcoal[66] and plasmapheresis[67]. Both hemodialysis and hemofiltration, however, have had limits in their applications for hepatic assist, because of the nature and size of metabolic substances occurring in hepatic failure. Direct hemoperfusion with activated charcoal and various resins also have had limits, because of their biocompatibilities. Plasma treatment with metabolic and/or detoxification systems is the only method to solve the problems mentioned above.

The methods of on-line plasma treatment with fresh sliced liver tissues and with multi-sorbents, was devised by Nose' and his colleagues in 1974[68], and 1978[69]. Further, an attempt with cultured hepatocytes which would realize both of the metabolic and detoxificative functions of liver, is under experimental investigation. Multi-sorbent systems contain anion exchange resin and activated charcoal for the removal of middle and macromolecules. Average reduction of bilirubin which increases in hepatic failure, is approximately 31% per treatment. Initial trials for acute liver failure did not show remarkable responses[70], but cholestatic patients with symptoms of pururitis, xanthomatous skin lesions and jaundice, showed dramatic improvement and surprisingly, a long alleviation of these symptoms[71]. These experiences indicate that membrane plasmapheresis with on-line detoxification can be used effectively on a chronic basis for hepatic support.

Because of nonspecific sorption characteristics of the sorbents, their use was limited clinically. Recent works, however, for developing immunosorbents, which are specific for the removal of the immunoproteins that subsequently increase in

autoimmune disorders, are of expected value for the selective removal of macromolecules (Table XIV)[72]. In these systems, biological materials are immobilized in solid adsorbents, which are then utilized in the form of plasma treatment or direct hemoperfusion. While this technology is a promising one for immuno-assest, it is necessary to hurry determining the entity of the diseases with unknown immuno-metabolic disorders.

Currently, this technology is under investigation not only for autoimmune diseases, but also for cancer[73].

VII. CONCLUSION

Current progress in nutritional support technologies has made possible the treatment of chronic malnutritional patients at home.

Also, current progress in immunological-metabolic assist technologies especially plasma separation and plasma treatment technologies, has opened the way for the treatment of immuno-metabolic diseases which are considered to be difficult to treat by conventional therapies. By using current available technologies, it has become possible not only in treating the disease state, but also in preventing the immuno-metabolic disorders which are common in the elderly. Further development and innovation of nutritional technologies will promise the satisfactory improvement of the malnutritional state of the elderly. By supporting adequate nourishment which is adjusted to each individual patient and correcting these disorders using progressed methodologies, the improvement of the nutritional state in the elderly can be achieved. In order to sustain

or provide a better quality life for the elderly, current artificial organs technologies can play an important role.

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LEGEND OF TABLES

TABLE I

Normal fibrinogen values in humans

Age (yr)	Value (mg/dl)
10–19	185–300
20–29	185–340
30–39	177–365
40–44	215–400
50–59	235–455
Over 60	260–500

TASK V: ADVANCES IN ANTIBIOTICS

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TASK V: ADVANCES IN ANTIBIOTICS

TABLE OF CONTENTS

I. OVERVIEW

In order to cope with the various types of infections, many types of antibiotics are clinically available. On the other hand, new drugs which deal with infections typical to senior citizens have been enthusiastically investigated. These include beta-lactam antibiotics, liposomal Amphotericin B and quinolones. High molecular compound drugs, with improved efficiency continuity and stability with less toxicity, and interferon have great potential application for the infection problems in the aging population.

In addition, direct continuous intravenous delivery of anti-infectious agents in a safe and accurate manner, is one of the most important key technologies in order to produce the maximum effects of these drugs. Simple, accurate drug delivery infusion pumps are available in at least 30 different designs. They are currently very widely used, not only in the hospital but also in the home environment. Utilization of drug delivery infusion pumps at home has contributed to the cost containment program of the patient who suffers from recurrent, persistent infections. Recent developments in new drug delivery systems have advanced quite remarkably. Liposome microcapsule, polymeric drug delivery systems, osmotic pumps and implantable infusion pumps are becoming more and more realistic.

In the elderly population, the resistance against infection and the susceptibility to various types of infections are the major medical concerns. This is due to the altered host defense mechanisms in the elderly. Even though some understanding of this phenomenon are available, more clarification is still mandatory in order to cope with this most difficult medical problem. This infection prone situation might be referred to as one of an age-induced immunodeficiency syndrome. Through several personal

communications, we recently learned that a Russian scientist, Dr. Nikolaiev in Kiev, demonstrated possible life extension of aged mice by feeding them activated carbon. He also suggested that similar effects are expected by the use of direct hemoperfusion of activated carbon in aged experimental animals. Although scientific documentation is not available, this experience suggests the involvement of humoral factors in the aging process.

Some form of treatment of infection in the elderly should be considered for these age induced humoral and cellular abnormalities. Simple antibiotic treatment is not expected to be as effective as the same treatment regimen for the younger generation. Efforts to normalize these age induced immunological abnormalities should be combined with antibiotic therapies. Therefore, in order to cope with infectious diseases in the elderly, not only development of new antibiotics and new drug delivery systems, but also development of immunomodulation technologies should be enthusiastically pushed on.

II. PRESENT STATUS AND FUTURE POSSIBILITIES

1. Altered Host Defense Mechanisms in the Elderly

The decreased resistance to infection in the elderly is a problem of long-standing interest. Recently, with aging of their populations, a renaissance of concern with this problem has occurred in industrialized societies.

Resistance to infection in the aged is altered. A number of factors complicate the understanding of the cause of this alteration. However, the available information supports the hypothesis that T-cell

function is altered in the aged. Peripheral blood lymphocytes from elderly volunteers in 3-day culture synthesize DNA less actively upon exposure to nonspecific mitogens or allogenic lymphocytes than do lymphocytes harvested from younger controls[1,2]. The duration of the cell cycle is prolonged, perhaps accounting for the increased time required to reach peak response[3]. Potentially, some type of thymic factor therapy could correct these abnormalities.

Chemotactic responses are normal in the majority of aged individuals studied[4]. In contrast, when hospitalized patients were studied, the prevalence of polymorphonuclear leukocyte dysfunction was increased in all age groups[5]. Recently, Charpentier and colleagues noted an alteration in oxidative metabolism of polymorphonuclear leukocytes and depressed phagocytosis, as evaluated by microscopy, in aged patients[6]. There are some humoral factors that can enhance or in certain disease states inhibit the polymorphonuclear leukocyte ability to respond to infection. Such humoral factors include specific antibodies, and antiglobulins which in vitro can inhibit phagocytosis, complement, and various inhibitors of chemotaxis described in individuals with neoplastic and hepatic disease[7,8]. These studies indicate that the function of polymorphonuclear leukocytes or lymphocytes in elderly people under no stress may differ considerably from that observed when they have developed a moderate or severe illness[9].

2. <u>Development of New Drugs</u>

(a) The Newer Antibiotics

Various kinds of cephalosporins have been released since

the discovery of a fungus, Cephalosporium acremonium[10] (Fig. 1).

The term "generations" is used as a tool to describe the gram-negative enteric bacillary activity of the cephalosporins. Although, currently available third-generation cephalosporins, which include cefotaxim (Haechst-Roussel), ceftizoxime (Smith, Kline & French), cefoperazone (Pfizer), ceftriaxone (Roche), and cefsulodin (Abbott) are marketed as antipseudomonal drugs, they fail to provide adequate activity against many Pseudomonas aeruginosa, one of enteric gram-negative bacilli. At present, three investigational beta-lactam antibiotics are much more potent for P. aeruginosa: ceftazidime (Glaxo), aztreonamm (Squibb) and imipenem (Merck)[11].

Much attention has been given to the synthesis of quinolones and to the evaluation of these newly prepared agents for antibacterial activity. The fluoroquinolones are very potent synthetic agents active against the enteric gram-negative bacilli and cocci, including P. aeruginosa[12].

Pneumonia and influenza together constitute the leading infectious cause of death in the elderly and the fourth most common cause of death overall in the elderly (Table I). Newer drugs described above are promised to be useful in treatment of these infectious diseases in the elderly.

Although the classical method of developing new drugs including the discovery of new agents and the modification of their structures needs tremendous efforts, a large number of

newer antibiotics will be continuously introduced for clinical use in the United States.

(b) Designs for Development of High Molecular Compound Drugs

In generally speaking, high molecular compound drugs are so-called polymeric forms of drugs. Low molecular units of these polymers are effective as known drugs. Polymeric forms are designed for improvement of efficiency continuity, for better stability, for less toxicity, for slow release of active units, and so on.

Ringsdorf reported the basic structural design of high molecular compounds as drug-carriers[13]. On its main polymer chain, the basic structure should contain three functional units:

1) Soluble Unit

This unit is a non-toxic co-polymerized block which is soluble in water and lipid.

2) Drug Unit

The specified bonding for fixation and release of the lower molecular drug should exist in this unit.

3) Transfer Unit

The function of this unit is specified attachment of the drug onto the target site. Available characteristics for the function are interactions of receptors, pH dependency, molecular weights and structures, and so on.

So far, studies on synthetic high molecular compounds for utilization as drug carriers have not succeeded. Recently, native polymers have attracted the attention of researchers[14]. Since native polymers are generally superior in biocompatibility

and non-toxicity, some of those compounds, e.g. soluble starch, might be available for carriers in high molecular compound drugs.

Not only Ringsdorf's concept, Goldberg also reported the concept of polymeric affinity drug design[15].

Investigations in this field should be enthusiastically pushed on for development of new drugs to specifically treat diseases of the elderly patient.

3. Development of New Drug Delivery Systems

(a) The Liposome as a Microcapsule

The liposome is a neutral or acidic lipid vessicle which can hold drugs within its membrane of two lipid molecule layers. The membrane acts as a barrier against water soluble substances such as ions and high molecular non-ions. Expected functions of liposome-capsule drugs are as follows:

1) slow release of drugs

-----long acting efficiency

-----inhibition of toxicity and anaphylaxis which may be encountered when drugs are given in large doses.

2) improvement in capability to approach target sites

3) bacteriocidal effect on intracellular and intra-lysosomal bacteria

Trials to achieve above mentioned results have already succeeded to a certain extent. Some agents were improved in those permeability through the blood-brain barrier with liposome microcapsules[16]. One of the valuable preparations is liposomal Amphotericine B which reduces the toxicity and enhances the efficacy of its free form against fungal infections[17] (Fig 2).

Since the effectiveness of free form Amphotericine B (Squibb) which has been the drug of choice for most serious systemic fungal infections is limited due to the severity of its acute and chronic toxicity, liposomal Amphotericine B is highly beneficial in the treatment of fungal infections in the elderly. Although undesired side effects of liposome microcapsules have been noted in humans[18], no evidence of chronic toxicity was observed in long term patients treated with liposomal Amphotericine B[17]. Successful results have also been reported regarding 3[19,20]. Not only utilization of antigen-antibody reactions, receptor specific reactions and physicochemical phenomena such as temperature effect have been investigated[20]; however, more enthusiastic effort is required to obtain target cell specific characteristics of liposomes.

(b) Polymeric Drug Delivery Systems

Biodegradable drug delivery systems have been developed using native high molecular compounds such as geratins. These systems implanted under the skin offer potential advantages in both release rate controlability and biodegradability. They achieve relatively constant release rates for about three days. Other polymer matrix drug delivery systems have been developed which permitted sustained release of high molecular drugs. Ethylene-vinyl acetate copolymers are common materials for matrix substrates. A variety of shapes of systems to achieve constant release rates were analyzed from a theoretical standpoint[21]; the best results were with a hemispheric device laminated with an impermeable coating, except for a small concavity in the center

face (Fig. 3). This can be envisioned as a small cantaloupe cut in half, where the orange pulp of the melon is the drug. The melon half is then coated everywhere except where the seeds were, so all the drug must be released through the small exposed section. Systems with these geometries do achieve constant release rate for macromolecular agents for over 60 days[22]. Not only as antibiotics delivery systems for chronic infections, these systems are also expected to be used as interferon delivery systems.

(C) Osmotic Pumps

Recently, membrane-controlled osmosis has been used as a basis to achieve rate-controlled drug release. Two types of osmotic pump systems have been reported: an oral dosage form[23], and an implantable form[24]. Each system contains a core of solid or liquid drug, coated with a semipermeable membrane having a single small orifice. The membrane selectivity admits water from the outside, which enters because of the osmotic activity of "osmotic core". The membrane structure does not allow expansion of the system volume; thus, fluid containing the drug must leave the interior of the system at the same rate that water enters by osmosis. An oral dosage form (Oros (TM)) probably working effectively as a one a day dosage form of antibiotics (Fig. 4). The implantable osmotic pump system (e.g. Alzet (TM)) achieved constant release rate (1 microliter/hr) of agents for over 1 week[24], and expected to be useful for antibiotics delivery system because of its high rate controlability.

(d) Implantable Infusion Pumps

One of the implantable infusion pumps which has been developed and tested is named Infusaid (Infusaid Corp., Sharon, MA). It is a disc-shaped cannister of light weight, biocompatible titanium, which contains a collapsible welded bellows. The bellows separates the cannister interior into two chambers, one of which contains a vapor-liquid mixture of a fluorocarbon propellant, the other containing the infusate. At body temperature, the vapor pressure exerted by the chemical power source forces fluid from the infusate chamber, and provides a constant rate of fluid ejection at a given temperature (Fig. 5). A large pump of this type has several advantages over the polymeric delivery systems, including:

1. the ability to deliver large volumes of fluid
2. versatility of drug administration
3. the nonthrombogenic delivery cannula allows a drug to be delivered into specific blood vessels or body cavities
4. the pump can be recharged without the need for reimplantation procedures

The pump is now undergoing clinical trials for infusion of anticoagulants[25], anticancer agents[26], insulin[27] and so on. Implantable infusion pumps have a possibility to be useful for the the treatment of chronic infections.

4. Immunomodulation

Since the occurrence of infectious diseases in the elderly

is based upon the age-induced immunodeficiency state, it is significantly beneficial to correct and to control the altered difference system. This process is called "Immunomodulation". At present, the development of immunomodulation technologies is one of highly innovative fields in medical sciences.

(a) Immunoactive Cell Infusion

Fresh leukocytes infusion is a useful and relatively common method for the treatment of uncontrollable infectious diseases accompanied by agranulocytosis. A large amount of fresh leukocytes can be harvested from a donor with plasmapheresis technologies. Not only leukocytes infusion, lymphocytes infusion may be useful in immunosuppressive elderly patients. Herzenberg has reported the method to sort T-cells and B-cells from donor blood[28]. Other sophisticated sorting technologies have been reported also[29,30].

(b) Immunoactivation

1. Polymer-Blood Interaction

As far as blood compatibility is concerned, the smaller the interaction between a polymer and blood is, the better the polymer is for blood contacting material. The effort to develop better biomaterials have been directed to diminish the material blood interaction.

On the other hand, Cellulose membrane-blood component interactions, transient leukopenia and complement system activation have been noted since 1960[31]. Recently, the immunomodulating effect of biomaterials through polymer-blood interactions have been enthusiastically

investigated. These include increments of phagocytosis by polymer membranes[32], lymphocyte activation by immobilized hemaglutinin[33], complements activation by Sepharose-serum protein A[34], and Sepharose alone[35]. This immunoactivating effect has been used already for the treatment of cancer[36].

It is highly suggestive that a large number of polymeric membrane can modulate immune systems in different manners. Although various kinds of interactions between polymeric membranes and immune systems require further studies, this method might be possible to apply for treatment of infections in the elderly immunosuppressed.

2. Interferon Inducer

Interferon was discovered as an antiviral protein by Isaacs and Lindenmann in 1957[37]. In addition to its antiviral effect, interferon has been found to suppress tumor growth and modulate the immune response. Its chemical structure has not been precisely identified yet, however, interferon may become a major part of therapy for viral diseases including chronic active hepatitis due to hepatitis B virus, herpes virus-induced infections, cytomegalovirus infections, and acquired immunodeficiency syndrome(AIDS). It also holds promise for the treatment of certain cancers[38].

The clinical use of interferon is presently limited, to a certain degree, by its many side effects including fever, fatigue, proteinuria, increased transaminases, and so on.

Since all side effects appear to be reversible and most are dose dependent, interferon therapy may have particular value for patients who are immunosuppressed.

Not only production of interferon by DNA recombinant methods (genetic engineering)[39], induction of interferon by high molecular compounds has attracted a large number of investigator's attention. Interferons are now classified into three types: alpha, beta and gamma interferons. Beta interferon can be stimulated in tissue culture with synthetic polyribonucleotides. The polyinosinicpolycytidilic acid has been known as the most active inducer of the beta interferon[40]. The maleic acid co-polymer, the polyacrylic acid, the divinylether-maleic acid co-polymer and other poly-saccharides have been extensively investigated as beta interferon inducers[41]. Interactions between cells and polymeric agents which have the activity to induce the beta interferon requires further study but shows promise for the treatment of viral diseases and some cancers.

3. Other Immunomodulating Agents

With the discovery of new and pharmacollogically better described agent, the pursuit of a method for the enchancement of nonspecific host defense against bacterial infection has received a new infusion of interest[42-47]. Muramyl dipeptide is a nonspecific immunostimulant defined as the smallest fragment of the myocobacterial cell wall capable of adjuvant activity[43]. Some investigators

have reported that the agent is effective against many different bacterial challenges[44-46]. So far, Muramyl dipeptide has not seemed to have a beneficial effect when given after the time of injury but before the time of bacterial challenge. However, because of the apparent safety and efficacy inferent in the use of the agent, clinical trials seem warranted.

Liposomes are known as potential immunomodulators which induce antibodies, activate immune systems, and macrophages, and so on[47,48]. Although further investigation is necessary, it can be useful for infectious diseases in elderly patients whose defense systems are suppressed.

(c) Immunoadsorption

In order to remove abnormal immunocomplex from patients of various kinds of immune diseases, plasmapheresis technique has been extensively used[49] (Fig. 6). Recently, using this technique, immunoadsorbent therapies for infectious diseases have been investigated.

These include endotoxin adsorption by immobilized Polymixin B[50], phagocytable substance removal using the charcoal filter in sepsis[51], and hepatitis B antigen adsorption using immobilized antibody filter[52]. The charcoal filter application to septic patients have already succeeded to a certain extent[51]. The immunoadsorption described above can be useful as a supportive method for the treatment of infectious diseases.

The normalization of the humoral factor abnormalities

induced by the aging process can be achieved by new immunomodulation technologies. It is highly anticipated that normalization of age induced immunological abnormality will enhance the effects of anti-infectious treatments available for the elderly.

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LEGEND OF TABLES

Table 1 Death rates by sex, age, and selected causes: 1980

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DEATH RATES BY SEX, AGE, AND SELECTED CAUSES: 1980

[Deaths per 100,000 resident population enumerated as of April 1. Causes of death classified according to ninth revision of the *International Classification of Diseases*]

CAUSE OF DEATH	Total [1]	MALE					FEMALE				
		Total [1]	15–24 years	25–44 years	45–64 years	65 yrs. and over	Total [1]	15–24 years	25–44 years	45–64 years	65 yrs and over
All causes [2]	878.3	976.9	172.3	238.0	1,270.0	6,367.9	785.3	97.5	116.2	670.9	4,484.1
Diseases of heart	336.0	388.6	3.7	34.6	505.3	2,778.6	305.1	2.1	11.9	177.3	2,027.5
Malignant neoplasms	183.9	206.3	7.8	25.8	348.0	1,371.6	163.6	4.8	30.1	265.8	787.8
Cerebrovascular diseases	75.1	63.6	1.1	5.1	50.0	557.0	86.1	.8	5.0	39.9	564.0
Accidents and adverse effects	46.7	67.4	96.7	66.6	61.3	124.4	27.1	26.0	17.3	21.6	76.4
Chronic obstructive pulmonary diseases [3]	24.7	36.1	.4	1.0	36.0	297.9	15.0	.3	.9	17.6	84.3
Pneumonia and influenza	24.1	25.1	.8	2.9	17.8	212.5	23.2	.8	1.8	8.7	154.5
Diabetes mellitus	15.5	13.0	.3	2.7	16.2	92.8	17.6	.3	2.0	17.7	103.7
Chronic liver disease and cirrhosis	13.5	16.0	.3	10.3	50.5	56.0	9.3	.3	5.0	23.2	24.8
Atherosclerosis	13.0	10.5	–	.1	4.0	104.0	15.3	–	.1	2.0	113.9
Suicide	11.9	16.6	20.2	24.0	23.7	26.0	6.5	4.3	7.7	8.9	6.1
Certain conditions originating in the perinatal period	10.1	11.9	(X)	(X)	(X)	(X)	8.4	(X)	(X)	(X)	(X)
Homicide and legal intervention	10.7	17.3	24.5	29.4	16.4	8.9	4.5	6.6	6.4	3.4	3.3
Nephritis, nephrotic syndrome and nephrosis	7.4	7.8	.2	1.2	7.1	33.6	7.0	(Z)	.7	5.5	42.1

– Represents zero. X Not applicable. Z Less than .05.
[1] Includes persons under 15 years old, not shown separately.
[2] Includes other causes, not shown separately.
[3] Includes allied conditions.

Source: U.S. National Center for Health Statistics, *Vital Statistics of the United States*, annual, and unpublished data.

Hab.[1]

(From Baldrige H et al eds: Statistical abstract of the United States 1984. U.S.Department of Commerce. Washington D.C., 1985)

LEGEND OF FIGURES

Figure 1 Cephalosporins marketed in the U.S.

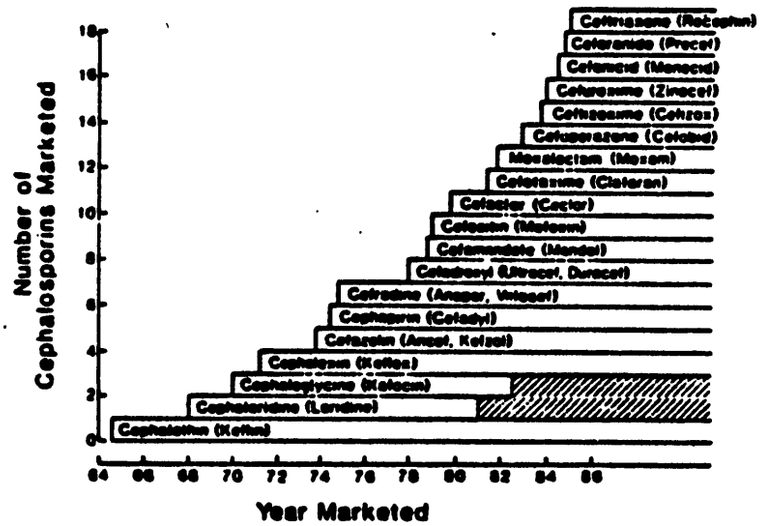
Figure 2 Effect and toxicity of free versus liposome-encapsulated amphotericin B

Fibure 3 Schematic diagram of zero-order release system for macromolecules

Figure 4 Schematic diagram of Oros™ system

Figure 5 Top view of Infusaid™ implantable infusion pump

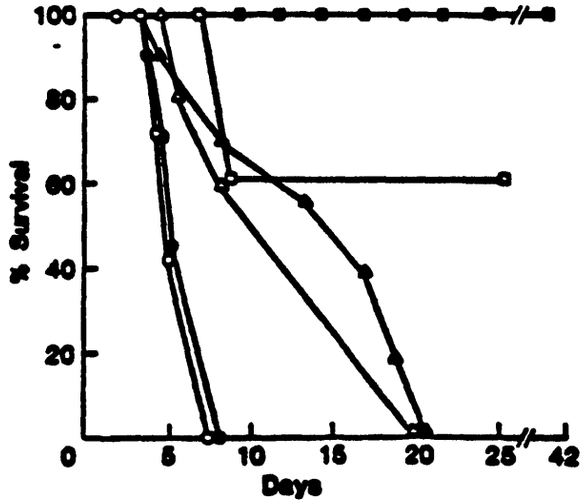
Figure 6 General scheme of plasmapheresis



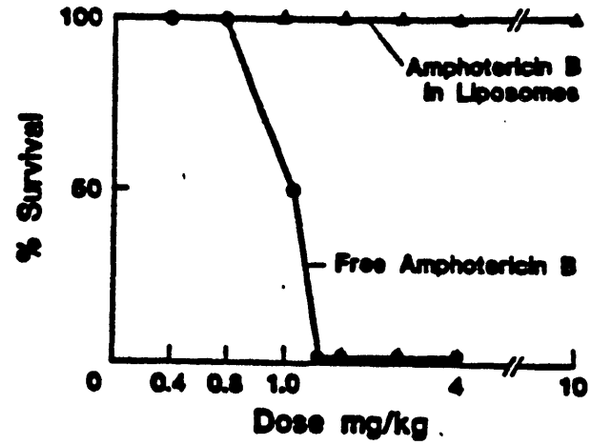
Cephalosporins marketed in the U.S.

Fig.1

(from Price CC et al: Cephalosporins. Disease-a-Month 31:1,1985)



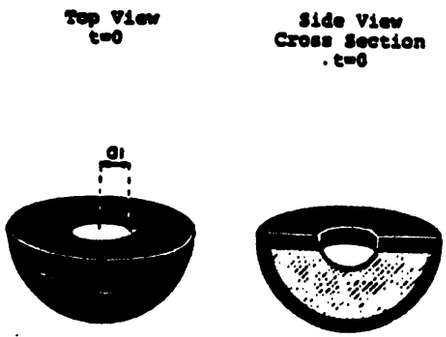
Effect of liposome-encapsulated amphotericin B on survival of mice infected with *Candida albicans*. Two days after iv administration of *C. albicans* the animals were either (●) not treated (controls) or treated with (○) empty liposomes (400 mg of total lipid/kg); (▲) free amphotericin B (0.8 mg/kg); or liposome-encapsulated amphotericin B in doses of (△) 0.8 mg, (□) 2 mg, or (■) 4 mg of amphotericin B in 400 mg of total lipid/kg.



Toxicity of free versus liposome-encapsulated amphotericin B in mice. The total lipid dose was 400 mg/kg.

Fig.2

(From Lopez-Berestein G et al: Treatment and prophylaxis of disseminated infection due to candida albicans in mice with liposome-encapsulated Amphotericin B. J.Infec.Disease 147:939,1983)



Schematic diagram of zero-order release system for macromolecules.

Fig.3

(from Langer R et al: Implantable drug delivery systems. Trans.Am.Soc.Artif.Organs 27:640,1981)

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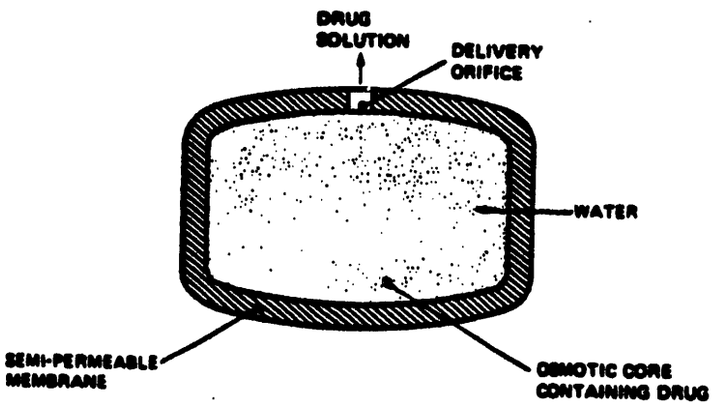
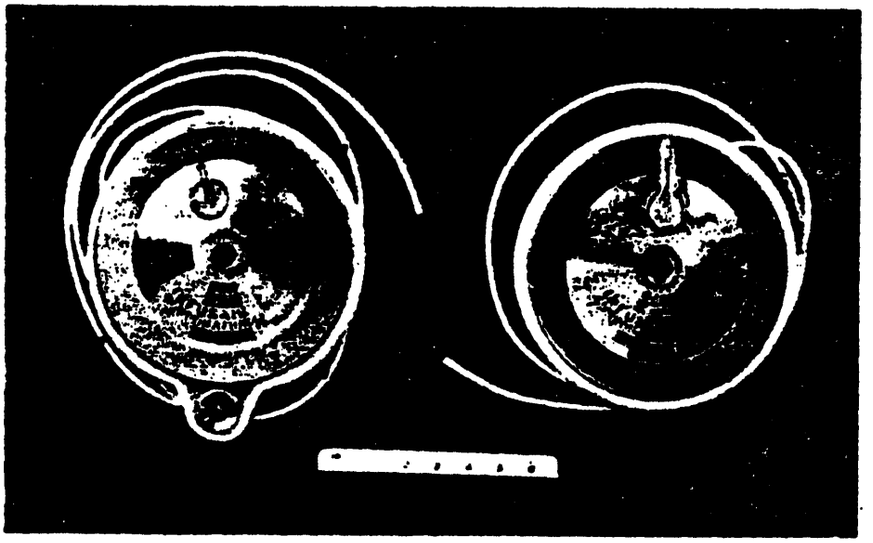


Schematic diagram of Oros® system.

Fig.4

(from Langer R et al: Implantable drug delivery systems. Trans.Am.Soc.Artif.Organs 27:648,1981)



Top view of Infusaid® implantable infusion pump.

Fig.5

(from Langer R et al: Implantable drug delivery systems. Trans.Am.Soc.Artif.Organs 27:640,1981)

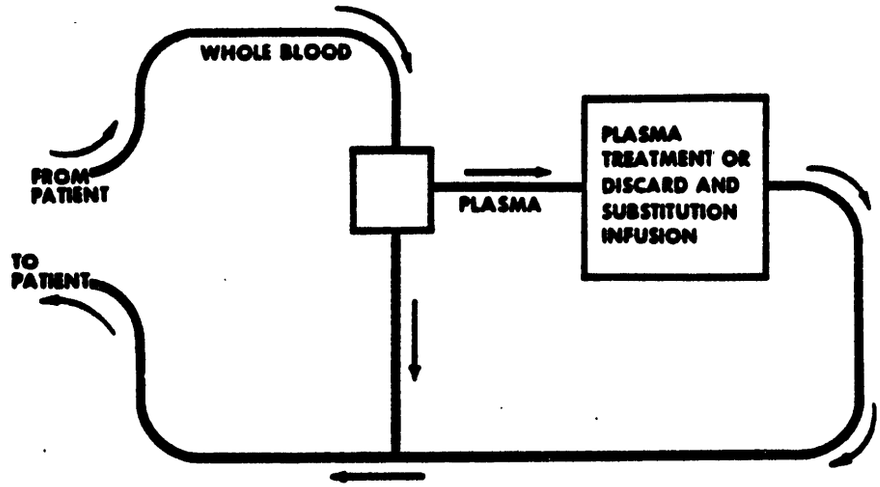


Fig.6

General scheme of plasmapheresis. Separation of the plasma from whole blood may be by centrifuge or membrane techniques. Plasma treatment may be by membrane filtration, sorption or other physicochemical techniques such as precipitation.

TABLE II

Implantable Vascular Access Devices*(14)

Company	Trade Name	Catalog No	Use	Internal Lumen of Catheter	Guaranteed Life of Septum	Approximate Price
Pharmacia	Port-A-Cath	550-400	Venous Kits	1.02 mm	(2,000 punctures = 22 ga 1,200 punctures = 19 ga)	$295 - $350
Pharmacia	Port-A-Cath	550-350	Arterial Kits	.51 mm		$295 - $350
Pharmacia	Port-A-Cath	550-300	Arterial	.51 mm		$250
Infusaid	Infuse-A-Port	35643	Venous	1.02 mm	(2,000 punctures w/22 ga Special Infusaid Needle)	$250
Infusaid	Infuse-A-Port	35272	Venous or Arterial	.8 mm		$295
Cormed	Medcom	80200	Venous or Arterial	1.00 mm	(1,500–2,000 punctures w/22 ga)	$295
Cormed	Medcom	80100	Venous or Arterial	.5 mm		$295
Cormed	Medcom	80300	Venous	1.5 mm		$295

*Partial listing of Products Available per manufacturer's recommendations

TABLE III

Adult Total Parenteral Nutrition Solution [31]

Base solution		
40–50% dextrose in water		500 ml
8.5%–10% crystalline amino acids		500 ml
Additives to each unit		
Sodium chloride, acetate, or lactate		40–50 mEq
Potassium chloride		20–30 mEq
Potassium acid phosphate (10–20 mM phosphorus)		15–30 mEq
Magnesium sulfate		15–18 mEq
Additives to any one unit daily		
Calcium gluconate 10%		4.5 mEq
Zinc sulfate		5–10 mg
Copper sulfate		1–2 mg
Iron–dextran		0.1 ml
Chromium chloride		10–20 mcg
Manganese chloride		0.5 mg
Selenium (sodium selenate)		60 mcg
Multivitamin infusion		10 ml
A	3300 IU	
D	200 IU	
E	10 IU	
Ascorbic acid	100 mg	
Folic acid	400 ucg	
Niacin	40 mg	
Riboflavin	3.6 mg	
Thiamine	3 mg	
B_6 (pyridoxine)	4 mg	
B_{12} (cyanocobalamin)	5 ucg	
Pantothenic acid	15 mg	
Biotin	60 ucg	
Additive to any one unit twice weekly		
Vitamin K		10 mg
Intravenous fat emulsion 10% or 20%		
500 ml 2–7 times weekly		50–100 gm
Carbohydrate calories		850 kcal/liter
Protein calories		150 kcal/liter
Fat calories		1000–2000 kcal/liter
Nitrogen		6.5–8 gm/liter
Amino acids		40–50 gm/liter

TABLE IV

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Pediatric Total Parenteral Nutrition Solution [31]

Base solution		
40% dextrose in water		500 ml
8.5% crystalline amino acids		500 ml
Additives		
Sodium chloride		25–30 mEq
Potassium acid phosphate		30–40 mEq
Magnesium sulfate		12–15 mEq
Calcium gluconate		25–35 mEq
Zinc sulfate		2 mg
Copper sulfate		0.5 mg
Iron-dextran		0.05 ml
Chromium chloride		10 mcg
Manganese chloride		0.25 mg
Selenium (sodium selenate)		30 mcg
Multivitamin infusion		10 ml
A	0.7 mg	
D	10 mcg	
E	7 mg	
K	200 mcg	
Ascorbic acid	80 mg	
Folic acid	140 mcg	
Niacinamide	17 mg	
Riboflavin	1.4 mg	
Thiamine	1.2 mg	
B_6 (pyridoxine)	1 mg	
B_{12} (cyanocobalamin)	1 mcg	
Dexpanthenol	7 mg	
Biotin	20 mcg	
Intravenous fat emulsion 10% 50–75 ml/kg 3–7 times weekly		
Infusion rate = 115 ml/kg/day		
115 kcal/kg/day		
3 gm protein/kg/day		

TABLE V

MODELS OF INFUSION PUMPS

Manufacturer	General Purpose	Microinfusion Purpose
ABBOTT	Life Care 3	
AMERICAN McGAW	Accu Pre	
AVI	Guardian 100	Guardian 100
CRITIKON	Simplicity 2100 A	
IMED	960	965
IVAC	560 1300	
TRAVENOL	Flo-Gard 8000 Flo-Gard 6100	
VALLEY LAB	Infutrol 6000b	Infutrol 6006b

TABLE VI

CONTINUOUS INSULIN DELIVERY SYSTEMS [24]

PUMP MODEL	MICROJET MC1-MC20	MILLI-KILL 1001	AUTOSYRINGE	SYRINGEDRIVER SD35	CPI 5100	PROMEDOS II
DISTINCTIVE FEATURE	Syringe	Syringe	Syringe	Syringe	Syringe	Peristaltic Pump
SIZE	17x7x3	14.4x6.8x3.3	10x6.3x2.5	10.7x5.3x3.3	14x6.3x3.4	11.4x6.6x2.7
WEIGHT (gr)	100	310	200	100	205	100
RESERVOIR CAPACITY	1-2 days	1-2 days	1-2 days	1-2 days	1-2 days	120 days
BATTERY LIFE	30 days	2 weeks	24 hours (accumulator)	30 days	1-2 days (accumulator)	2 months
ALARM	yes	no	yes	no	yes	yes
REASONS FOR ALARM SIGNAL	Empty reservoir		Empty reservoir		Empty reservoir	
	Battery failure		Battery failure		Battery failure	
	Pump runaway		Pump runaway		Pump runaway	Pump runaway

TABLE VII

feeding tubes for *Enteral Nutrition* [33]

	Material	Length	Gauge	Luer
Clinifeeding System 1 (Russel)	PVC	80 cm	1 mm internal bore	Male
Clinifeeding System 1/85 (Russel)	PVC	85 cm	1 mm internal bore	Male
Vygon Code 327	PVC	125 cm	6FG*	Male
Vygon Code 2327	Silicone	125 cm	6FG	Male
Duo-Tube (Argyle)	Silicone	102 cm	5/6/8FG	Male
Entrifax nasogastric tube (Searl)	Polyurethane Hydrosmer coated	93 cm	8FG	Female
Entrox nasogastric tube (Searl)	Polyurethane Hydrosmer coated	81 cm	6FG	Female
Nasoduodenal tube (Portex)	PVC	105 cm	6-36FG	Female

*FG (French gauge) = external circumference in mm.

TABLE VIII-1

COMMERCIAL BLENDERIZED DIETS, NUTRITIONAL SUPPORT SYSTEMS [32]
(COMPARISON/1000 CC STANDARD STRENGTH)

Product (Manufacturer)	Form	kcal	Osmolarity (mOs/kg)	CHO (g)	PRO (g)	FAT (g)	Na (mEq)	K (mEq)	Cl (mEq)	Fe (mg)	Ca (mg)	P (mg)
Compleat-B (Doyle)	L	1070	406	135 (49%)	42.7 (16%)	42.7 (35%)	38.1	38.8	34.5	12.0	667	1333
Compleat-Modified Formula (Doyle)	L	1070	Not available	141 (53%)	42.8 (16%)	37.8 (31%)	38.1	38.8	33.3	12.0	670	800
Formula 2 (Cutter)	L	1000	400-500	125 (49%)	37.5 (15%)	40.0 (36%)	38.0	40.0	38.0	12.5	720	800
Meritene Liquid (Doyle)	L	1000	800 (Vanilla)	115 (49%)	40.0 (16%)	38.3 (35%)	38.0	42.0	47.0	13.0	1200	1200
Meritene Powder (Doyle) (as prepared with whole milk)	P	1070	600 (Plain)	110 (49%)	40.2 (15%)	34.0 (36%)	41.6	75.0	61.0	17.3	2300	1923
Nutri 1000 (Cutter)	L	1000	800	101 (39%)	40.0 (15%)	58.0 (47%)	23.0	30.0	Not available	9.4	1200	Not available
Sustacal (Mead Johnson)	P	1010	625	120 (54%)	51.2 (20%)	34.0 (22%)	40.5	65.0	35.2	10.0	1030	1303
Vitaneed (Organon)	L	1000	375	125 (50%)	35.0 (14%)	40.0 (36%)	21.5	22.0	24.0	8.0	800	800

TABLE VIII-2

COMMERCIAL BLENDERIZED DIETS, NUTRITIONAL SUPPORT SYSTEMS (32)
(COMPARISON/1000 CC STANDARD STRENGTH) (Continued)

Product (Manufacturer)	Carbohydrate	Protein	Fat	Flavor	Generic Description
Compleat-B (Doyle)	Hydrolyzed cereal solids, green peas, pea and peach purees, maltodextrin, orange juice	Beef purée, nonfat dry milk	Beef purée, corn oil	Unflavored	Meat-based blenderized tube feeding
Compleat-Modified Formula (Doyle)	Hydrolyzed cereal solids, green beans, pea and peach purees, orange juice	Beef purée, calcium caseinate	Beef purée, corn oil	Unflavored	Milk-based blenderized tube feeding
Formula 2 (Cutter)	Nonfat dry milk, cream, carrots, orange juice, green beans, wheat flour	Wheat, beef, egg, milk	Egg yolk, corn oil, beef fat	Orange	Oral or tube blenderized feeding
Meritene Liquid (Doyle)	Sweet skim milk, corn syrup solids, sucrose	Sweet skim milk, sodium caseinate	Corn oil	Vanilla, chocolate, eggnog	Supplemental or total diet
Meritene Powder (Doyle) (as prepared with whole milk)	Whole milk, nonfat dry milk, corn syrup solids	Whole milk, nonfat dry milk	Whole milk	Plain, vanilla, chocolate, eggnog	Supplemental or total diet
Nutri 1000 (Cutter)	Sucrose, lactose, corn syrup solids	Skim milk	Corn oil	Vanilla, chocolate	Oral or tube feeding
Sustacal (Mead Johnson)	Whole and nonfat dry milk, sucrose, corn syrup solids	Whole milk, nonfat dry milk	Whole milk	Vanilla, chocolate	Oral or tube feeding
Vitaneed (Organon)	Maltodextrin	Beef, sodium and calcium caseinates, vegetables	Soy oil	Unflavored	Blenderized tube feeding, low sodium, lactose-free

TABLE IX

Available plasma filters, membrane and module

Filter	Type	Max. pore size (μm)	Material	ID (μm)	Wall thickness (μm)	Effective length (mm)	Effective surface area (m^2)
Membrane							
Asahi Hi-05	HF	0.2	Cellulose diacetate	330	75	157	0.5
Kuraray PVA SA	HF	0.4	Polyvinyl alcohol	330	125	275	0.6
Toray Plasmax PS-05	HF	0.4	PMMA	370	85	175	0.5
Mitsubishi MPS	HF	0.2	Polyethylene	270	60	175	0.65
Fresenius Plasmaflux	HF	0.55	Polypropylene	330	140	200	0.5
Takeda separator	HF	0.55	Polypropylene	330	140	155	0.2
Travenol CPS-10TM	HF	0.55	Polypropylene	320	150	214	0.17
Teijin TP-50	HF	0.2	Cellulose diacetate base	330	75	150 (?)	0.5
Cobe Centry TPE	Plate	0.6	Polyvinyl chloride derivative	NA	—	NA	0.13
Terumo pile type	Plate	0.45	Cellulose acetate	NA	170	NA	0.4

	Priming volume (ml)	Container: Material	Container: Dimensions L×φ (mm)	Sealant	Sterilization method	Wet or dry
Module						
Asahi Hi-05	65	Polycarbonate	255 × 43	Polyurethane	Ethylene oxide	Glycerin, dry
Kuraray PVA	70	Polycarbonate	380 × 67	Polyurethane	Steam autoclave	Water, wet
Toray Plasmax PS-05	59	Polypropylene Polystyrene	240 × 73	Polyurethane	γ-Ray	Water, wet
Mitsubishi MPS	60	Polycarbonate	225 × 53	Polyurethane	Formaldehyde	Formaldehyde, wet
Fresenius Plasmaflux	54	Macrolon	250 × 50	Polyurethane	Ethylene oxide	Surfactant, dry
Takeda separator	21	Polycarbonate	245 × 56	Polyurethane	Ethylene oxide	Surfactant, dry
Travenol CPS-10TM	22	—	—	—	—	—
Cobe Centry TPE	—	—	—	—	Ethylene oxide gas	Dry
Terumo pile type	80	Polycarbonate	25 × 150	Silicone rubber adhesive	Ethylene oxide gas	Dry

HF, hollow-fiber; NA, not available; PMMA, polymethylmethacrylate.

TABLE X

Automated blood cell separation systems

Type	Manufacturer	Models	Introduced	Components separated	Membrane type
Continuous-flow centrifuge	Fenwal	CS-3000	1979	Cells, plasma	None
	(Travenol)	Celltrifuge 11	1981	Cells, plasma	None
	IBM Biomedical	2997	1977	Cells, plasma	None
Intermittent-flow centrifuge	Haemonetics	30	1973	Cells, plasma	None
		V-50	1980	Cells, plasma	None
		PEX	1980	Cells, plasma	None
	Cobe Laboratories		1981	Plasma only	Sheet
Continuous-flow membrane	Parker-Hannifin	Cryomax	1979	Plasma only	Hollow fiber
	Fenwal (Travenol)		1981	Plasma only	Hollow fiber

TABLE XI

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Diseases treated with therapeutic apheresis—plasmapheresis (plasma exchange)

Medical discipline	Protein-related	Antibody-related	Immune complex-related
Hematology	Waldenstrom's macroglobulinemia	Idiopathic thrombocytopenic purpura Factor VIII auto-antibody Rh disease Autoimmune hemolytic anemia	Thrombotic thrombocytopenic purpura
Rheumatology	Raynaud's disease	Systemic lupus erythematosus	Rheumatoid arthritis Systemic lupus erythematosus Scleroderma Other
Neurology		Myasthenia gravis Multiple sclerosis Polymyositis Polyneuropathy	Guillain-Barré syndrome
Oncology	Multiple myeloma	Other cancers	
Nephrology		Progressive nephritis Glomerulonephritis Goodpasture's syndrome	Transplant rejection (?) Polyarteritis nodosa
Other	Toxins Poisons Hypercholesterolemia Thyrotoxicosis Primary biliary Cirrhosis Hypertriglyceridemia Hepatic insufficiency	Chronic active hepatitis Diabetes mellitus Pemphigus vulgaris Asthma	

TABLE XII

SECONDARY FILTERS

	Type	Max. Pore Size (um)	Material	ID (um)	Wall Thickness (um)	Eff. Length (mm)	Eff. Surface Area (m^2)
ASAHI							
Cascadeflo	HF	-	CDA	220	80	183	1.7
KURARAY (Evaflux)							
2A	HF	-	EVA	200	50	190 230	1.0, 2.0
3A	HF	-	EVA	200	50	190 230	1.0, 2.0
4A	HF	-	EVA	200	50	190 230	1.0, 2.0
TEIJIN							
TA-100	HF	-	CDA	250	30	250	0.8
TA-200	HF	-	CDA	250	30	250	0.8
TERUMO							
CF-01	Plate	-	CA	-	110	70	1.0
TORAY							
AS-08	HF	-	PMMA	370	85	105	0.8
ASC-08	HF	-	PMMA	370	85	105	0.8

HF: hollow-fiber, CDA: cellulose diacetae, EVA: ethylenevinyl alcohol copolymer, CA: cellulose acetate, PMMA: polymethylmethacrylate

TABLE XIII

MACROMOLECULE REMOVAL BY ASAHI PLASMAFLO

	Amount Removed		Initial Concentration	
Total Protein	22.3 ± 3.3	gm	6.2 ± 0.2	gm/dl
Albumin	12.1 ± 2.1	gm	3.5 ± 0.2	gm/dl
Globulin	10.1 ± 1.3	gm	2.7 ± 0.2	gm/dl
Fibrinogen	2,960 ± 550	mg	398 ± 93	mg/dl
Total Cholesterol	480 ± 140	mg	169 ± 28	mg/dl
Immunoglobulin G	2,640 ± 420	mg	803 ± 142	mg/dl
Immunoglobulin A	790 ± 130	mg	303 ± 104	mg/dl
Immunoglobulin M	620 ± 170	mg	284 ± 54	mg/dl
Immune Complexes	345,343 ± 381,123	U	600 ± 641	U/ml
Rheumatoid Factor	144,900 ± 23,900	RLS Units	208 ± 61	RLS Units/ml

TABLE XIV

Immunoadsorption systems described in the literature [72]

Immunoadsorbent	Substance removed	Application	Author
Protein A	IgG IgG immune complexes	In vitro	Rawer et al
Synthetic blood group B antigenic determinants	Anti-B antibodies	In vitro	Chang
Glomerular basement membrane antigen	Anti-GBM antibodies	Dogs	Terman et al
Bovine serum albumin	Anti-BSA antibodies	Dogs	Terman
Protein A	IgG	Dogs	Terman et al
Heparin-agarose	LDL	Dogs	Burgstaler et al
Anti-LDL-antibodies	LDL	Pigs	Stoffel et al
Glutaraldehyde treated human erythrocytes	Complement components	Sheep	Schmer et al
Heparin agarose	LDL	Sheep	Schmer et al
Staphylococcus aureus Cowan I	IgG	Human	Bansal et al
DNA	Anti-DNA antibodies	Human	Terman et al
Staphylococcus aureus Cowan I	IgG	Human	Ray et al
Blood group A and B antigen	ABO antibodies	Human	Benzinger et al
Anti-LDL antibodies	LDL	Human	Borberg et al
Protein A	IgG	Human	Terman

LEGEND OF FIGURES

1. Schema of blood access for TPN.[16]
2. Schematics of plasma separation by centrifugal and membrane devices
3. Principle of on-line membrane plasmapheresis. Separation of plasma from blood is achieved by utilizing membrane of 0.2-0.6 um porosity.
4. Scanning electron micrograph of membrane structure of various hollow fiber membranes. Left: Polyethylene (Mitsubishi 270H), Right: Polymethylmethacrylate (Toray PS-05).
5. Cross section view of hollow fiber type membrane plasma separator (Mitsubishi MPS-0165)
6. Structure of the Cobe plate-type membrane plasma separator
7. Filtration flux as a function of transmembrane pressure for plasma separators, and ultrafiltration by hemofilters and dialyzers
8. Classification of secondary filtration by temperature
9. Schematic of membrane plasmapheresis with on-line plasma treatment. Top: sorbent treatment, Middle: Cryofiltration, Lower: secondary filtration with recirculating flow, a process that differs from cryofiltration in the selection of filtering membrane and temperature of operation.

10. Cascade membrane technology for selective removal of macromolecules. General objectives for success of this technology are filter membranes of various porosities suitable for the selective removal of macromolecules from blood.

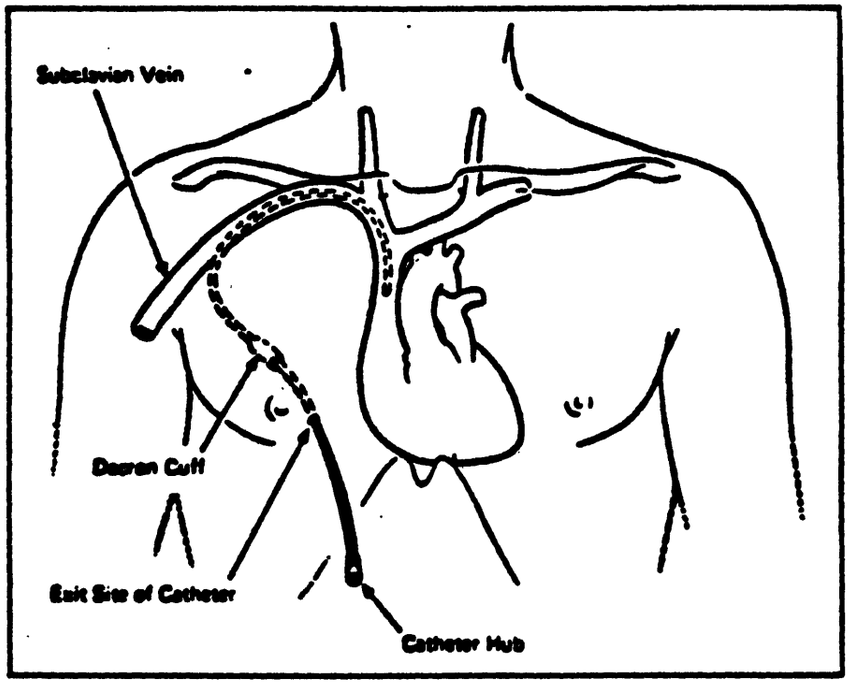

Figure 1

Schema of blood access for TPN[16].

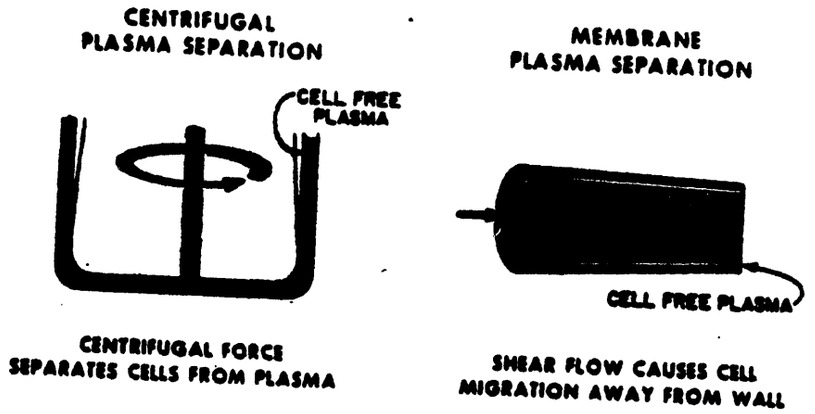

Figure 2

Schematics of plasma separation by centrifugal and membrane devices

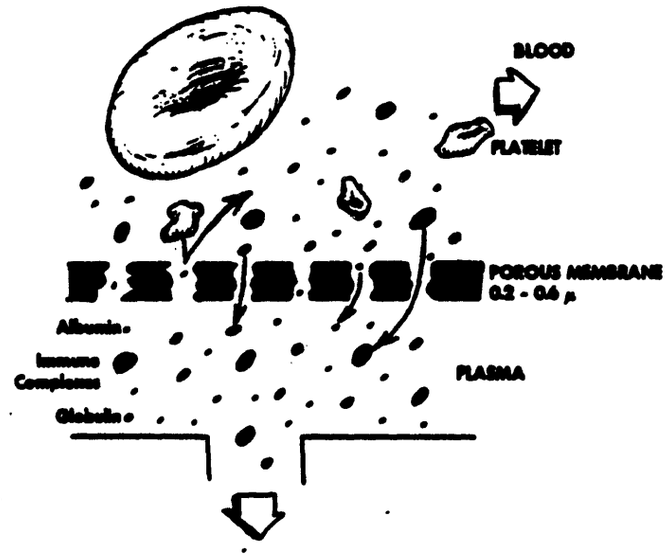

Figure 3

Principle of on-line membrane plasmapheresis. Separation of plasma from blood is achieved by utilizing membrane of 0.2-0.6 um porosity.

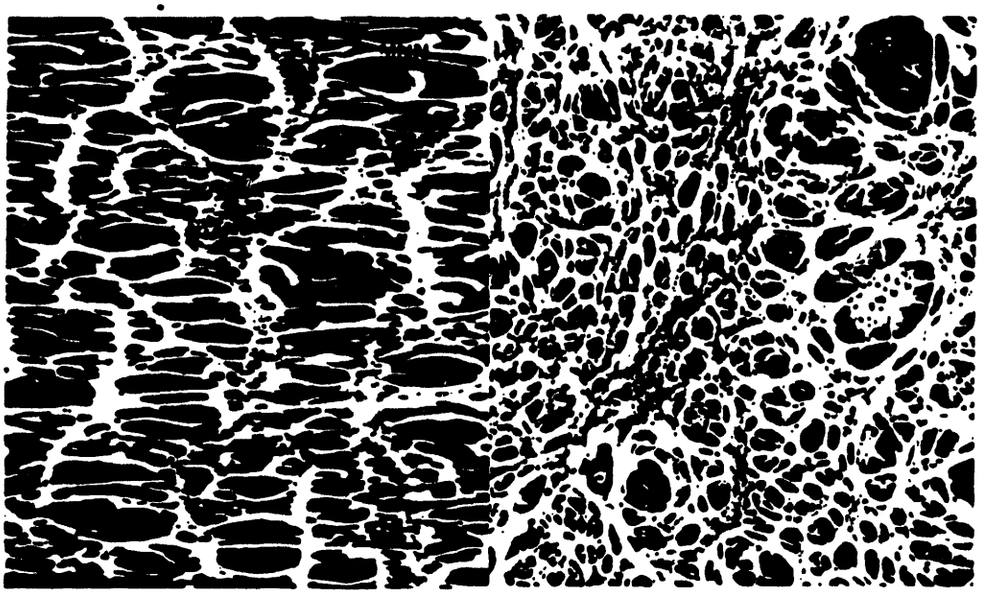

Figure 4

Scanning electron micrograph of membrane structure of various hollow fiber membranes. Left: Polyethylene (Mitsubishi 270H), Right: Polymethylmethacrylate (Toray PS-05).

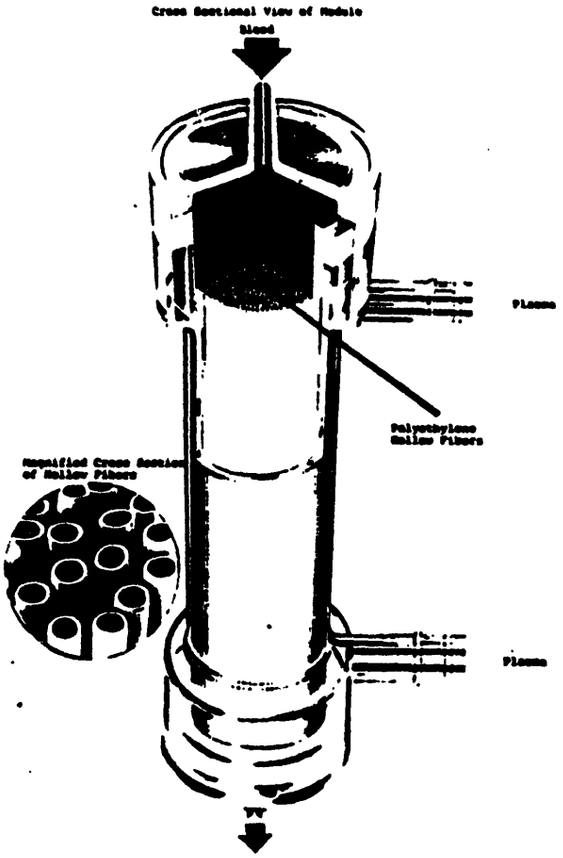

Figure 5

Cross section view of hollow fiber type membrane plasma separator (Mitsubishi MPS-0165).

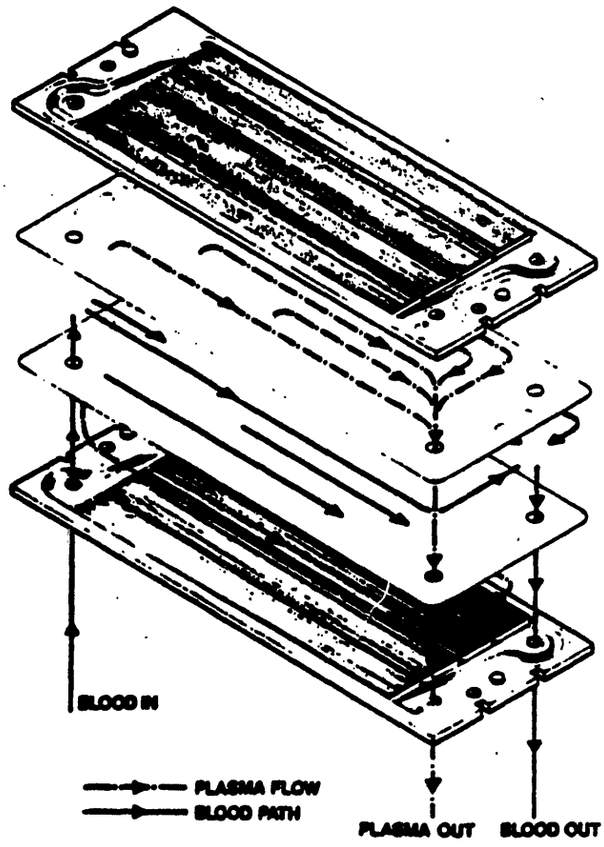

Figure 6

Structure of the Cobe plate-type membrane plasma separator

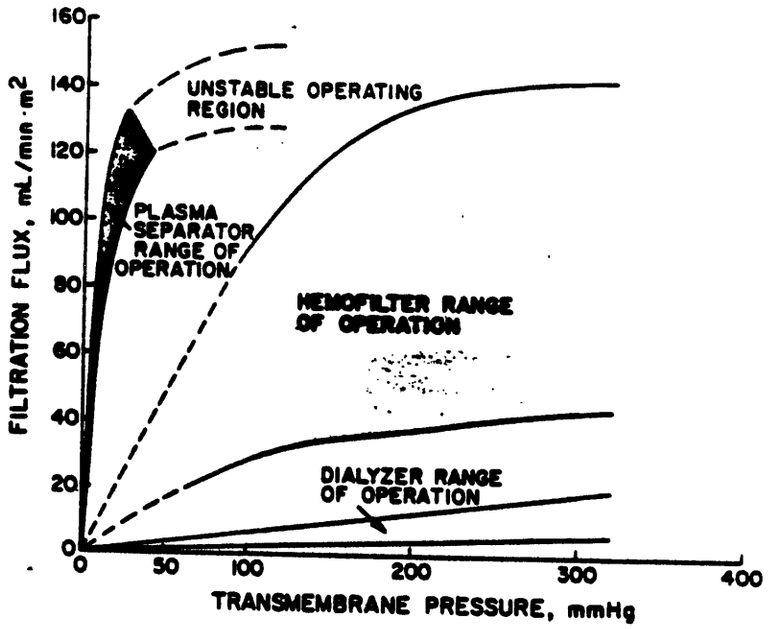

Figure 7

Filtration flux as a function of transmembrane pressure for plasma separators, and ultrafiltration by hemofilters and dialyzers

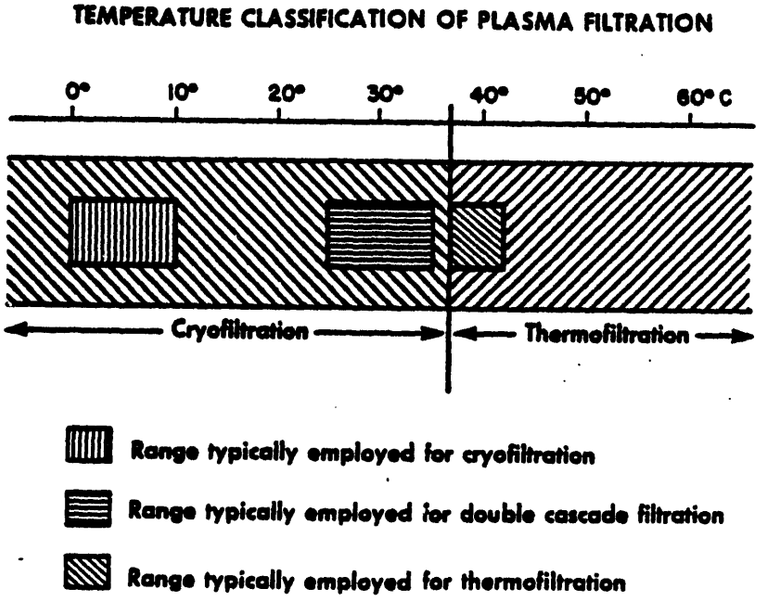

Figure 8

Classification of secondary filtration by temperature

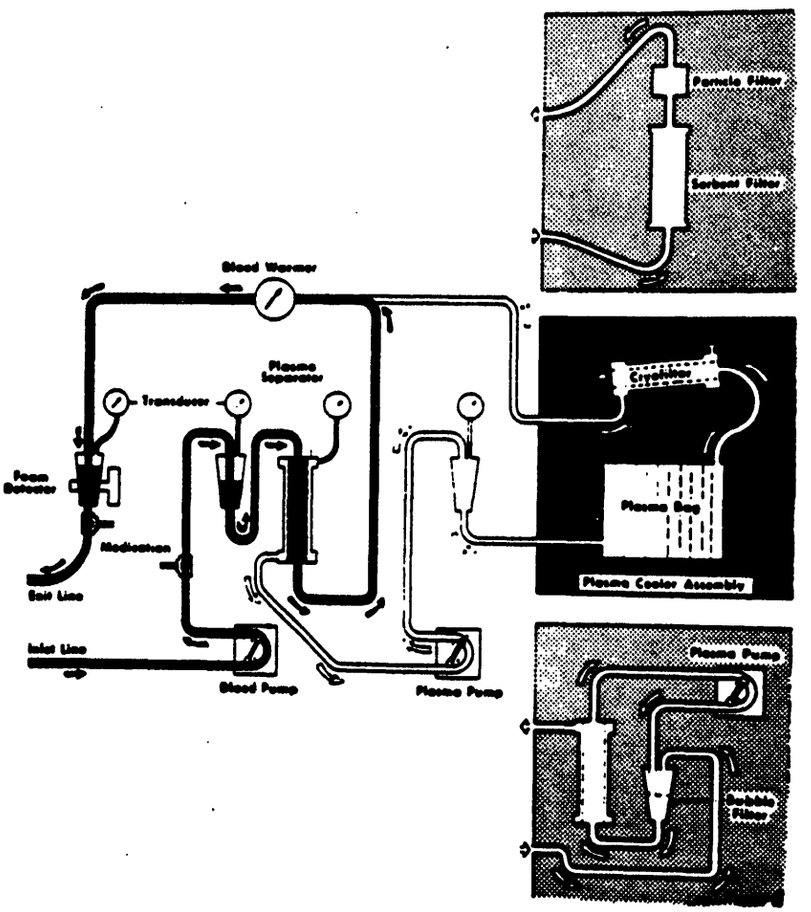

Figure 9

Schematic of membrane plasmapheresis with on-line plasma treatment. Top: sorbent treatment, Middle: Cryofiltration, Lower: secondary filtration with recirculating flow, a process that differs from cryofiltration in the selection of filtering membrane and temperature of operation.

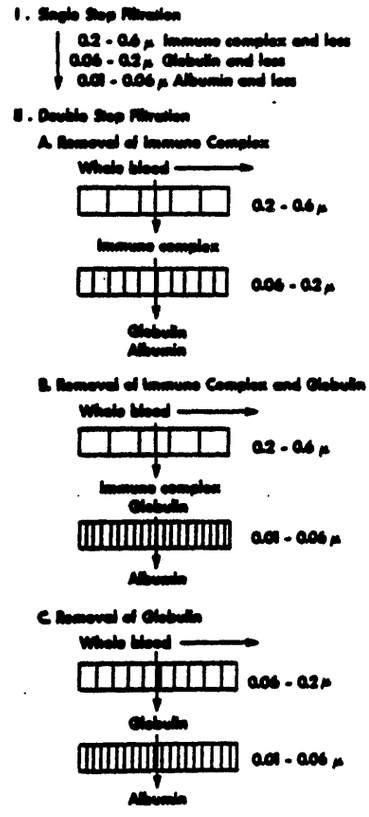

Figure 10

Cascade membrane technology for selective removal of macromolecules. General objectives for success of this technology are filter membranes of various porosities suitable for the selective removal of macromolecules from blood.

COSTS OF HUMAN GENOME PROJECTS
Tentative Meeting Agenda, August 7, 1987
Conference Room C/D, Office of Technology Assessment

9:00-9:30	Coffee and pastries	
9:30-9:50	Introduction	
	Opening statement and charge to panel	Bob Cook-Deegan
	Chairman's preface	Paul Berg
	Introduction of panel	participants
9:50-10:30	RFLP Map	
	average 1 centimorgan	$
	average 10 centimorgan	$
	associated infrastructure	$
10:30-11:30	Physical Map	
	production of clones	$
	ordering	$
	repositories	$
	databases	$
11:30-12:30	Technological Developments	
	sequencing	$
	large fragment handling	$
	automation and robotics	$
	software	$
12:30-1:30	LUNCH	
1:30-2:30	Organization	
	advisory body	$
	intergroup communications	$
	quality control	$
	personnel training	$
2:30-3:15	Other Costs	$
3:15-4:30	Discussion: What are the implicit assumptions?	
4:30	Summary and Concluding Remarks	Paul Berg