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PRELIMINARY BENEFIT ANALYSIS OF BIOLOGICAL SPACE PROCESSING

ECON INCORPORATED

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NINE HUNDRED STATE ROAD
PRINCETON, NEW JERSEY 08540
609 924-8778

FINAL

PRELIMINARY BENEFIT ANALYSIS OF BIOLOGICAL SPACE PROCESSING

Final Report

prepared for

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Office of Applications

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ECON, Incorporated

900 State Road
Princeton, New Jersey
08540

4020 Moorpark Avenue
San Jose, California
95117

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NOTE OF TRANSMITTAL

This preliminary analysis of the economic benefit of space processing of biological materials was performed for the Special Programs Division, Office of Applications, National Aeronautics and Space Administration, under Contract NASW-2558.

The principal investigator for this study at ECON was Mr. Jay Perrine. The NASA technical officer was Dr. James H. Bredt.

B. P. Miller

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1. INTRODUCTION

1.1 THE INTEREST OF THE BIOMEDICAL COMMUNITY IN THE SPACE ENVIRONMENT

The biomedical community became interested in utilizing the space environment from two different directions. One was spacecraft system engineering, which has traditionally involved obtaining desired outcomes in space despite an alien environment. The effects of the space environment became so interesting that ideas began emerging for ways to exploit it, including the processing of biological materials. The other came from within the biomedical community with its effort to manipulate biological materials in an environment that may be more optimum for certain processes than that found on the surface of the earth.

Natural space environment properties include the following:

1. Convection-free micro-gravity environment
2. Ready availability of vacuum
3. Solar and cosmic radiation unattenuated by the atmosphere of the earth
4. Oxygen-free atmosphere.

Of these properties, virtual weightlessness is the most valuable to bioprocessing as it cannot, as yet, be duplicated on earth for more than a few seconds. Examination of the attributes of weightlessness to bioprocessing will be made.

Advances in many areas of biomedical science are currently restrained by an inability to separate, definitively, biological materials that are closely related in physical properties but varying by physiological or biochemical characteristics. Electrokinetic phenomena (i.e., electrophoresis, sedimentation potentials, electroosmosis, and streaming potentials) are but a few of the physical properties of biological material upon which separation techniques have been developed.[1] Electrophoresis is now widely used both as an analytical and preparative method in the laboratory and as a diagnostic tool in medicine. It is doubtful that the full potential of electrophoretic separation has been realized. Improvements in both resolution and quantity of separates can be anticipated.

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[1] A list of references is provided, beginning on p. 62.

Electrophoresis is defined as the transport of electrically charged particles in aqueous media, under the influence of a direct current electrical field.[2] Most materials when dissolved in a given aqueous medium acquire a characteristic electrical charge, and their migration velocity per unit electric field (defined as the electrophoretic mobility of the substance) is thus fixed. The particles may be simple ions, complex biological macromolecules and colloids, or even particulate matter - either living cells, such as bacteria or erythrocytes, or inert material, such as oil emulsion droplets and clay. Because of its unique resolving ability, electrophoresis is most often used for separation of proteins in biological fluids, with three primary purposes:[3]

1. Identification of a particular molecular species
2. Quantitative analysis of each species in a mixture
3. Actual preparative separation of isolated fractions.

Originally, electrophoresis was carried out in free solutions but it was soon recognized that problems arise due to convective disturbances in the bulk of fluid. Several major causes of these disturbances can be categorized:[4]

a. The solute to be separated, if present in significant concentration, adds to the density of the supporting electrolyte. This difference in density between solution and pure solvent causes gravity-caused convective flow, unless means are found to prevent it.

b. In some instances the particles may be sufficiently large to sediment noticeably. While there are techniques which utilize differential sedimentation to accomplish meaningful separations, within the context of electrophoresis such sedimentation is usually undesirable.

c. The passage of electric current causes heating of the solution. As the vessels are externally cooled, a radial temperature gradient arises, again causing gravity-conditioned convection.

d. The electric charge exhibited by the vessel walls within which electrophoresis is carried out causes an electroosmotic streaming of the fluid. This disturbance is independent of gravity and is a consequence of the electrical properties of the system as a whole.

As defined above, electrophoresis is a separation process occuring within the bulk of the liquid phase (and not at the electrodes) and based on the differences in electrical transport rates. Electrophoresis alone, however, does not provide for the ultimate separation of various molecular species of proteins present, as their characteristic mobilities may be overlapping. Highest resolution is obtained if a second separation parameter is employed by introducing an element of discontinuity into the liquid phase.[5] Two methods are most often used. In high density gel electrophoresis an element of molecular sieving is superimposed on the electrical separation process by progressively increasing the density of the supporting gel matrix. A protein sample is introduced in a narrow zone at the top of two gel columns, and through the combined effects of differential electrical transport and sieving the proteins separated into individual zones along the length of the columns. They can be recovered, in minute quantities only, through sectioning or elution of the gel. In isoelectric focusing, a continuous pH gradient is established and the proteins become immobilized at the pH corresponding to their characteristic isoelectric point (mobility of proteins is pH dependent, the narrow pH zone of zero mobility is the isoelectric point). The separation obtainable by isoelectric focusing is comparable to that in high density gels, and should be contrasted with ordinary electrophoresis where, at best, only six fractions are detectable in serum.

Two shortcomings of terrestrial electrophoresis are obvious:[6]

1. While electrophoresis is excellent for analytical purposes, it has failed as a preparative tool and only minute quantities can be actually separated. There are no theoretical reasons why electrophoresis could not be used on as broad an industrial scale as some of the other

electrically driven processes such as electrolysis, electrocoating, etc. Two major problems prevent scaling of the equipment to industrial proportions: necessity of heat dissipation and difficulty of uniform packing of anticonvective supporting media.

2. None of the above described anticonvective means is readily applicable to separation of living cells and other particulate matter. Best results are achieved with stabilization of liquids in thin films, but the apparatus has low throughputs and lacks high resolution.

There is a widely held belief that many desirable biological separations, especially of cellular components, would be possible, if convective turbulence and sedimentation could be eliminated. The micro-gravity environment of space should provide the proper environment for electrophorectic separation of cells. It can be envisaged that space electrophoresis may result in a significant broadening of the scope of applications of this separation technique - in micro-gravity increased purity (factor 5-10 in resolution) is expected as well as higher throughput.

1.2 SPACE BIOPROCESSING EXPERIENCE TO DATE

The idea of using space flight to stabilize liquid media for electrophoretic separation was proposed late in 1969 for the NASA Materials Sciences Manufacturing in Space (MS/MS) program.[7] Following analytical studies and advice from the scientific community, the first electrophoresis experiment at zero gravity was carried out on the return trip from the moon on Apollo 14, with an attempted separation of red and blue dyes. Photographic records showed that the separation of the dyes was sharper than was possible with comparable equipment on earth. It was also demonstrated that the component parts of the apparatus worked as designed.

A second zero gravity experiment was conducted on Apollo 16 using the basic operating elements of the Apollo 14 unit for the electrophoresis of polystyrene latex.[8] These stable, nondegradable particles were used as a model for living cells. Two sizes of latex particles were run separately and together in order to provide comparative data. During the experiment itself, the sample bands were severely distorted by electroosmosis which caused buffer flow along the walls of the columns counter to the direction of electrophoretic migration of the latex particles.

For the Apollo-Soyez Test Program, plans were to use parts of the Apollo 14 and Apollo 16 systems that operated correctly, improve the techniques that proved faulty and add an isotachophoresis segment to the experiment. The Apollo-Soyez electrophoresis experiment MA-011 was rewarding, as the following paragraph from the MA-011 preliminary report indicates:[9]

"With the successful separation of the standard particles (fixed red blood cells) and the human kidney cells there is no longer a question of electrophoretic possibilities in zero gravity. The lack of significant electroosmosis, the loading and returning of a sterile system, the capture of the resulting separation, the preservation of the viable cells in orbit and their subsequent return, all represent a "first" for space electrophoresis. In addition, the newer methods of separation represented by the isotachophoresis runs proved the feasibility of conducting large particle processing by this method. The red blood cells in both columns demonstrated sharp boundaries indicative of successful isotacho runs."

At this time, experimentation of bioprocessing is continuing with the Space Processing Applications Rocket (SPAR) project. These experiments will continue until the Spacelab becomes operational.

1.3 SPACE SHUTTLE SOON TO BE A REALITY

Space Shuttle operations are scheduled to begin in the early 1980s. The operational goal of the Space Shuttle Program is to provide low cost transportation to and from earth orbit, utilizing reusable orbiters with cargo bays 15 x 60 feet in size. NASA is currently determining the traffic model.

1.3.1 Spacelab

Some of the missions will be equipped with a Spacelab which is a laboratory designed for space operations, composed of modules and pallets in the orbiter suitable for accommodating instrumentation for conducting research and applications activities on Shuttle Sortie missions. On a given mission, the Spacelab configuration can be comprised of a module only, a pallet only, or a combination of a module and a pallet, leaving the arrangement flexible for specific experiment or processing applications. The Spacelab program is under the direction of the European Space Agency in cooperation with NASA. Flights will last from 3 to 30 days and scientists will have the opportunity to fly with their experiments. The Space Shuttle/Spacelab will provide the attractive features of the space environment with the capability for frequent, repetitive reuse of the processing equipment.

1.3.2 Capabilities and Opportunities for Bioprocessing on Spacelab

The 1974 NASA Preliminary Sortie Payload Descriptions describes fifteen space processing applications payloads.[10] Of these, bioprocessing is designated as part or all of six payloads which will comprise some 40, or more, missions over a decade. The Space Bioprocessing Program is designed to explore the possibility of accomplishing bioprocessing and manufacturing that is too difficult, costly, or impossible to accomplish on earth.

Details of apparatus to be available on the Spacelab are not yet resolved as the entire program is still in the development stage. Work is underway to develop equipment necessary to perform electrophoresis in space, while research and development in space processing is continuing with ground based investigations and the suborbital rocket experiments.

Despite the lack of exact specifications of apparatus for the Spacelab, it is known that weightlessness provides better control of certain parameters in biological and biochemical manufacturing, e.g.,[11]

- Absence of convection and sedimentation
- More stable emulsions from immiscible fluids
- Separation of materials difficult to isolate in one-g
- Processing in liquid float zones without the use of a container
- Mass transfer in liquids, wholly controlled by diffision.

Space processing of biological materials is an emerging technology. Many possible applications have been defined. Included are the following:[12]

Separation: Electrophoresis, dialysis and other separation techniques may lead to ultra-purification of fragile biological substances, e.g.,

- Specific cell types and mutants
- High density lipoproteins
- High purity erythroprietin
- Factor VIII (antihemophilic factor)
- Virus sub-unit vaccines
- Sub-types of immunoglobulin G
- High purity biologicals uncontaminated by antigenic residues.

Biosynthesis: Zero-g fermentation and tissue culture may lead to new syntheses of these biologicals which are impractical to produce on Earth, e.g.,

- Medically important biologicals produced from hydrocarbons and other immiscible substrates
- New vaccines and antibiotics
- New hormones and enzymes from specific cell lines
- Production of reactive intermediates which are required in the manufacture of certain biologicals on Earth
- Manufacture of certain primary metabolites (amino acids, nucleotides, etc.), made possible by altered microbial feedback controls, due to zero-g.

There are already many uses for pure cell lines in the manufacture of a variety of vaccines and other biologicals through tissue culture. We are presently at the threshold of a large potential for clinical use of pure cell populations to correct genetic or acquired deficiencies.

One can also envisage far reaching applications of better protein fractionation in space. Human plasma proteins and a variety of enzymes, protein hormones, etc., are presently fractionated on a large industrial scale for medical and research usage. The methods presently used all lack the sensitivity and resolution of electrophoresis and often give products of insufficient purity at low yields. Thus, it is hoped that the space bioprocessing payloads will be directly applicable to ground-based industrial/biological processes.

NASA and ESA are responsible for developing the space technology needed for practical space processing applications. There are numerous opportunities for bioprocessing in space on the Spacelab. The details will be developed through the interaction of private industry, the scientific community, NASA and ESA.

1.4 STUDY PURPOSE

1.4.1 Begin Analysis of Benefits that may Accrue from Bioprocessing in Space

The purpose of this study is to perform a preliminary economic benefits assessment of space processing of certain biological materials. The objective of this assessment is to provide improved understanding of the economic potential of space processing for those selected biological materials. Additionally, areas which are significant for further analysis and decision making will be indicated. In pursuing this task, two case studies are made of the applications of space processed biological materials. The two materials investigated here are human lymphocytes and urokinase. The users of the first material, if it can be successfully separated so as to yield medical usefulness, would be patients, or potential patients, of kidney transplants. The other material, urokinase, would be utilized by persons suffering from diseases involving blood clots.

1.4.2 Benefits Only

It should be made clear at this point that this study does not attempt to determine costs. Thus, this study is not a cost-benefit analysis. However, the analysis presented here could be used in a cost-benefit analysis once the costs are generated. The responsibility for generating cost data lies with NASA at this time.

2. CASE STUDY DISEASES AND TREATMENT SYSTEMS

2.1 END STAGE RENAL DISEASE

The healthy human body contains two kidneys which maintain the delicate chemical balance required for normal body functioning. Each day the kidneys filter some 200 quarts of blood and about two quarts of wastes and harmful substances are discharged as urine. Because each kidney can process volumes many times greater than it normally does, one kidney can suffice if the other is removed or ceases to function. If the kidneys do not remove wastes from the blood, uremia, or urea in the blood develops. Advanced uremia will ultimately lead to death. The severity of uremia parallels the extent of kidney failure. When the kidneys are chronically at a functional level of 5 percent or less the condition is known as End Stage Renal Disease (ESRD). This condition is irreversible.

2.1.1 Epidemiology of ESRD

In any one year, approximately 50,000 people face kidney failure.[13,14,15] Of these, about 10,000 are medically suitable candidates for dialysis or transplantation,[16] the two current means of treatment. Although the 50,000 figure is difficult to substantiate with vital statistics, the figure is commonly mentioned in the literature. The number of persons who are medically suitable for dialysis or transplant are estimated to be about 10,000 annually and is becoming easier to pinpoint because of improved government statistics on the matter.

The improvement in government statistics on ESRD care has come about because of the commitment of the federal government through enactment of Section 2991 of Public Law 92-603, to cover costs of treatment of ESRD. This is the first major chronic disease for which the government has assumed financial responsibility. This coverage is not entirely universal as it is available only to those who qualify for Social Security coverage, thus some 5 to 10 percent of the ESRD population may not be eligible for coverage. Testimony at House hearings on the ESRD Medicare coverage have revealed that costs are running much higer than anticipated. Currently government costs are running over $300 million per year and are expected to reach the $1 billion mark within ten years.[17] Data collection on ESRD treatment coverage is an evolving

technique on the part of the government and should be greatly improved in about a year's time when the combined Social Security Administration and Bureau of Quality Assurance reporting and computer analysis system is operational.[18]

ESRD tends to afflict people of all socio-economic levels.[19] The sex and age distribution is less evenly distributed. A slightly higher incidence of ESRD is found among males than females. Fifty-four percent of patients on hemodialysis were between the ages of 40 and 65 when they began dialysis.[20] However, less than 5 percent of the patients were under age 20 and less than 9 percent were over age 65.[21] Seventy-five percent of the males and 65 percent of the women were of working age.[22] This mean age was 48 for men and 47 for women.

2.1.2 Present Treatment of ESRD

2.1.2.1 Dialysis

When the human kidneys fail to function a machine can be utilized to filter wastes and water from the blood. The process is called hemodialysis, or peritoneal dialysis if the fluid in the intestinal cavity is filtered rather than the blood. If dialysis is not utilized, the ESRD patient will die within about a month's time. On April 1, 1976, the last available count, the total number of patients on dialysis was 18,323.[23] This information is from the National Dialysis Registry which collected the data from 546 centers but as of May is no longer gathering data in lieu of the new joint Social Security - B.Q.A. system, which is not yet operational. Although there may be more patients than are reported by the Registry, this is the most accurate figure available.

Dialysis can take place in one of three settings:

1) a hospital,
2) a treatment center, or
3) the home.

The hospital is convenient for the physician because if the patient needs medical attention the personnel is available. Additionally some patients present complex medical problems which predispose them from home dialysis. Hospital dialysis accounted for 52 percent of all dialysis patients in the most recent Registry.[24] Treatment center dialysis accounted for one-quarter of dialysis patients and offers some of the benefits of a hospital but still involves transportation of the patient to the center. Home dialysis is claimed to be cheaper than facility or hospital dialysis because of the reduced cost of medical personnel other than the doctor. The patient or spouse performs many of the tasks often performed by nurses or technicians.

2.1.2.2 Transplants

The other medical treatment for ESRD is to surgically transplant another functioning kidney into the patient's intestinal cavity. Table 2.1.1 gives the total number of transplants performed in the United States at slightly less than 15,000, and averaging around 2,000 per year. The sources of healthy kidneys for such transplants are either living persons who are willing to give up one of their functioning kidneys (usually a relative of the recipient), or those who have healthy kidneys and are suddenly killed or die (generally automobile accident victims).

Table 2.2.1 indicates the breakdown of transplants by donor source, the largest percentage being cadaveric donors. Table 2.1.2 gives the survival rate of transplanted kidneys. From experience in the United States, generally it can be observed that transplants from relatives function longer than from cadavers, and the record for five-year transplant survival has improved in recent years. Taking the five-year figures for the year 1970 from Table 2.1.2, there was an overall functioning kidney survival rate of 47 percent.

Table 2.1.1 Kidney Transplant Statistics for the United States

TOTAL KIDNEY TRANSPLANTS BY YEAR

	1953-1966	1967	1968	1969	1970	1971	1972	1973	1974	1975	TOTAL TO DATE
United States	1,146	462	701	870	1,137	1,674	2,221	2,402	2,181	1,742	14,536

TRANSPLANTS RECORDED TO DECEMBER 1, 1975

United States

Donor Source	Number of Transplants	% of Total
Parent	2,367	16.28
Sibling	2,896	19.92
Cadaver & Unrelated Living	8,823	60.70
Monozygotic Twin	69	.48
Other Related Living	381	2.62
Total Recorded	14,536	100.00

SOURCE: American College of Surgeons, N.I.H.

Table 2.1.2 Functional Survival of First Kidney Transplant

Table 3.—Percent Functional Survival (±SE) of First Transplant

Donor Source	Year of Transplant	Sample Size	1 yr	2 yr	3 yr	4 yr	5 yr
Sibling	1951-1966	246	63 8±3 1	57 2±3 2	53 0±3 2	49 2±3.2	46 2±3 2
	1967	148	77.0±3 5	70.2 ±3 8	65 4±3.9	58 4±4 1	55.2±4.2
	1968	203	80 3±2.8	74 3±3.1	71 3±3.2	65 6±3 4	61.8±3.5
	1969	217	76 5±2 9	71 8±3 1	69 4±3 1	64 3±3 3	60 8±3 7
	1970	266	81 1±2 4	78.2±2 6	72 8±2.9	69 6±3 3	
	1971	406	73 7±2 2	69 6±2.3	67 7±2.5	...	. .
	1972	447	79 9±1.9	73.7±2 5	...	...	..
Parent	1951-1966	412	56 0±2 5	49.7±2 5	44 9±2.5	42.3±2 5	39 9± 2 5
	1967	152	71.7±3 7	61.8±3 9	55 9±4 0	52 5±4.1	50.1±4.1
	1968	208	73 1±3 1	67 8±3 2	60 4±3.4	53.6±3 5	51 0±3 6
	1969	234	69.2±3.0	62.2±3 2	56 3±3 3	49.2±3 4	42 0±3 8
	1970	261	73 8±2 7	68.3±2.9	62 3±3 1	57.3±3 6	
	1971	326	73 7±2 4	66.8±2 7	62 3±3.1		..
	1972	359	71 7±2.4	61.1±3 1	.	.	..
Cadaver	1951-1966	685	35 6±1.8	27 9±1 7	22 4±1.6	19.4±1 5	16.0±1 4
	1967	395	45 6±2 5	38.9± 2 5	34 2±2.4	29 2±2 3	26.7±2 3
	1968	649	47 6±2 0	40 4±1.9	35 2±1.9	32.8±1 9	30.2±1 9
	1969	847	54 2±1 7	47 2±1 7	42 1±1.7	37 9±1.7	35 2±1.9
	1970	1,147	55.3±1 5	47.2±1 5	42 0±1 5	40 6±1 6	.
	1971	1,559	53.1±1 3	45.7±1 3	41 8±1.4	.	
	1972	1,707	50 6±1 2	42 6±1 4			...

SOURCE: American College of Surgeons/N.I.H.

The other significant factor in kidney transplantation is the patient survival rate. Table 2.1.3 lists kidney transplant patient survival rates for up to five years. The same generalizations of kidney function survival apply to patient survival; however, patient survival is greater than kidney function survival with 56 percent of the 1969 graft population surviving 5 years. Of all transplant patients for which there is follow-up data, 67 percent are still alive and of those 70 percent still have functioning kidney transplants.[25] A transplant patient often outlives his transplant. A patient with a nonfunctioning transplant either receives another transplant or returns to dialysis. There is often a considerable wait to receive a transplant due to availability and tissue matching. A cadaveric kidney is only viable for about 3 days before it must be used or discarded.

Kidney transplants are not yet a solution for every patient because of the high failure rate. There is no single cause of graft failure, but over 60 percent of the transplants reported as failing were lost due to the body's rejection.[26] Approximately 10 percent of kidney grafts are lost due to technical difficulties.[27]

Presently patients with kidney transplants are given some type of antilymphocyte globulin which essentially suppresses all lymphocyte activity.[28] One side effect of such an action is a marked increase in the incidence of cancer in transplant patients.[29]

The immunologic system of the human body is not well understood; medical research is continually making new discoveries in this field. It is known that immunity is caused by the formation of substances called antibodies. Immunities have been found to be specific, that is, they protect the person only against the disease-causing agent used to develop the immunity. The thrust of present research is to find the specific immunity factor or factors attacking a transplanted organ, such as a kidney.

Table 2.1.3 Kidney Transplant Patient Survival

Table 4.—Percent Patient Survival (±SE) of First Transplant

Donor Source	Year of Transplant	Sample Size	1 yr	2 yr	3 yr	4 yr	5 yr
Sibling	1951-1966	246	68.1±3.0	61.9±3.2	58.3±3.2	56.0±3.3	54.0±3.3
	1967	148	83.6±3.1	76.9±3.6	72.4±3.8	66.1±4.1	63.3±4.2
	1968	203	86.1±2.3	82.6±2.8	79.8±2.9	76.3±3.1	73.3±3.3
	1969	217	82.6±2.6	78.5±2.9	77.4±2.9	72.4±3.2	71.1±3.5
	1970	266	86.0±2.2	84.2±2.3	81.0±2.6	81.0±2.6	...
	1971	406	85.2±1.9	81.8±2.1	80.3±2.3		
	1972	447	90.9±1.4	86.8±2.1	...		
Parent	1951-1966	412	61.0±2.5	56.5±2.5	53.0±2.6	51.1±2.6	50.5±2.6
	1967	152	75.4±3.6	69.0±3.8	63.8±4.0	62.2±4.1	60.3±4.2
	1968	208	80.0±2.8	76.2±3.0	71.7±3.2	67.2±3.5	65.6±3.6
	1969	234	78.7±2.8	73.7±3.0	69.8±3.2	64.6±3.5	61.8±3.8
	1970	261	84.2±2.4	80.0±2.6	78.9±2.7	77.6±2.9	..
	1971	326	86.1±2.0	82.3±2.3	80.4±2.6		
	1972	359	86.6±1.9	81.8±2.6			...
Cadaver	1951-1966	685	42.1±2.0	34.4±1.9	28.8±1.9	25.7±1.8	23.1±1.8
	1967	395	56.3±2.7	49.5±2.7	45.1±2.8	40.8±2.8	39.2±2.8
	1968	649	58.6±2.1	51.6±2.1	46.6±2.2	44.7±2.2	43.1±2.2
	1969	847	65.5±1.7	59.3±1.8	55.1±1.9	51.7±1.9	50.6±2.0
	1970	1,147	69.2±1.5	63.3±1.6	58.4±1.7	57.6±1.7	. .
	1971	1,559	69.2±1.3	63.4±1.4	61.5±1.5		.
	1972	1,707	71.8±1.2	65.6±1.6			.

SOURCE: American College of Surgeons/N.I.H.

2.1.3 Potential Alternative Treatment of Kidney Transplant Rejection By Regulating Lymphocytes

It is not clearly understood yet what effect the antilymphocyte globulins have on human immune mechanisms, especially in terms of specific immulogic responses such as graft (transplant) rejection. Lymphocytes play a pivotal role in many immune functions. Tissue typing of both donor and recipient is often performed to try and match the HL-A antigens. To date, two major types of human lymphocytes have been identified, T and B lymphocytes. However, it is hypothesized that there are many subgroups within these major types. It is hoped that the sorting of lymphocytes into subgroups will isolate the lymphocyte or lymphocytes which specifically affect transplant immunologic responses. If those functionally specific lymphocytes can be segregated, it is theorized that an enhancing antibody could be developed to promote kidney transplant acceptance.

Lymphocytes are one type of white blood cells, or leukocytes. There are five types of leukocytes: neutrophiles, baseophiles, eosinophiles, lymphocytes, and monocytes. Lymphocytes, monocytes, and neutrophiles react phagocytically, that is, they engulf foreign cells when encountered.

2.1.4 Limits of Earth Processing for Lymphocyte Separation

The present constraint on sorting, or separating lumphocytes into the many subgroups which are theorized to exist, is the large cell size. Present ground-based separation technology, such as electrophoresis, is limited in the size of the material which can be separated due to convective turbulence and sedimentation, both gravity induced factors. Thus, further research on human immunology is constrained by technical difficulties in cell separation procedures due to natural environmental characteristics. It is necessary to either eliminate gravity or develop procedures to separate cells in another manner. It is theorized, and indeed early space experimentation is supporting

the theory, that a convection free weightless environment may provide the proper setting for utilizing electrophoresis to separate biological materials by the size of cells. It is also theorized that isotachophoresis performed in space would yield very distinct separation resolutions.

2.2 THROMBOEMBOLIC DISEASES

2.2.1 Epidemiology of Thromboembolic Diseases

Clot diseases can be divided into two categories, stationary and mobile. Thrombus is the medical term for a stationary clot. A mobile clot, one that is in motion or has migrated from a vein into an organ, such as the lungs, is called an embolus. Thus, generally diseases related to clots are called thromboembolic diseases.

A clot or thrombus, starts out in a stationary situation and can become mobile,or an embolus. A clot in the leg, for example, known as deep vein thrombosis, if uncorrected, can lead to two major and serious diseases: pulmonary embolism, a mobile clot which has lodged in the lungs and can cause death within minutes or an hour of its occurrence; and chronic venous insufficiency.

Thromboembolic diseases can affect the eyes (retinal vein thrombosis), cause heart attacks (myocardial infarction) and cause problems in other parts of the body.

Urokinase, a drug which appears to be able to dissolve blood clots, has been tested experimentally in the United States but only to a limited degree. The one disease for which data exists on urokinase efficiency is pulmonary embolism. Because of the limited data availability, pulmonary embolism statistics will be used in this report to generically represent thromboembolic diseases. Thus total benefits may be somewhat understated because urokinase may be of some benefit to diseases other than pulmonary embolism, as has been found to be true in countries where urokinase is commercially available.[30] However, due to the complete uncertainty of the medical efficacy of urokinase on thromboembolic diseases other than pulmonary embolism, only pulmonary embolism will be referenced in this study. About 300,000 persons are hospitalized annually and more than 50,000 die with pulmonary embolism.[31] This number of deaths annually due to pulmonary embolism is difficult to substantiate with vital statistics. Dr. Isadore Rossman researched the question of accuracy of diagnosis of death as reported

on death certificates. When autopsy reports were compared with death certificates, an underreporting situation was found.[32] Rossman indicated that only one-half of one percent of death certificates listed pulmonary embolism as the cause of death while the actual percentage is more like three percent of all deaths.[33] Using Rossman's estimate, the total number of persons dying from pulmonary embolism each year would be over 50,000.

Thromboembolic diseases mostly afflict the elderly. There is a high incidence of clot formation in patients who have undergone surgery and are immobilized for a period of time following the surgery. This is one reason patients are asked to move around after surgery sooner than was the practice in the past.

2.2.2 Present Treatment of Thromboembolic Diseases

2.2.2.1 Heparin

Presently the treatment of thromboembolic diseases consists of either an anticoagulent regime or surgery. Heparin is the generic name of a pharmaceutical product that acts as an anticoagulent, that is, it prevents blood from clotting. Heparin is often given as a therapeutic agent in routine dosages for extended periods of time. Heparin is made from an enzyme which is found in the human body.

2.2.2.2 Surgery

Heparin may prevent further clotting action while the body naturally breaks down the thrombus, or clot. Heparin alone cannot dissolve the clot, it can only prevent the formation of new ones. When a clot is in danger of migration, or has migrated and lodged in a new location, such as the lungs, surgery may be necessary to physically remove the embolus, or migrated clot. Thus surgery, commonly a pulmonary embolectomy, is often performed, as a remedy. It is major surgery and expensive. Once an embolus has reached the lungs, however, the body is in a life critical situation. Twenty to fifty percent of the deaths resulting from pulmonary embolism occur within a few minutes to an hour.[34]

2.2.3 Potential Alternative Treatment Utilizing Urokinase

Urokinase is an enzyme found naturally in the human body which acts as a plasminogen activator. Urokinase produced in the kidneys can be found in trace amounts in the urine. It has been established by the biomedical research community that urokinase is capable of activation of the fibronolytic system. That is, urokinase added to the bloodstream appears able to lyse, or dissolve, blood clots.

When a clot, or thrombus, forms in the body, a precursor in the blood called fibronogen has changed into fibrin, the material which composes the clot. Fibrin is deposited by the body in an early phase of tissue repair. When a thrombus is young, it is composed of soluble fibrin, which is denoted $\text{fibrin}_{(se)}$. In a matter of about a week after the thrombus has initially formed a substance called Factor XIIIa combines with $\text{fibrin}_{(se)}$ to produce an insoluble form of fibrin, denoted $\text{fibrin}_{(insol)}$.

To produce the lysing action, urokinase is given to the patient. Urokinase activates another precursor occurring naturally in the blood called plasminogen. The combination of urokinase and plasminogen produce plasmin which is capable of digesting proteins such as fibrin. Thus, plasminogen, urokinase and fibrin are components of the fibrinolytic system.

At present, urokinase is not commercially available in the United States. Two drug companies have applied to the FDA for approval to market the substance.[35] In 1967 the National Heart and Lung Institute organized a controlled clinical trial to evaluate the thrombolytic capability of urokinase. Pulmonary embolism was chosen as the disease model in which to evaluate a thrombolytic agent because dianostic techniques (pulmonary angiography and perfusion lung scanning) permitted quantitative assessment of both preinfusion severity and resolution of emboli. Phase 1 of the trial was called the Urokinase Pulmonary Embolism Trial (UPET) while Phase 2 was called the Urokinase - Streptokinase Pulmonary Embolism Trial (USPET).

Phase 1 established that urokinase increased the resolution rate of pulmonary thromboemboli, especially massive emboli, as judged by arteriography, hemodynamics, and lung scanning.[36] Figure 2.2.1 gives the relative improvement of urokinase over heparin from the UPET while Figure 2.2.2 indicates the relative improvement over time of heparin and urokinase patients in the test. There was no significant difference in mortality between the two groups. This may have been due to the small sample but the carefulness which characterized the selection of patients may have weeded out the high risk patients from the sample.

2.2.4 Limits of Earth Processing for Cell Separation to Obtain Urokinase Producing Cells from Kidney Cells

Urokinase can be obtained from two basic methods: extraction from urine or extraction from kidney cells. The first method, extraction from urine, is the technique utilized by foreign pharmaceutical firms which offer urokinase commercially. There are drawbacks to this technique.

Some 1500 liters of urine are needed to obtain one dose of urokinase. In addition to the logistics of obtaining large quantities of urine, there are purity problems because fever producing precursors often cannot be removed from the urine.

The other technique is to separate the urokinase producing cells from other kidney cells either before or after all the cells have been propagated. A procedure has been developed by Abbott Labs making use of tissue culture techniques using the Mass Tissue Culture Propagator.[37] In this procedure, all kidney cells are propagated, not just the ones which produce urokinase. A 95 percent reduction in the number of cells to be cultured would greatly reduce production costs and possibly lead to greater purity.[38] However, at present, techniques do not exist which allow successful kidney cell separation on earth. It has been theorized that electrophoretic separation of kidney cells in a gravity-free environment might prove to be the answer.

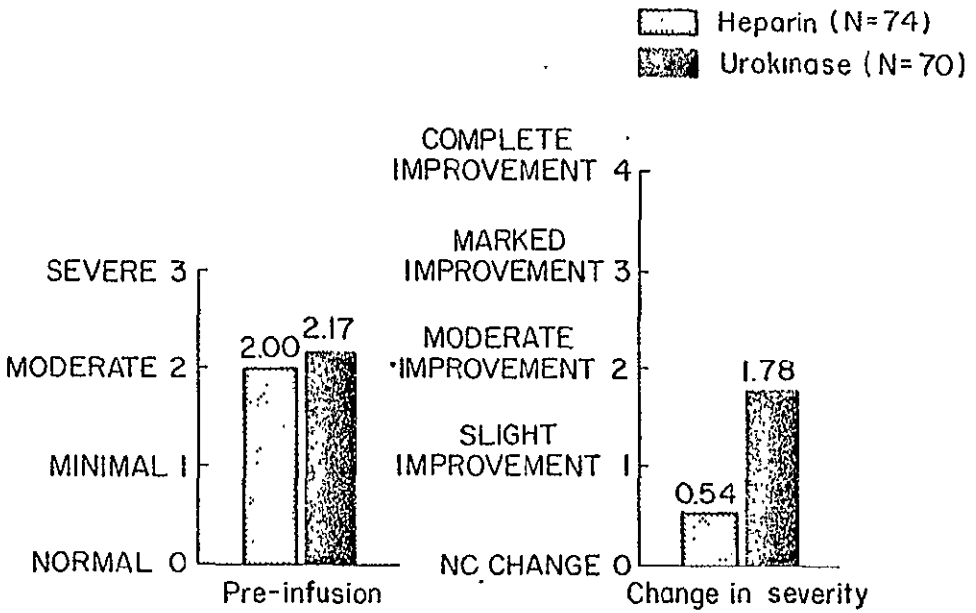


Figure 2.2.1 Relative Pulmonary Embolism Patient Improvement after 24 Hours Comparing Urokinase and Heparin Treatment

SOURCE: American Heart Association, U.P.E.T.

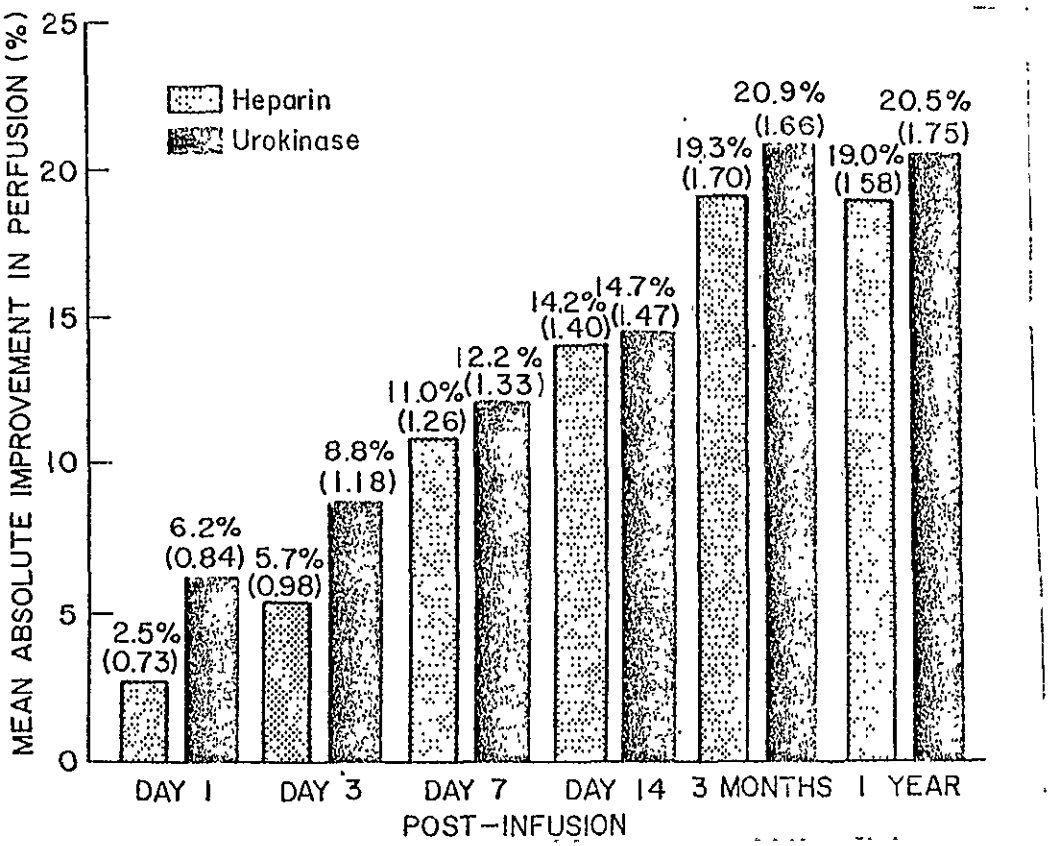


Figure 2.2.2 Relative Improvement Over Time Comparing Patients Treated with Urokinase and Heparin

SOURCE: American Heart Association, U.P.E.T.

Thus if kidney cells could be transported to space, separated as to cell function, and returned to earth in a viable condition, only the urokinase-producing cells would have to be propagated in earth-based facilities.

3. POTENTIAL IMPACT OF SPACE PROCESSING ON CASE STUDY DISEASES

3.1 MODELLING OF PRESENT AND FUTURE TREATMENT SYSTEM IMPACTS ON SURVIVAL

3.1.1 Model Concepts

In a quantitative approach to human disease process analysis, it is common to speak of "states" that a patient may occupy. Clearly, two such states could be "healthy" and "sick". A more detailed breakdown might include the states "healthy", "slightly affected", "sick", and "seriously affected". Of course, the choices of states are unlimited.

In modelling an individual's movement through the various states, we are in effect, defining the process that the disease takes. In mathematical terminology, we are defining the "transitions" allowed and the "likelihood" of each transition. For example, healthy people can go from the "healthy" state to the "sick" state, and a sick person can go from the "sick" state to the "healthy" state. Allowing "death" to be one state, we note that it is possible for persons in the "sick" state to go to the "death" state, but not vice versa. It is most useful to make a diagram of the possible states and the transitions allowed. Figure 3.1.1 illustrates such a diagram. A more complicated example illustrates a more realistic problem, as portrayed in Figure 3.1.2. This example illustrates a particular structure to the problem under analysis. Sick people can become healthy without any treatment and without a doctor's attention. Sick people can administer Treatment No. 1 to themselves, but not Treatment No. 2. If a doctor is seen, then both treatments are viable. Death can be reached from any state directly, except from "Under Doctor's Care". Here it is assumed that treatment is immediately given, after which the patient either transitions to the "healthy" state or to the "death" state. How one defines the problem structure dictates the definition of states and the allowable transitions among them.

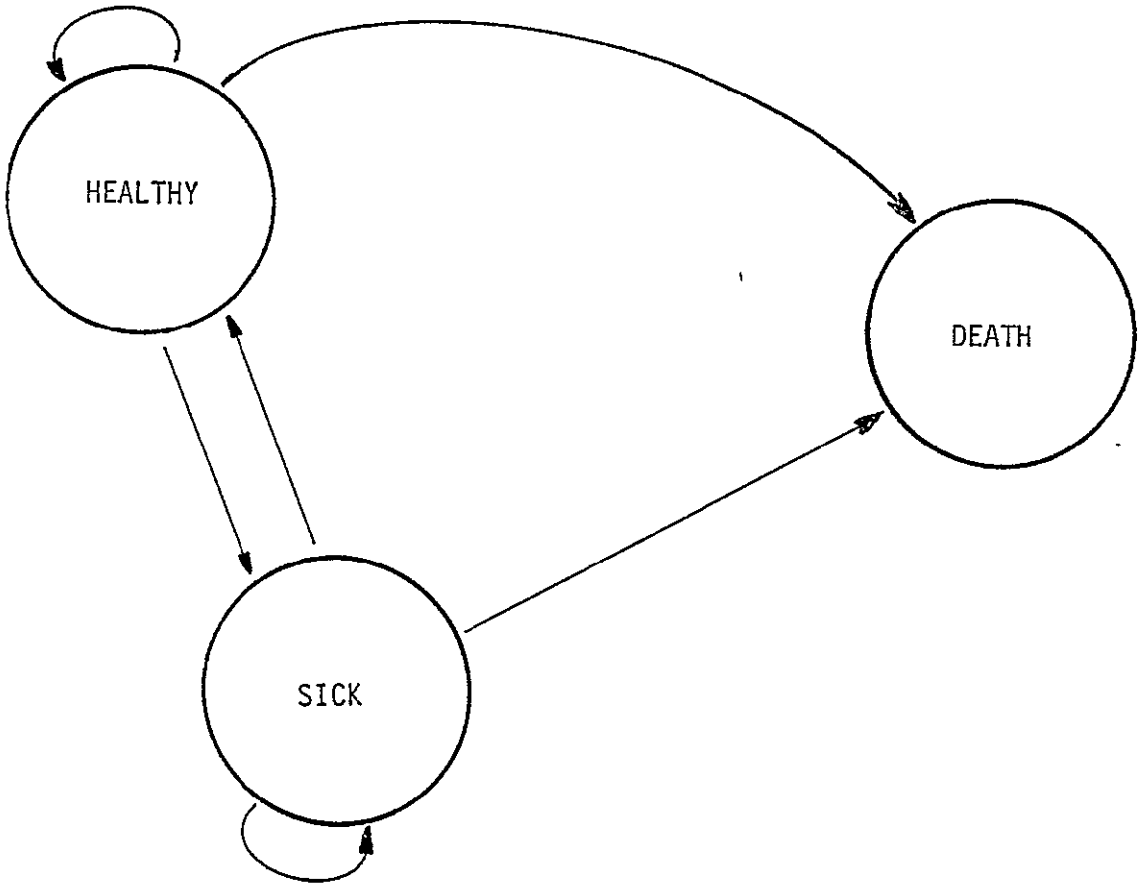


FIGURE 3.1.1 SIMPLE EXAMPLE OF ALLOWABLE TRANSITIONS AMONG DISCRETE STATES

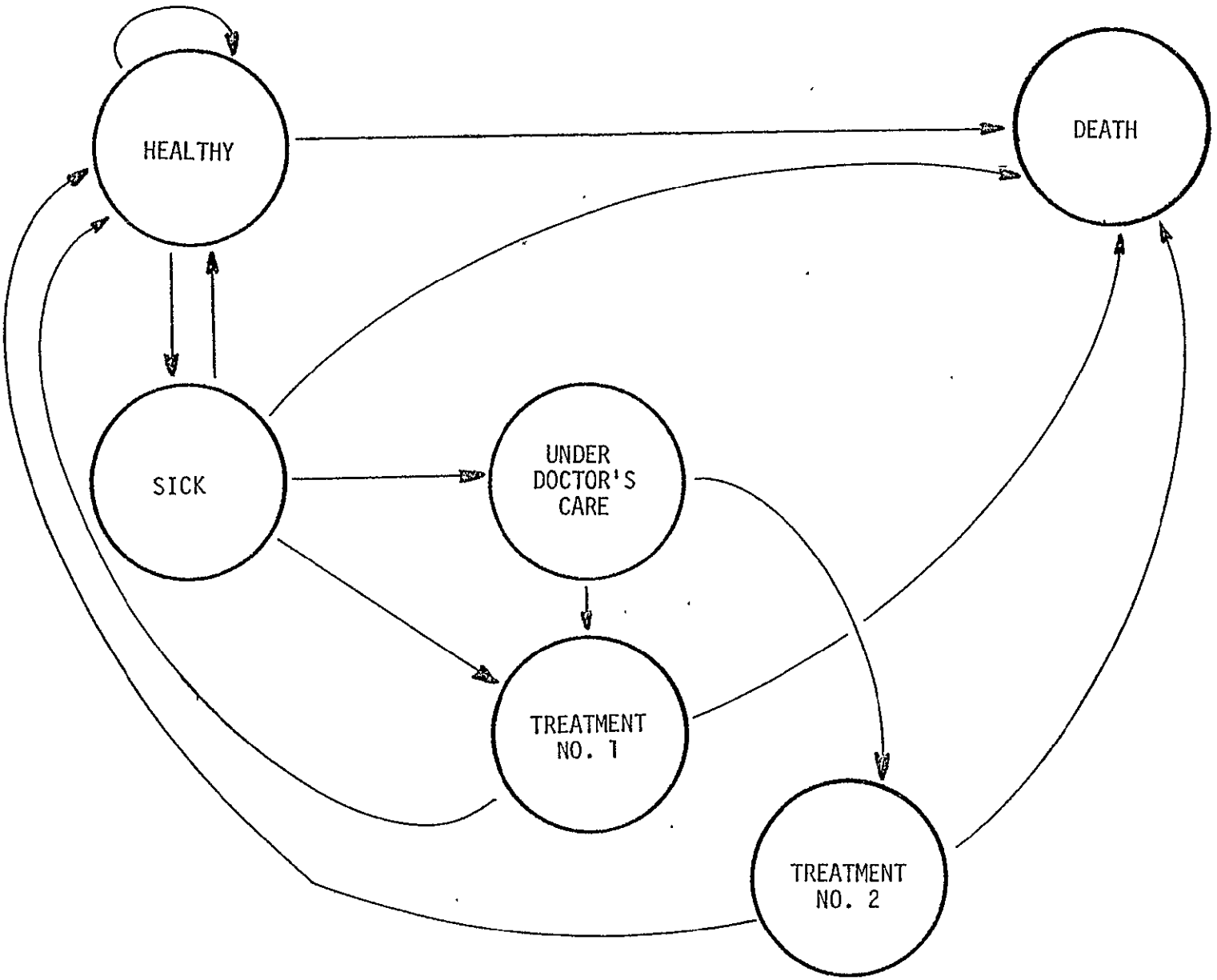


FIGURE 3.1.2 EXAMPLE OF ALLOWABLE TRANSITIONS AMONG DISCRETE STATES

The next step in defining a mathematical model such as this is to indicate the likelihood of each possible transition. That is, if a patient is in State i, what is the probability he will transition to State j? These probabilities can be written alongside the transition arrows as shown in Figure 3.1.3.

In this example, 90% of healthy people remain healthy; 9% contract the disease under question; 1% die of other causes. Once sick, a patient has a 10% change of becoming healthy without doing anything. He has a 10% chance of dying immediately from the disease; there is a 60% chance he will seek a doctor's care; and there is a 20% chance he will administer Treatment No. 1 to himself. If he goes under a doctor's care, 25% of the time, the doctor will administer Treatment No. 1 and 75% of the time, the second treatment. Of those receiving the first treatment, there is a 50 - 50 chance of surviving. Of those receiving the second treatment, there is a 95% chance of survival.

Having stated the transition probabilities, we identify now the times at which transitions are allowed. In a "discrete" process, the transitions occur at predetermined times, such as once every day, or once every hour. If the transitions can occur at any point in time, and if this time depends only on the current state and the state to be transitioned to, the process is called "continuous". For example, the time in State "Treatment No. 1" may be one day, while the time in State "Treatment No. 2" may be one week.

The final issue of concern in such a model (which our examples already implicitly assumes given) is whether or not the process is "Markovian". If the likelihood of transitioning from State i to State j depends only on i and j, and in no way depends on what states have been occupied prior to arriving in State i, we call the process "Markovian". Otherwise, it is called "Non-Markovian". In our example, having stated the transition probabilities in the manner we have, we have already assumed the process to be Markovian. For example, we have assumed that a patient has a 50 - 50

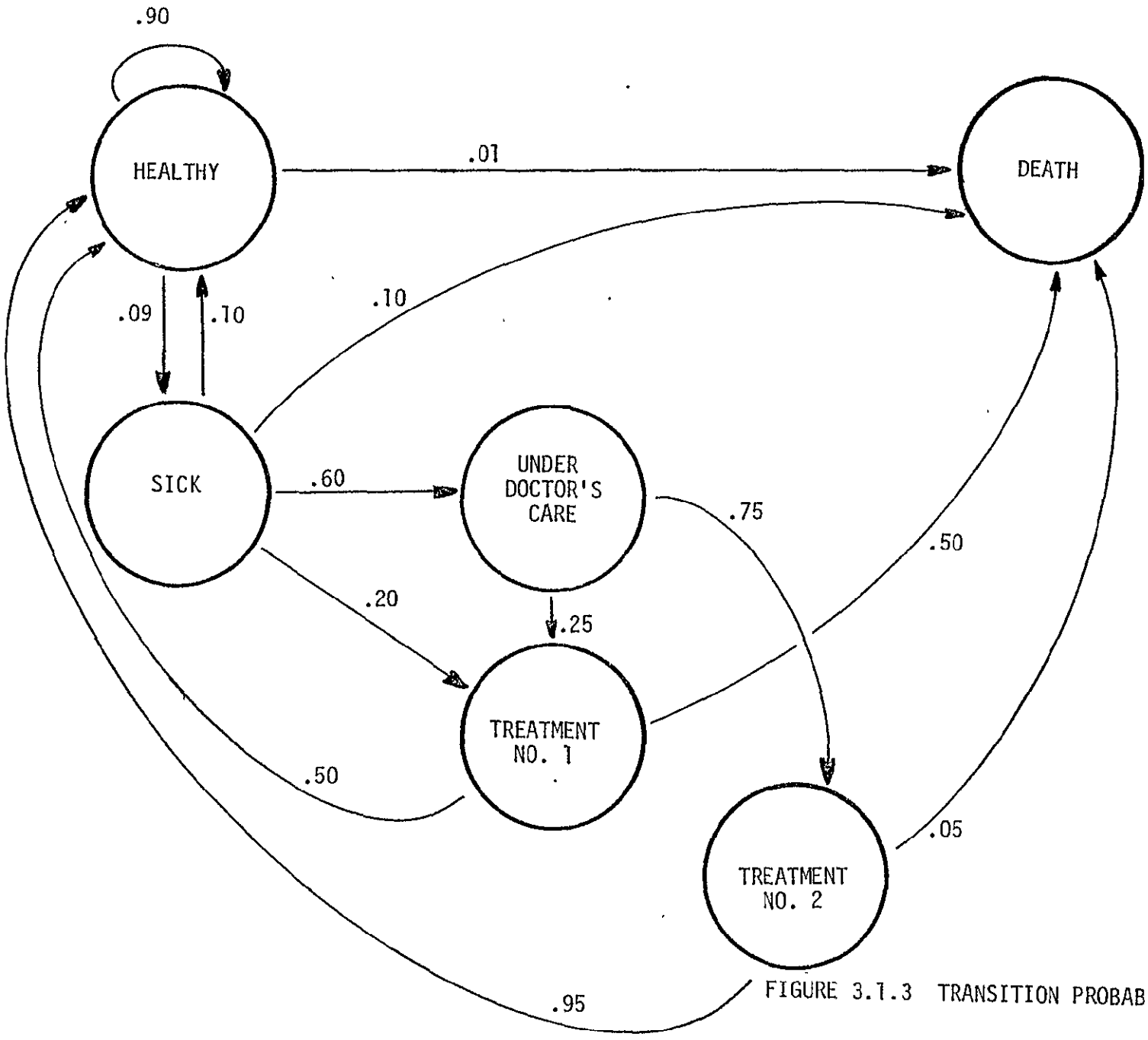


FIGURE 3.1.3 TRANSITION PROBABILITIES

chance of survival after Treatment No. 1, regardless of whether it is self-administered or given by a doctor. If this assumption is not valid for a given problem, what is required is a more detailed breakdown of the states in order to maintain the Markovian property. Figure 3.1.4 illustrates such a change to the model.

Through a redefinition of the states, we have maintained the Markovian property and have distinguished the likelihood of success with self-administration of the first treatment from that administered by a doctor.

The benefit of maintaining the Markovian property is that most mathematical results are simplified and the characteristics of the process easily understood and described. With the availability of modern high-speed computers, however, the necessity of making compromising assumptions in order to maintain the Markovian property has been lessened. Today, more realistic modelling can be utilized through simulation techniques wherein each transition is randomly simulated. The history of the transitions can be kept and utilized to the extent necessary to determine subsequent transitions. Additionally, probability distributions and other characteristics can be both used and determined through the simulation process.

3.1.2 Model

In the study of the effect of biological space processing, we chose the area of lymphocyte cell separation, and urokinase cell separation, and then on specified disease treatments, we specifically address the diseases known as End Stage Renal Disease (ESRD) and pulmonary embolism. The application of the model to the two disease treatments will be covered separately.

The treatments for ESRD known today are dialysis and transplant and for pulmonary embolism, surgery and the administration of the drug heparin. As stated earlier in this report, it is believed that through lymphocyte separation in space, a better understanding of the body's immunological system will come about, resulting in better tissue matching and hence, a greater success rate in transplant operations.

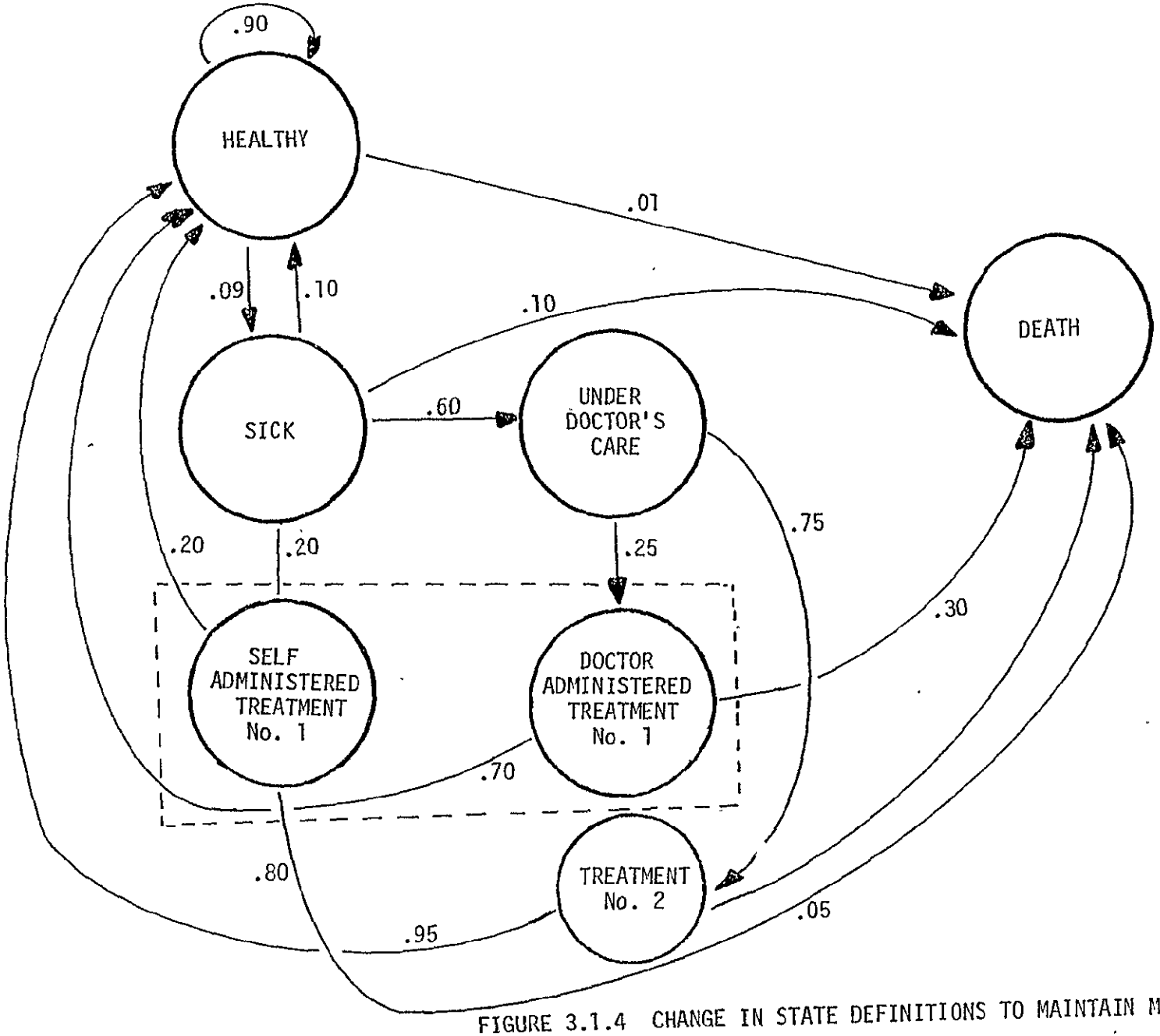


FIGURE 3.1.4 CHANGE IN STATE DEFINITIONS TO MAINTAIN MARKOVIAN PROPERTY

Initially eight states were defined as shown in Figure 3.1.5. In this figure the possible transitions are shown. Note that all five states encircled are possibly reached after contraction of ESRD. These five states were singled out for the model thereby ignoring healthy people and those who had kidney disease, but not ESRD. We defined a discrete Markov Process for these five states, dictating that each year, a transition would occur (possibly resulting in no movement at all, but transitioning back to the same state).

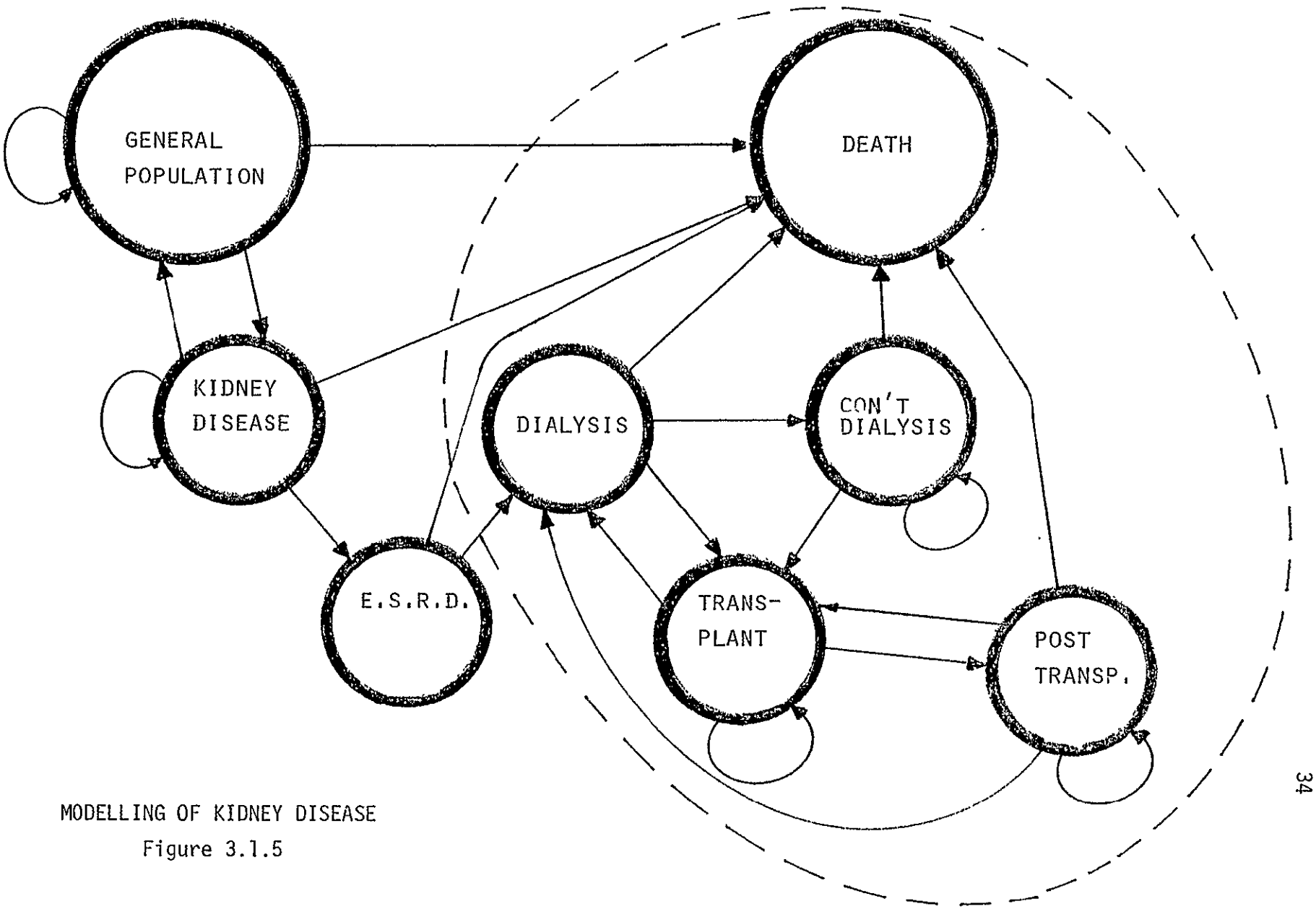
What we desired to collect were a host of statistics that would allow us to compare the potential benefits of space processing of lymphocyte separation. We defined three cases with which to exercise the model: (1) current status; (2) partial improvement due to space processing; and (3) optimistic improvement due to space processing.

Among the statistics we collected for each case were:

(1) How long did the patient live after contracting ESRD?
(2) How many years after contracting ESRD did the patient enter each state?
(3) How many years did the patient "reside" in each state?
(4) Cost to Public Sector
(5) Cost to Private Sector

Through consultation with experts in the area of kidney disease and kidney transplants, and by absorbing as much data as were available on the problem, we determined transition probabilities for each of the three cases.

A convenient method used to represent the transition probabilities is through a matrix. The matrix is arranged with the present states listed vertically on the left of the matrix and the states which can be entered horizontally across the top. Thus, by following the column across the matrix the probabilities can be seen for entering any other state. There are certain transitions that are not possible and those transition boxes are darkened on the matrix in the figures (or given a value of zero). Figures 3.1.6, 3.1.7 and 3.1.8 show the transition matrix for each of the three cases of kidney disease treatment.



MODELLING OF KIDNEY DISEASE

Figure 3.1.5

	1ST YEAR DIALYSIS	CON'T DIALYSIS	TRANSP.	POST TRANSP.	DEATH
1ST YEAR DIALYSIS		.7	.2		.1
CON'T DIALYSIS		.92	.02		.06
TRANSPLANT	.45		.03	.42	.10
POST TRANSPLANT	.125		.03	.82	.025
DEATH					1.0

FIGURE 3.1.6 PROBABILITY MATRIX ESRD BASELINE CASE

SOURCE:

Probability transitions determined from analyzing the statistics on the number of persons contracting ESRD annually, the number receiving dialysis, the number receiving transplants and the estimates of the percent dying the first year of ESRD. Sources include:

- House of Representatives, Hearings Before the House Subcommittee on Oversight on Medicare's End-Stage Renal Disease Program, G.P.O., June 24 - July 30, 1975.
- National Dialysis Registry, National Institute of Arthritis and Metabolic Diseases, N.I.H., Bethesda, Maryland, October 1, 1975.
- Advisory Committee of the Renal Transplant Registry, The Twelfth Report of the Human Renal Transplant Registry, J.A.M.A., August 18, 1975.
- Rogosin Kidney Center, Annual Report, The New York Hospital - Cornell Medical Center, New York, New York 1975.

	1ST YEAR DIALYSIS	CON'T DIALYSIS	TRANSP.	POST TRANSP.	DEATH
1ST YEAR DIALYSIS		.60	.30		.10
CON'T DIALYSIS		.85	.09		.06
TRANSPLANT	.30		.03	.60	.07
POST TRANSPLANT	.10		.03	.85	.02
DEATH					1.0

FIGURE 3.1.7 PROBABILITY MATRIX OF ESRD PARTIAL IMPROVEMENT CASE

SOURCE:
Probability transition determined mainly by utilizing the transplant success rate being experienced at the Rogosin Kidney Center with a projection of increased length of time before rejection of the transplant. See:

- Rogosin Kidney Center, Annual Report, The New York Hospital - Cornell Medical Center, New York, New York, 1975.

An assumption was made that if the survival rate for kidney transplants was lower than for dialysis more patients and doctors would elect that treatment made than present. Thus the probability of transition to the transplant state was arbitrarily increased.

	1ST YEAR DIALYSIS	CON'T DIALYSIS	TRANSP.	POST TRANSP.	DEATH
1ST YEAR DIALYSIS		.45	.45		.10
CON'T DIALYSIS		.79	.15		.06
TRANSPLANT	.16		.02	.77	.05
POST TRANSPLANT	.05		.02	.91	.02
DEATH					1.0

FIGURE 3.1.8 PROBABILITY MATRIX OF ESRD OPTIMISTIC IMPROVEMENT

SOURCE:
Probability transitions determined after detailed discussions with Rogosin Kidney Center medical staff and recognition of the maximum impact to be the 60% of rejection cases sited as caused by the bodies immunological response.

Costs were obtained through research on government testimony, Social Security Benefits reports, Office of Management and Budget reports and an organization composed of dialysis patients. The initial cost factors used are shown below and detailed breakdowns appear in the appendix. These figures were inflated at a 6 percent compound interest rate to reflect 1985 dollars (the first year benefits can be expected).

State	Public Sector Costs	Private Sector Costs
First Year Dialysis	$16,200	$15,250
Continuing Dialysis	21,300	7,100
Transplant	13,000	6,500
Post-Transplant	0	- 500
Death	0	2,500

In operating the model for any of the three cases, an individual once contracting ESRD was assumed to enter in the first state -- "First Year Dialysis". At the first transition, he was randomly placed in the second, third, or fifth states (since these are the only states possible). On each subsequent transition, the patient moved from state to state according to the probabilitlies given in the transition matrix, until the "death" state was reached, at which point an iteration was complete. Statistics were gathered for that patient as he moved from state to state. This process was repeated many times (Monte Carlo Simulation) in order to have reasonable confidence that the statistics generated were correct.

Results of the analysis are presented in Section 3.2.

The treatments of thromboembolic diseases, specifically pulmonary embolism in this study, are heparin therapy and surgery. Additionally, the use of the drug urokinase is speculated to become an effective treatment regime once it receives FDA approval for use in the United States and becomes commercially available. It is anticipated that not only will urokinase lyse, or dissolve, clots of the lungs, but also have the same effect on clots in other parts of the body.

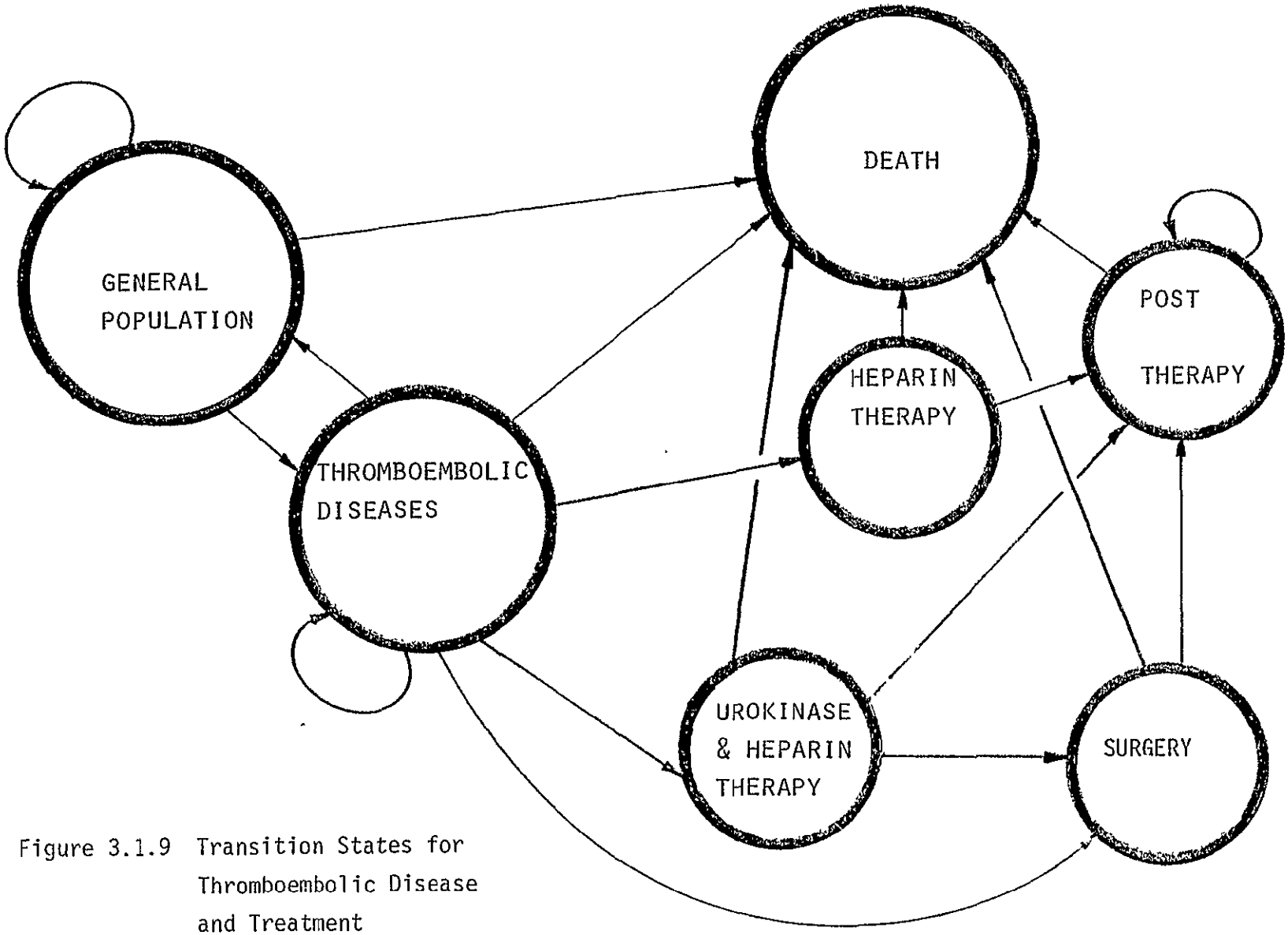


Figure 3.1.9 Transition States for Thromboembolic Disease and Treatment

Initally seven states were defined as shown in Figure 3.1.9. For the simulation all states were utilized except the state representing the general population. The state of thromboembolic diseases was not eliminated due to the uncertainty of the transition probabilities for the treatment modes. The uncertainty exists because urokinase is not yet available and thus, no utilization rate exists.

What we desired to collect were a host of statistics that would allow a comparison of the pre and post introduction of urokinase as a treatment regime, and any impact the space processing may have on drug costs. Four cases were defined: (1) current status; (2) initial improvement due to the introduction of urokinase; (3) partial improvement due to increased use of urokinase and a reduced mortality from its use; and, (4) optimistic improvement with increased use of urokinase, decreased mortality and reduced cost of urokinase.

Among the statistics we collected for each case were:

(1) How long did the patient live after contracting pulmonary embolism;
(2) How long did the patient "reside" in each state, particularly the post-treatment state which represents recovery;
(3) Costs to the individual.

Transition probabilities were determined for each of the four cases through consultation with experts familiar with urokinase efficacy and by analyzing the literature on pulmonary embolism. The transition probability matrices are given for each of the four cases in Figures 3.1.10, 3.1.11, 3.1.12, and 3.1.13.

Cost estimates are based on actual experience in the case of a surgeon's fees, to an approximation based on costs in other countries in the case of urokinase. The degree of severity of an emboli determines costs and the range is great. One patient may need surgery followed by intensive care while another patient may be treated medically, only to have to undergo surgery later. The average cost figures used are listed below:

	T.E. DISEASE	HEPARIN	SURGERY	UROKINASE	POST-LYSE	DEATH
T.E. DISEASE	.05	.75	.11	.0		.09
HEPARIN		.05	.06	.0	.80	.09
SURGERY		.03	.02	.0	.83	.12
UROKINASE			.0	.0	.0	1.0
POST-LYSE	.10				.88	.02
DEATH						1.0

Figure 3.1.10 Probability Matrix of Thromboembolic Baseline Case

SOURCE:

Probability transitions determined by analyzing the statistics on pulmonary embolism and urokinase experimentation. Sources include:

- Abstracts of the International Symposium on Urokinase, Rome Italy, 1975.
- National Heart, Blood Vessel, Lung and Blood Program, Vol. 1 National Heart and Lung Institute Summary, National Heart and Lung Institute-National Institutes of Health, DHEW, 1973, p. 10.
- American Heart Association, The Urokinase Pulmonary Embolism Trial, A National Cooperative Study, Monograph #39, Supplement to Circulation, April 1973, and "Urokinase-Streptokinase Embolism Trial, Phase 2 Results" J.A.M.A. Sept. 16, 1974, Vol. 229, No. 12.
- Meeting with Grant Barlow, Abbott Labs, N. Chicago, Ill. Feb. 2, 1976

	T.E. DISEASE	HEPARIN	SURGERY	UROKINASE	POST-LYSE	DEATH
T.E. DISEASE	.05	.30	.06	.50		.09
HEPARIN		.05	.03	.15	.68	.09
SURGERY		.02	.02	.06	.78	.12
UROKINASE			.03	.06	.82	.09
POST-LYSE	.10				.88	.02
DEATH						1.0

Figure 3.1.11 Probability Matrix of Thromboembolic Initial Improvement Case

SOURCE:
Probability transitions determined by analyzing the statistics on plumonary embolism and urokinase experimentation. Sources include:

- Abstracts of the International Symposium on Urokinase, Rome Italy, 1975.
- National Heart, Blood Vessel, Lung and Blood Program, Vol. 1 National Heart and Lung Institute Summary, National Heart and Lung Institute-National Institutes of Health, DHEW, 1973, p. 10.
- American Heart Association, The Urokinase Pulmonary Embolism Trial, A National Cooperative Study, Monograph #39, Supplement to Circulation, April 1973, and "Urokinase-Streptokinase Embolism Trial, Phase 2 Results" J.A.M.A. Sept. 16, 1974, Vol. 229, No. 12.
- Meeting with Grant Barlow, Abbott Labs, N. Chicago, Ill. Feb. 2, 1976.

	T.E. DISEASE	HEPARIN	SURGERY	UROKINASE	POST-LYSE	DEATH
T.E. DISEASE	.05	.14	.06	.66		.09
HEPARIN		.05	.03	.20	.63	.09
SURGERY		.02	.02	.06	.78	.12
UROKINASE			.03	.06	.86	.05
POST-LYSE	.10				.88	.02
DEATH						1.0

Figure 3.1.12 Probability Matrix of Thromboembolic Partial Improvement Case

SOURCE:
Probability transitions were determined by lowering the mortality rate and selecting a higher probability for transitioning to the urokinase treatment state.

	T.E. DISEASE	HEPARIN	SURGERY	UROKINASE	POST-LYSE	DEATH
T.E. DISEASE	.02	.14	.06	.76		.02
HEPARIN		.05	.03	.20	.63	.09
SURGERY		.02	.02	.06	.78	.12
UROKINASE			.03	.06	.89	.03
POST-LYSE	.10				.88	.02
DEATH						1.0

Figure 3.1.13 Probablility Matrix of Thromboembolic Optimistic Improvement Case

SOURCE:
Probability transitions were determined by lowering the mortality rate and selecting a higher probability for transitioning to the urokinase treatment state.

State	Private Sector Costs
Heparin Therapy	$5580.
Surgery	6440.
Urokinase	
Normal	5970.
Optimistic	4140.
Death	2500.

3.1.3 Other Medical Treatment Survival Rate Models

Although the model described in the previous subsection was derived by analysis of the health care systems and without specific regard to similar work previously performed for the sake of medical analysis, the precedence for such an approach as this is firmly established in the literature.

Burton, Damon, and Dellinger[39] have described procedures to estimate transition probabilities using a combination of expert judgment and empirical evidence. This work was specific to patient states for the elderly. A patient was classified into one of thirty-two states (Pfeiffer Patient States)[40], reflecting the patients physical health, mental health, social resources, economic resources, and mobility.

Cretin[41], in a doctoral thesis in modelling patient survival of myocardial infarction patients studied the short- and long-term effects of changes in pre-hospital and in-hospital care on survival after heart attacks. A state transition model from heart attack to death was defined.

Bush, Chen and Zaremba[42] used Markov processes to evaluate treatment programs. Weiss and Zelen[43] used them to analyze the benefit of clinical trials.

An exhaustive survery was not undertaken, rather the above cases served to substantiate the credibility of the model developed here. We have listed the above only as a sample of the application of this modelling procedure to the analysis of medical processes.

3.2 Model Runs and Results

3.2.1 ESRD

One thousand iterations were run for the probability transition matrices in Figures 3.1.6, 3.1.7 and 3.1.8 utilizing a Monte Carlo simulation. The results of the simulation are given in Table 3.2.1.

As the transplant rejection rate and the death rate decrease, the life expectancy of the average patient increases. The assumption was made that as the kidney transplant rejection rate decreases, more patients will elect that form of treatment and thus the probability of transitioning to the transplant state was increased in the optimistic case. Through a reduced mortality for transplant patients, and an increase in the number of patients choosing that treatment, the expected patient life after contracting ESRD was extended by almost 4 years in the optimistic case. Because the costs to both the government and the individual are both less for the post-transplant state a reduced cost situation is encountered, even with the extended four years of life.

3.2.2 Pulmonary Embolism Disease

The probability matrices in Figures 3.1.10 to 3.1.13 were run utilizing a Monte Carlo simulation technique. The results of the runs are given in Table 3.2.2.

Equal mortality rates were encountered in the urokinase efficacy experiments conducted in the United States. When this was entered in the initial improvement case, no increase in longevity was witnessed, but an increase in costs was encountered due to the high expected price of urokinase.

In a parametric analysis the mortality was reduced in the partial and optimistic improvement case. The result was a sharp increase in the mean life expectancy of almost 13 years in the optimistic case.

Table 3.2.1 RESULTS OF ESRD TREATMENT SIMULATION

MEASURE	BASELINE		PARTIAL IMPROVEMENT		OPTIMISTIC IMPROVEMENT	
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION
"Age" * AT DEATH	13.72	10.18	15.05	10.88	17.11	11.44
COST TO PUBLIC SECTOR PER INDIVIDUAL OVER INDIVIDUAL'S LIFE						
UNDISCOUNTED	430,262	(365,221)	324,313	(287,594)	195,514	(198,158)
DISCOUNTED AT 10%	208,280	(132,714)	162,947	(113,368	108,231	(93,147)
COST TO PRIVATE SECTOR PER INDIVIDUAL						
UNDISCOUNTED	151,362	(126,065)	124,584	(107,105)	95,597	(76,894)
DISCOUNTED	73,843	(45,563)	62,246	(41,116)	41,890	(34,725)

* THROUGHOUT, "AGE" IS MEANT TO BE YEARS AFTER CONTRACTING ESRD

TABLE 3.2.2 RESULTS OF THROMBOEMBOLIC TREATMENT SIMULATION

MEASURE	BASELINE CASE		INI. IMPROV. CASE		PAR. IMPROV. CASE		OPT. IMPROV. CASE	
	MEAN	STAN. DEV.	MEAN	STAN. DEV.	MEAN	STAN. DEV.	MEAN	STAN. DEV.
"AGE"* AT DEATH	17.42	(10.98)	17.11	(11.02)	21.64	(17.88)	30.79	(18.17)
COST TO PRIVATE INDIVIDUAL	13,555	(8,876.)	14,356	(9,748.)	17,477	(14,151)	16,963	(10,461)

* "AGE" IS YEARS AFTER CONTRACTING PULMONARY EMBOLISM

4. POTENTIAL ECONOMIC BENEFITS OF BIOPROCESSING IN SPACE FROM CASE STUDY DISEASE TREATMENT IMPACT

The total potential economic benefits of space processing of biological material are beyond the scope of this study, only the benefits that may accrue from the two case studies are discussed here. The case study benefits will be discussed by disease.

4.1 Estimation of Benefits to ESRD Treatment

4.1.1 Reduction in Number of Deaths

The treatment which was expected to benefit from space processing was kidney transplant treatment. Table 3.2.1 indicates the impact of a reduced expected mortality rate resulted in an expected increase in life expectancy, or extended years of survival after the onset of ESRD. The optimistic case realized a mean increase of almost four years of life expectancy after onset of ESRD. Thus, if the reduced mortality comes to pass as a result of improved immunology techniques which were affected by space processing the average person contracting ESRD could expect to live 17 years after contracting ESRD, rather than the previously expected 13. The standard deviation for the optimistic case is over 11 years meaning that the person might only live 3 more years or last as long as 28 years more. When this extension of life expectancy is experienced by the 10,000 new ESRD patients, each year the number of reduced annual deaths, or prolonged lives becomes significant.

Caution must be used in over projecting the total years of life extension as the age of the patient at the time of contracting ESRD must be considered.

4.1.2 Increase in Number of Kidney Transplants and Decrease in Rejection Rate of Transplants

It is assumed that if lymphocytes can be successfully separated into subgroups that an enhancing antibody can be developed which may significantly decrease

the 60 percent transplant failure rate caused by the body's rejection. If this rejection rate decreases, it can be assumed that a significant increase in the number and percent of patients receiving transplants will occur. This is reflected in the probability increase from .20 to .45 in Figures 3.1.6 and 3.1.8 in the transition from first year dialysis to transplant.

A concomitant increase in demand to secure sufficient numbers of cadaver kidneys would occur, but this is considered surmountable with improved donor education programs, universal donor cards, and so forth.

The increase in the number of people with functioning kidney transplants would yield a healthier population, with a decrease in dependence on machine dialysis.

4.1.3 Reduction of Costs from Reduction in Number of Patients on Dialysis

Once a successful kidney transplant has occurred, the costs to both the federal government and the private individual decrease due to the lack of a need for medical intervention except for check-ups. Comparing the baseline case with the optimistic case, the model run results shown in Table 3.2.1 indicate a reduction of expected discounted individual costs from $73,843 to $41,890. These figures are the expected costs incurred during one individual's lifetime. This reduction occurs despite an increase in the number of years for which costs can accrue.

The reduction in costs to the government sector is equally dramatic. Again, taking the optimistic case compared to the baseline case, the potential expected discounted reduced government costs for one individual is about $100,000 over a mean 17 years, despite an extended expected longevity. This is in large part due to the lack of government incurred costs for a successfully transplanted ESRD patient.

To gauge the potential magnitude of benefits possible from reduced government costs in ESRD treatment determined from this preliminary analysis a specific block of time will be examined wherein the baseline case will be compared to the partial improvement and the optimistic case. The time period begins in 1985, the soonest that benefits are expected to begin after the Space Shuttle becomes operational, and extends until the year 2000. The time block is thus 15 years. Costs determined in 1975 dollars were inflated at a 6 percent compound interest rate for ten years thus yielding 1985 dollars. Cost streams were then generated for 10,000 patients starting in each of the fifteen years and continuing until the year 2000. These cost streams were generated for the baseline case, the partial improvement case and the optimistic case. Each of the cost streams was discounted back to 1985 thus yielding a comparison of discounted cost streams. The total expected government cost for this time block was $12.7 billion ($1985, 10% discount rate) while the partial improvement case was $10.3 billion ($1985; 10% discount rate) and the optimistic improvement case costs were $7.2 billion ($1985; 10% discount rate). Thus, the total potential cost saving benefit to the government may be between $2 and $5 billion over a 15 year period.

These benefits are considered for the U.S. only. Outside the United States where dialysis machines may not be as readily available the benefits may be relatively more substantial, although perhaps predominately to the individual.

4.1.4 Increase in Benefits to those Surviving Transplantation beyond Normal Rejection Period.

If space processing can contribute to developing techniques to reduce kidney transplant rejection, the people realizing such changes would realize several benefits. First would be added years of life. Second would be an opportunity to earn income during the added years for transplant patients are often healthy enough to lead fairly active lives.

4.1.5 Total Benefits for ESRD Treatment

The potential total benefits for ESRD treatment include the extension of life expectancy for ESRD patients and the savings of billions of dollars of costs of alternative treatments which would not be necessary if transplant acceptance rates were improved.

During a fifteen-year period from 1985 to 2000, an approximate total of 150,000 people will be medically suitable for treatment of End Stage Renal Disease. It has been determined from the use of the model that on the average a person could live 4 years longer from changes in medical treatment developed as a result of space processing. If such measures were to come about and were implemented on a wide scale then each of the 150,000 people stands to live 4 years longer, on the average. Thus during the life time of these people, which would undoubtedly stretch beyond the 15-year time period, but whose treatment would begin in that period, a total life extension of 600,000 man years may be obtained.

The potential economic benefit to the government may be $2 to $5 billion ($1985; 10% discount rate) over a fifteen year period. The potential benefit to private individuals would be smaller, but significant.

4.2 Estimation of Benefits to Pulmonary Embolism Treatment

4.2.1 Reduction in Number of Deaths

Initial experimentation with urokinase has not yielded any change in mortality. However, indications from foreign users of the drug are that a reduction in mortality may occur. It is for this reason that a decreased probability of death was entered in the transition probability matrix of the partial improvement and optimistic improvement cases. This resulted in a significant increase in the expected life expectancy of a pulmonary embolism patient, 13 years in the optimistic case.

4.2.2 Decreased Hospital Stay

The one characteristic that urokinase has unquestionably exhibited is the ability to "clear up" clots within short periods of time. It is anticipated that this will yield reduced mortality. Due to the internal nature of clots and the life-critical nature of the disease, it is not yet clear what test procedures and other procedures can be foregone during the treatment of a pulmonary embolism with urokinase, at present it appears that urokinase will not reduce total hospital stays, but may reduce the need for some expensive procedures like surgery. The price of urokinase may be several thousand dollars for a 4 million unit dose[44] thus offsetting the cost of a more lengthy hospital stay.

4.2.3 Reduced Urokinase Production Costs

Propriety information prohibits complete exploration of this question. It is known that the cost of one dose of urokinase utilizing the urine extraction technique was about $1,500, the selling price would undoubtedly be considerably higher. The selling price of urokinase outside the United States is similarly high. The cost of urokinase from the tissue culture growth technique is not known.

Grant Barlow of Abbott Labs in Chicago has related that less than 5 percent of kidney cells are capable of producing urokinase,[45] yet they will have to propagate all of a kidney's cells before they can extract the specific cells they desire. Dr. Barlow has calculated that Abbott Labs would experience decreased production costs if they could effectively fractionate the urokinase producing cells in space from the other kidney cells prior to propagation, at an estimated cost of $300 or $400 per pound for space processing.

Limitations of time and resources as well as limited access to proprietary information have not permitted a thorough analysis of the potential cost reduction. However, a parametric analysis was performed with the model using a 10:1 cost reduction for the price of urokinase. If the expected costs are compared for the first few years, the optimum improvement case proves less expensive. No perceived total expected costs were achieved for the 30-year duration but it must be recalled that the life expectancy after contracting a pulmonary embolism is virtually doubled in the optimistic improvement case, and allowing for patients to repeat treatment during that time period, it would be slightly higher. In addition to reduction of urokinase production costs, it appears conceivable that the volume of production may be greater with a space processing segment in the manufacture of the drug due to a comparative reduction in the space needed to grow tissue cultures.

4.2.4 Total Benefits for Thromboembolic Disease Treatment

The benefits of space processing in the manufacture of urokinase are difficult to determine this early in the understanding of treatment procedure utilizing urokinase and without more definitive data. Clearly if urokinase can reduce mortality a benefit of longevity would result and increased productivity and income earning potential which would not be possible under present mortality rates. If space processing can reduce costs in the manufacture of the drug, this savings would be passed on to the patient relative to the potential cost of complete ground-based processing. The magnitude of these benefits cannot be measured due to limited access of proprietary information and the need for better clinical data on urokinase efficacy.

5. ALTERNATIVE TECHNOLOGY POTENTIALS AND CONCLUSIONS

5.1 Alternative Technology Potentials

Two alternative technologies which appear potentially capable of performing cell separation are the fluorescent-activated cell sorting and affinity chromatography. The first technique utilizes a process whereby certain cells are tagged with fluorescein and then sent through an orifice at a high rate of speed. At the moment that each drop containing a cell is sent out, an electrical charge is given to the droplet based on predetermined characteristics which are measured with the aid of a laser. The electrically charged cell droplet streams are then pulled into one of several test tubes by passing through an electrical field.

The fluorescent-activated cell sorter is available commercially but has not yet undergone use in testing and experimentation necessary to determine whether this apparatus is appropriate for lymphocyte subgroup separation or urokinase producing cell separations. Questions have been raised by the biomedical community[46] regarding cell viability after (and if) the apparatus can successfully perform the separations. Further testing of cell separations using the fluorescent-activated cell sorter will be needed to determine its full potential. Several years of time and large expenditures of funds are needed before determination can be made. Based on discussions with biomedical researchers who are theorizing that electrophoretic separation in space will be successful, the fluorescent-activated cell sorter cannot yet be ruled out as a potential alternative technology.

There have been developed affinity chromotography methods, which make use of the property of biospecific absorption, or the affinity of an enzyme for an insolubilized ligand, for the recovery and purification of cells. Both the specificity of initial binding to the insolubilized liquid and the specificity of subsequent elution from this material are key aspects to the success of this technique. These methods can provide a high degree of

purification, together with high yield, in one rapid step. Some research is underway to determine if cell sorting of lymphocyte subgroups can be made.[47] This technique has been successful in separating T from B lymphocytes.[48]

Several other alternative technology candidates, such as the ultra-centrifuge, have been ruled out based on technical inability to perform the necessary functions. At the time of this writing, no other presently developed alternative technologies are known which can successfully separate large cells. It is conceivable that another technology could be developed before the Shuttle has become a reality.

5.2 Conclusions

The purpose of this study was to perform a preliminary analysis of the potential benefits that may accrue from space processing of biological materials. Two case studies were chosen, the separation of lymphocyte cells into subgroups, and the fractionation of kidney cells into urokinase producing cells. Both case studies would utilize the technique of electrophoresis as the specific separation technology in space. Although both case studies would utilize the same separation technique the purpose of the separation is different in each case. In the lymphocyte separation case, it was determined that, if successful, the separation would help further medical research; while urokinase producing cell separation would be a cost reducing production technique. The urokinase case would be a step in the direction of recurring space processing as distinct from space-based experimentation. In performing the preliminary benefit analysis, it was determined that adequate information existed for at least one disease treatment for each of the case studies.

While undertaking a systems analysis of the possible treatment modes for the diseases under examination, a model was developed to systematically gather statistics on the potential outcomes of changes in treatment brought about

by space processing. The model was sufficiently utilized to ascertain that it is a valuable tool in this type of analysis. The question remains, however, whether the information which has been utilized to date is sufficiently accurate to produce valid results. Investigation was not made into the probabilities of a successful space segment outcome, rather the space segment was treated deterministically - as a success.

This preliminary benefit analysis did find that within its limited scope, that if the space segment and certain ground-based research and processing are successful, the potential benefits in economic and life-extending measures are quite substantial. The ESRD treatment program presently funded on an 80 percent level by the government would stand to realize drastic cost reductions. The potential reduction in deaths and human suffering to be gained from space based experimentation, although less quantifiable, would be significant. In the case of pulmonary embolism, a similar life-extension type benefit would stand to be realized, but additionally a possible reduction in the production costs of urokinase would result.

The results of this preliminary analysis indicate that the federal government is in a position to benefit from continued support of bioprocessing in space. In addition to the traditional role of government support of high risk development support, the federal government stands to benefit directly in the case of End Stage Renal Disease which may cost the government upwards of one billion dollars per year for ESRD treatment if treatment changes to improve kidney transplant survival are not made.

6. RECOMMENDATIONS

Because of the magnitude of benefits indicated in this preliminary analysis of bioprocessing in space from two specific disease treatment applications of one space processing procedure, it is recommended that further research and analysis be conducted on the case studies utilized in this study; namely, the space-based separation of lymphocytes into subgroups and the separation of urokinase producing cells from other kidney cells. In performing this generic task the following subtasks are recommended:

a. It is recommended that the model developed for analysis of changes in costs and mortality of disease treatments be verified with more definitive data and comparison with actual statistics. In addition, the model should be improved to utilize multiple probability transition matrices, each one related to patient age or years since the disease was contracted. Additional patient transition states may be utilized to more discretely define a patient's progress.

b. Improvement in the data base is needed to permit more accurate benefit assessments. The need for improvement in the data base is particularly relevant for the urokinase treatment mode.

   More complete information is necessary regarding the technical capabilities of the medical procedures under study. It is recommended that a closer relationship be developed with technical sources in future work of this nature. An example would be for NASA to contract with a pharmaceutical manufacturer for technical information exchange.

c. That benefit analysis work be performed on other impactable treatments which could potentially result from successful space separation of lymphocytes and urokinase producing cells from kidney cells. Examples of other impacts would be organ transplants other than kidneys in the case of lymphocyte separation, and other thromboembolic diseases besides pulmonary emboli in the case of urokinase.

d. It is recommended that any future study in the area of treatment alteration benefits as a result of space processing be subjected to a risk analysis. The present study has treated the benefits in a binary fashion, that is either there are no benefits or they are the totals which have been mentioned. What is more useful to a decision-making body and to NASA is a probability distribution of a successful outcome.

To determine how to best commit assets, decision makers must forecast or guess the future. Uncertainty about the exact course of future events creates risk-fluctuations in the resulting costs, benefits, and cash-flow patterns. Decision making should explicitly take into account these uncertainties, which require the quantification of risk. In conventional analysis, basic input parameters and resulting computed parameters are treated as single-value functions, that is the values are assumed to be known with certainty, when in fact they are not. Risk analysis explicitly considers the uncertainty associated with the basic input parameters required for evaluating a venture and determining the resulting risk. Risk is measured in terms of the chance that key performance measures, financial and technical, will meet or exceed specified values.

The analysis of risk, then, requires adding a third dimension to the dimension of dollars and time of conventional analysis - namely, the dimension of uncertainty. This means that each major input assumption must be described, not just by single estimate, but by an entire range of possible values with an associated likelihood of the variable falling into various sectors within the range. In other words, the probability distribution of the key parameters must be specified as uncertainty profiles. Introducing uncertainty to the input parameters gives the derived or computed results an uncertainty dimension (probability density function), which, when replotted yields the risk profile. To

restate: Uncertainty refers to the chance of the input parameters taking different values. Risk refers to the resulting variability of computed performance parameters. Uncertainty makes space processing a probabilistic quantity. Therefore, benefits of space processing should be characterized by a probability distribution that represents the chance of achieving each of the possible disease treatments. ECON has considerable experience in the application of risk analysis to space technology and has developed several sophisticated computer-based mathematical models to perform such analysis.

In performing a risk analysis the entire development procedure is modelled from research and development,through the space segment to an operational mode where the new product, in this case new medical products, are marketed. At each of the intermediate steps a probability distribution is attained from experts in the field. Each expert is only consulted on the probable outcome of an event for which he has expertise. The output would be risk profiles of program success for each parameter such as costs, benefits, and new product development success.

In addition to the improvement of the benefit analysis of bioprocessing in space, it is suggested that a similar technique be applied to all proposed space processing scientific projects. If each space processing proposal could be evaluated in terms of potential economic payoff, then the scientific proposals could be ranked to provide decision makers with a measure with which to determine usage of a limited resource.

In the National Research Council paper on Costs and Benefits of Practical Applications of Space Systems [49], Kelley and others advocate that a cost-benefit discriminator be utilized to aid in making funding decisions. Naturally this would not be the only criteria used by decision makers, but it could provide a far more rigorous method for ranking and prioritizing proposed projects than presently exists.

An existing computer program for this purpose has been developed by ECON personnel using public funds[50]. The program evaluates multiple projects, and multiple costs within multiple budget constraints. The methodology has been funded and is completed, leaving only the operational use of the software to pursue this analytical and decision-aiding technique.

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      INTEGER YRS(15),A(8),NY(8),Z(8),CS,CSP,NITS(8)
      REAL P(15,8,8),C(8),CC(100),AVEA(8),SQA(8),AVEZ(8),SQZ(8),AVENY(8)
     1,SQNY(8),AVECC(100),SQCC(100),DUM1(429),DUM2(429),DCC(100),AVEDCC(
     2 100),SQDCC(100),
     3 PROB(8),D(8),DD(100),AVEDD(100),SQDD(100),DDD(100),AVEDDD(100),
     4 SQDDD(100)
      EQUIVALENCE (DUM1,AVEALP),(DUM1(2),AVEA),(DUM1(10),AVEZ),
     1 (DUM1(18),AVENY),(DUM1(26),AVETCC),(DUM1(27),AVEDTC),
     2 (DUM1(28),AVECC),(DUM1(128),AVEDCC),
     3 (DUM1(228),AVETDD),(DUM1(229),AVEDTD),(DUM1(230),AVEDD),
     4 (DUM1(330),AVEDDD)
      EQUIVALENCE (DUM2,SQALP),(DUM2(2),SQA),(DUM2(10),SQZ),
     1 (DUM2(18),SQNY),(DUM2(26),SQTCC),(DUM2(27),SQDTCC),
     2 (DUM2(28),SQCC),(DUM2(128),SQDCC),
     3 (DUM2(228),SQTDD),(DUM2(229),SQDTD),(DUM2(230),SQDD),
     4 (DUM2(330),SQDDD)
      NS = 6
      NSM1 = NS - 1
      NSM2 = NS - 2
      DO 99 L=1,429
      DUM1(L) = 0.
      DUM2(L) = 0.
99    CONTINUE
      READ(8,100) NIT
100   FORMAT(I5,F6.3)
      READ(8,100) MAXYR,DISC
      MXYRM1 = MAXYR - 1
      READ(8,101) C
101   FORMAT(8F10.2)
      READ(8,101) D
      DO 10 I=1,MAXYR
      READ(8,102) YRS(I),((P(I,J,K),K=1,NS),J=1,NS)
102   FORMAT(I5/(6F10.3))
      IF(I.GT.1) YRS(I) = YRS(I-1) + YRS(I)
      IF(YRS(I).GE.MAXYR) GO TO 20
10    CONTINUE
20    NI = I
      DO 125 L=1,NS
      NITS(I) = 0
125   CONTINUE
      DO 200 L=1,NIT
      DO 130 I=1,MXYRM1
      CC(I) = 0.
      DCC(I) = 0.
      DD(I) = 0.
      DDD(I) = 0.
130   CONTINUE
      TDD = 0.
      DTDD = 0.
      TCC = 0.
      DTCC = 0.
      DO 22 I=1,NS
      A(I) = MAXYR + 1
      NY(I) = 0
      Z(I) = 0
```

```
 22     CONTINUE
 25     M = 1
        Z(1) = 1
        CS = 1
 30     I= MAT(M,YRS,MAXYR,NS)
        X = RAN(135713)
        CSP = NEWST(P,I,CS,X,NI,NS)
        A(CSP) = MIN0(A(CSP),M)
        IF(CSP.EQ.NS) GO TO 150
        NY(CSP) = NY(CSP) + 1
        IF(CS.NE.CSP) Z(CSP) = Z(CSP) + 1
        CC(M) = C(CSP)
        DD(M) = D(CSP)
        DCC(M) = C(CSP)*(1.+DISC)**(-(M-1))
        DDD(M) = D(CSP)*(1.+DISC)**(-(M-1))
        TCC = TCC + CC(M)
        DTCC = DTCC + DCC(M)
        TDD = TDD + DD(M)
        DTDD = DTDD + DDD(M)
        M = M + 1
        CS = CSP
        IF(M.LT.MAXYR) GO TO 30
        CSP = NS
150     ALPHA = M
        A(CSP) = M
        DO 155 I=1,NS
        IF(I.EQ.1) GO TO 153
        IF(A(I).EQ.MAXYR+1) A(I) = 0
        IF(A(I).EQ.0) Z(I) = 0
153     IF(A(I).NE.0) NITS(I) = NITS(I) + 1
155     CONTINUE
        AVETCC = AVETCC + TCC
        SQTCC = SQTCC + TCC**2
        AVETDD = AVETDD + TDD
        SQTDD = SQTDD + TDD**2
        AVEALP = AVEALP + ALPHA
        SQALP = SQALP + ALPHA**2
        AVEDTC = AVEDTC + DTCC
        SQDTCC = SQDTCC + DTCC**2
        AVEDTD = AVEDTD + DTDD
        SQDTD = SQDTD + DTDD**2
        DO 160 I=1,NS
        AVEA(I) = AVEA(I) + A(I)
        SQA(I) = SQA(I) + A(I)**2
        AVEZ(I) = AVEZ(I) + Z(I)
        SQZ(I) = SQZ(I) + Z(I)**2
        AVENY(I) = AVENY(I) + NY(I)
        SQNY(I) = SQNY(I) + NY(I)**2
160     CONTINUE
        DO 170 I=1,MXYRM1
        AVEDCC(I) = AVEDCC(I) + DCC(I)
        SQDCC(I) = SQDCC(I) + DCC(I)**2
        AVECC(I) = AVECC(I) + CC(I)
        SQCC(I) = SQCC(I) + CC(I)**2
        AVEDDD(I) = AVEDDD(I) + DDD(I)
```

```
      SQDDD(I) = SQDDD(I) + DDD(I)**2
      AVEDD(I) = AVEDD(I) + DD(I)
      SQDD(I) = SQDD(I) + DD(I)**2
170   CONTINUE
C     WRITE(9,6001) (A(I),I=2,NS),Z,(NY(I),I=1,NSM2),ALPHA,TCC,DTCC,TDD,
C    1 DTDD
6001  FORMAT(19I3,5F12.2)
200   CONTINUE
      AVEALP = AVEALP/NIT
      SQALP = SQRT((SQALP-NIT*AVEALP**2)/(NIT-1))
      DO 250 I=1,NS
      PROB(I) = 1.0*NITS(I)/NIT
      IF(NITS(I).NE.0) AVEA(I) = AVEA(I)/NITS(I)
      IF(NITS(I).GT.1) SQA(I) = SQRT((SQA(I)-NITS(I)*AVEA(I)**2)/(NITS(
     1 I)-1))
      IF(NITS(I).NE.0) AVEZ(I) = AVEZ(I)/NITS(I)
      IF(NITS(I).GT.1) SQZ(I) = SQRT((SQZ(I)-NITS(I)*AVEZ(I)**2)/(NITS(I
     1 )-1))
250   CONTINUE
      DO 300 L=18,429
      DUM1(L) = DUM1(L)/NIT
      IF((DUM2(L)-NIT*DUM1(L)**2).LE.0.) GO TO 300
      DUM2(L) = SQRT((DUM2(L) - NIT*DUM1(L)**2)/(NIT-1))
300   CONTINUE
      WRITE(6,6101)
6101  FORMAT(T13,'PROB. OF'/T13,'ENTERING'/T3,'STATE',5X,'STATE'/
     1 T2,8(1H*),3X,8(1H*))
      WRITE(6,6102) (J,PROB(J),J=1,NSM1)
6102  FORMAT(I5,F14.3)
      WRITE(6,6002)
6002  FORMAT(//T27,'STANDARD'/T2,'VARIABLE',6X,'MEAN',7X,'DEVIATION'/
     1 1X,9(1H*),3X,8(1H*),5X,9(1H*)/)
      WRITE(6,6003) DUM1(1),DUM2(1),(L,DUM1(L+1),DUM2(L+1),L=2,NSM1),
     1 (L,DUM1(L+9),DUM2(L+9),L=1,NSM1),(L,DUM1(L+17),DUM2(L+17),L=1,NSM
     2 1),(DUM1(L),DUM2(L),L=26,27),(DUM1(L),DUM2(L),L=228,229)
6003  FORMAT(' AGE DEATH',F9.2,F14.2//4(' AGE IN S',I1,F9.2,F14.2/)
     1 /5(' Z   IN S',I1,F9.2,F14.2/)/5(' NYR IN S',I1,F9.2,F14.2/)
     2 /' TOT COST',F10.2,F14.2//' TOT DCOST',F9.2,F14.2/
     3 /' TOT IND C',F9.2,F14.2//' TOT IND D',F9.2,F14.2/)
      WRITE(6,6104)
6104  FORMAT(//T23,'GOVERNMENT COSTS',T93,'INDIVIDUAL COSTS'/
     1 T2,59(1H*),T72,59(1H*))
      WRITE(6,6006) DISC,DISC
6006  FORMAT(//T41,'DISCOUNTED AT',F5.2,T111,'DISCOUNTED AT',F5.2/T39,
     1 22(1H*),T109,22(1H*)/)
      WRITE(6,6004)
6004  FORMAT(' COST AT',T27,'STANDARD',T52,'STANDARD',T72,' COST AT',
     1 T97,'STANDARD',T122,'STANDARD'/
     1 4X,'AGE',T16,'MEAN',T27,'DEVIATION',T41,'MEAN',T52,'DEVIATION',
     2 T75,'AGE',T86,'MEAN',T97,'DEVIATION',T111,'MEAN',T122,'DEVIATION'
     2 /1X,9(1H*),3X,8(1H*),5X,9(1H*),3X,8(1H*),5X,9(1H*),
     3 T72,9(1H*),3X,8(1H*),5X,9(1H*),3X,8(1H*),5X,9(1H*)/)
      WRITE(6,6005) (L,DUM1(L+27),DUM2(L+27),DUM1(L+27+100),DUM2(L+
     1 27+100),L,DUM1(L+229),DUM2(L+229),DUM1(L+229+100),DUM2(L+229+100
     2 ),L=1,MXYRM1)
```

```
6005  FORMAT(10(I6,F15.2,F14.2,F11.2,F14.2,T71,I6,F15.2,F14.2,F11.2,F14.
     1 2/)/)
      STOP
      END
```

NEWST FORTRAN

```
      FUNCTION NEWST(P,I,CS,X,NI,NS)
      INTEGER CS
      REAL P(15,8,8)
      Z = 0.
      DO 10 J=1,NS
      Z = Z + P(I,CS,J)
      IF(Z.GT.X) GO TO 20
10    CONTINUE
      STOP 456
20    NEWST = J
      RETURN
      END
```

MAT FORTRAN

```
      FUNCTION MAT(M,YRS,MAXYR,NS)
      INTEGER YRS(NS)
      DO 10 I=1,MAXYR
      IF(M.GT.YRS(I)) GO TO 10
      GO TO 20
10    CONTINUE
      STOP 123
20    MAT = I
      RETURN
      END
```

RESULTS OF ESRD TREATMENT SIMULATION

MEASURE	BASELINE		PARTIAL IMPROVEMENT		OPTIMISTIC IMPROVEMENT	
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION
"AGE" (A) AT DEATH	13.72	10.18	15.05	10.88	17.11	11.44
"AGE" WHEN ENTERING (FOR FIRST TIME)						
CONTINUING DIALYSIS	1.96	2.90	2.97	4.61	4.07	6.37
TRANSPLANT	5.27	6.65	4.53	5.31	3.03	3.48
POST-TRANSPLANT	6.41	6.47	6.72	6.11	4.57	4.15
NUMBER OF YEARS IN						
CONTINUING DIALYSIS	10.64	9.42	7.00	7.03	3.60	4.78
TRANSPLANT	0.55	0.90	1.37	1.40	1.55	1.27
POST-TRANSPLANT	1.14	3.21	4.81	6.62	10.20	9.60
COST TO PUBLIC SECTOR PER INDIVIDUAL OVER INDIVIDUAL'S LIFE ($)						
UNDISCOUNTED	430,262	(365,221)	324,313	(287,594)	195,514	(198,158)
DISCOUNTED AT 10%	208,280	(132,714)	162,947	(113,368)	108,231	(93,147)
COST TO PRIVATE SECTOR PER INDIVIDUAL ($)						
UNDISCOUNTED	24,371	(49,075)	80,859	(92,668)	95,597	(76,894)
DISCOUNTED	12,191	(22,792)	32,053	(34,060)	41,890	(34,725)

(A) THROUGHOUT, "AGE" IS MEANT TO BE YEARS AFTER CONTRACTING ESRD

BASELINE CASE ESRD TREATMENT MODEL RUN

STATE	PROB. OF ENTERING STATE
1	1.000
2	0.841
3	0.367
4	0.193

VARIABLE	MEAN	STANDARD DEVIATION
AGE DEATH	13.72	10.18
AGE IN S2	1.96	2.90
AGE IN S3	5.27	6.65
AGE IN S4	6.41	6.47
Z IN S1	1.39	0.70
Z IN S2	1.16	0.42
Z IN S3	1.45	0.80
Z IN S4	1.20	0.49
NYR IN S1	0.39	0.70
NYR IN S2	10.64	9.42
NYR IN S3	0.55	0.90
NYR IN S4	1.14	3.21
TOT COST	430262.75	365221.56
TOT DCOST	208280.50	132714.25
TOT IND C	151362.12	126065.50
TOT IND D	73843.31	45563.25

BASELINE CASE ESRD TREATMENT MODEL RUN
(con't)

GOVERNMENT COSTS

COST AT AGE	MEAN	STANDARD DEVIATION	DISCOUNTED AT 0.10 MEAN	STANDARD DEVIATION
1	31424.41	11808.75	31424.41	11808.75
2	27329.41	16406.15	24843.82	14916.66
3	26376.08	17202.82	21797.70	14218.75
4	24845.90	17845.50	18667.25	13407.04
5	23228.48	18317.36	15866.07	12510.48
6	21889.77	18583.46	13592.24	11538.76
7	21244.67	18594.75	11992.13	10496.45
8	20534.59	18691.15	10537.80	9591.57
9	19394.22	18793.81	9047.63	8767.62
10	18147.48	18741.78	7696.26	7948.44
11	17018.35	18722.53	6561.14	7218.77
12	16074.30	18565.26	5633.84	6507.35
13	15245.00	18525.80	4857.30	5903.29
14	14131.35	18286.82	4093.17	5297.36
15	13143.60	17939.34	3461.10	4724.20
16	12487.50	17755.33	2989.24	4250.69
17	11733.65	17464.47	2553.49	3800.93
18	11158.00	17205.58	2207.44	3404.16
19	10403.35	16816.92	1871.07	3024.74
20	9438.90	16307.44	1543.28	2666.45
21	8999.15	16076.66	1337.64	2389.80
22	8453.55	15716.04	1142.34	2123.76
23	7904.55	15319.02	971.05	1881.94
24	7532.20	15049.01	841.19	1680.72
25	7107.60	14743.10	721.61	1496.86
26	6746.75	14457.23	622.70	1334.40
27	6395.05	14173.97	536.59	1189.31
28	6189.40	13974.70	472.12	1065.99
29	5711.75	13537.87	396.08	938.79

BASELINE CASE ESRD TREATMENT MODEL RUN
(con't)

INDIVIDUAL COSTS

COST AT AGE	MEAN	STANDARD DEVIATION	DISCOUNTED AT 0.10 MEAN	STANDARD DEVIATION
1	11264.70	3677.38	11264.70	3677.38
2	10483.00	7514.22	9529.65	6830.21
3	9182.60	6449.14	7588.39	5329.93
4	8661.90	6690.16	6507.37	5027.05
5	7979.10	6612.30	5449.65	4516.45
6	7619.10	6874.86	4730.53	4269.07
7	7506.70	6995.94	4237.00	3949.30
8	7327.50	7135.12	3760.10	3661.53
9	6692.90	6715.09	3122.07	3132.76
10	6461.10	7046.80	2740.10	2988.53
11	5909.40	6735.37	2278.24	2596.85
12	5735.30	6953.88	2010.12	2437.31
13	5294.20	6665.16	1686.81	2123.71
14	4836.30	6420.40	1400.84	1859.83
15	4576.20	6442.09	1205.04	1696.45
16	4322.70	6340.68	1034.83	1517.93
17	4056.60	6213.63	882.83	1352.30
18	3898.60	6217.87	771.32	1230.20
19	3658.70	6111.66	658.05	1099.24
20	3284.10	5828.50	536.98	953.02
21	3154.10	5833.97	468.83	867.20
22	2947.20	5638.40	398.26	761.93
23	2770.10	5524.17	340.29	678.63
24	2628.30	5391.90	293.52	602.17
25	2447.40	5185.55	248.48	526.48
26	2339.20	5142.12	215.90	474.61
27	2215.30	5044.25	185.87	423.25
28	2155.20	4986.91	164.39	380.40
29	1959.60	4731.37	135.88	328.10

PARTIAL IMPROVEMENT CASE ESRD TREATMENT MODEL RUN

STATE	PROB. OF ENTERING STATE
1	1.000
2	0.799
3	0.662
4	0.522

VARIABLE	MEAN	STANDARD DEVIATION
AGE DEATH	15.05	10.88
AGE IN S2	2.97	4.61
AGE IN S3	4.53	5.31
AGE IN S4	6.72	6.11
Z IN S1	1.88	1.05
Z IN S2	1.43	0.65
Z IN S3	1.99	1.15
Z IN S4	1.56	0.80
NYR IN S1	0.88	1.05
NYR IN S2	7.00	7.03
NYR IN S3	1.37	1.40
NYR IN S4	4.81	6.62
TOT COST	324313.06	287594.44
TOT DCOST	162947.12	113368.25
TOT IND C	124584.00	107105.00
TOT IND D	62246.61	41116.11

PARTIAL IMPROVEMENT CASE ESRD TREATMENT MODEL RUN
(con't)

INDIVIDUAL COSTS

COST AT AGE	MEAN	STANDARD DEVIATION	DISCOUNTED AT 0.10 MEAN	DISCOUNTED AT 0.10 STANDARD DEVIATION
1	11204.40	3580.84	11204.40	3580.84
2	9588.50	8305.97	8716.45	7550.25
3	8129.00	7317.29	6717.72	6047.57
4	7066.00	7596.84	5308.37	5708.11
5	6463.20	7656.23	4414.24	5229.54
6	6053.70	7766.80	3758.62	4822.79
7	5686.30	7692.17	3209.56	4342.19
8	5550.20	7789.75	2848.04	3997.48
9	5135.10	7500.59	2395.42	3499.16
10	4536.40	7165.77	1923.83	3038.97
11	4207.80	7105.16	1622.25	2739.35
12	4271.10	7368.67	1496.93	2582.68
13	3884.30	6957.16	1237.63	2216.75
14	3698.00	6944.67	1071.17	2011.63
15	3546.00	6754.34	933.78	1778.67
16	3637.40	6991.52	870.76	1673.74
17	3567.60	6984.58	776.41	1520.08
18	3254.50	6470.23	643.89	1280.12
19	3188.50	6658.04	573.48	1197.52
20	2692.80	6059.45	440.29	990.78
21	2713.40	6042.89	403.32	898.25
22	2459.20	5898.44	332.32	797.07
23	2360.90	5790.98	290.03	711.40
24	2238.20	5654.12	249.95	631.45
25	2175.60	5829.69	220.88	591.87
26	1937.00	5220.46	178.77	481.85
27	1895.90	5552.84	159.07	465.93
28	1816.90	5188.61	138.59	395.79
29	1630.70	4907.82	113.08	340.34

PARTIAL IMPROVEMENT CASE ESRD TREATMENT MODEL RUN
(con't)

GOVERNMENT COSTS

			DISCOUNTED AT 0.10	
COST AT AGE	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION
1	30072.37	11663.35	30072.37	11663.35
2	23760.34	17294.28	21599.61	15723.11
3	21970.83	17791.04	18157.45	14703.90
4	19044.59	18249.37	14308.48	13710.73
5	17144.94	18101.12	11710.26	12363.45
6	15786.25	17932.39	9801.93	11134.94
7	14819.20	17771.90	8364.83	10032.13
8	14327.75	17744.23	7352.39	9105.89
9	13314.90	17363.09	6211.41	8100.25
10	12042.70	17021.76	5107.19	7219.11
11	11069.65	16651.03	4267.70	6420.02
12	10794.75	16496.03	3783.43	5781.98
13	10146.50	16225.37	3232.87	5170.11
14	9516.00	15899.63	2756.35	4605.75
15	9232.50	15748.29	2431.19	4147.16
16	9136.85	15661.93	2187.19	3749.47
17	8882.10	15533.33	1932.95	3380.60
18	8446.50	15217.72	1671.04	3010.82
19	7922.85	14833.67	1424.97	2668.02
20	7202.05	14532.79	1177.58	2376.27
21	7054.85	14229.56	1048.57	2115.20
22	6447.40	13856.48	871.25	1872.50
23	6189.50	13626.50	760.36	1674.02
24	5759.35	13097.53	643.20	1462.76
25	5357.50	12749.34	543.93	1294.43
26	5124.95	12514.00	473.02	1155.04
27	4738.55	12227.47	397.60	1025.98
28	4685.20	12055.23	357.38	919.57
29	4337.70	11706.17	300.80	811.77

OPTIMISTIC IMPROVEMENT CASE ESRD TREATMENT MODEL RUN

STATE	PROB. OF ENTERING STATE
1	1.000
2	0.603
3	0.777
4	0.692

VARIABLE	MEAN	STANDARD DEVIATION
AGE DEATH	17.11	11.44
AGE IN S2	4.07	6.37
AGE IN S3	3.03	3.48
AGE IN S4	4.57	4.15
Z IN S1	1.77	0.94
Z IN S2	1.26	0.52
Z IN S3	1.97	1.06
Z IN S4	1.68	0.83
NYR IN S1	0.77	0.94
NYR IN S2	3.60	4.78
NYR IN S3	1.55	1.27
NYR IN S4	10.20	9.60
TOT COST	195514.44	198158.37
TOT DCOST	108231.06	93147.81
TOT IND C	75597.00	76894.37
TOT IND D	41890.05	34725.24

OPTIMISTIC IMPROVEMENT CASE ESRD TREATMENT MODEL RUN
(con't)

GOVERNMENT COSTS

COST AT AGE	MEAN	STANDARD DEVIATION	DISCOUNTED AT 0.10 MEAN	DISCOUNTED AT 0.10 STANDARD DEVIATION
1	27293.64	11827.17	27293.64	11827.17
2	17347.50	17839.93	15770.20	16218.40
3	14839.40	17470.30	12263.61	14438.70
4	12166.25	16992.62	9140.52	12766.76
5	10856.50	16202.31	7415.12	11066.48
6	9432.95	15435.25	5857.05	9584.29
7	8440.35	14936.42	4764.25	8431.41
8	8035.30	14572.37	4123.37	7478.15
9	7066.75	13986.60	3296.65	6525.02
10	6312.65	13336.60	2677.14	5656.15
11	5803.15	12916.30	2237.31	4979.95
12	5810.95	12834.09	2036.69	4498.37
13	5304.65	12533.68	1690.20	3993.70
14	5106.30	12257.97	1479.10	3550.78
15	4670.45	11744.10	1229.88	3092.66
16	4394.00	11414.09	1051.90	2732.49
17	4554.90	11459.06	991.29	2493.86
18	4175.55	11121.85	826.12	2200.44
19	3761.95	10656.96	676.63	1916.80
20	3538.30	10396.92	578.54	1700.03
21	3356.45	10165.82	498.92	1511.12
22	3233.65	10007.90	436.97	1352.41
23	3213.20	9768.79	394.73	1200.08
24	2955.85	9438.60	330.11	1054.11
25	2834.65	9368.74	287.79	951.19
26	2719.45	9275.57	251.00	856.12
27	2739.30	9281.95	229.85	778.82
28	2907.60	9640.32	221.79	735.36
29	2647.05	9083.07	183.56	629.86

OPTIMISTIC IMPROVEMENT CASE ESRD TREATMENT MODEL RUN
(con't)

INDIVIDUAL COSTS

COST AT AGE	MEAN	STANDARD DEVIATION	DISCOUNTED AT 0.10 MEAN	STANDARD DEVIATION
1	10831.20	3805.66	10831.20	3805.66
2	6962.70	8456.31	6329.31	7687.51
3	5348.90	7133.95	4420.25	5896.26
4	4490.50	7468.18	3373.39	5611.20
5	4099.60	7283.37	2799.90	4974.72
6	3691.10	7330.34	2291.72	4551.61
7	3385.40	7404.24	1910.90	4179.54
8	3184.30	7097.60	1633.99	3642.23
9	2615.30	6459.08	1220.02	3013.23
10	2398.50	6429.46	1017.20	2726.66
11	2240.00	6394.54	863.62	2465.37
12	2242.70	6270.40	786.04	2197.74
13	1974.90	6038.06	629.25	1923.96
14	2015.20	6214.00	583.72	1800.01
15	1762.20	5732.28	464.04	1509.52
16	1751.80	5891.10	419.36	1410.31
17	1953.60	6216.49	425.16	1352.90
18	1545.90	5328.69	305.85	1054.26
19	1507.10	5599.98	271.07	1007.22
20	1304.80	5096.53	213.34	833.33
21	1283.00	5194.12	190.70	772.07
22	1243.40	5145.73	168.02	695.34
23	1312.20	5218.81	161.20	641.11
24	1234.30	5230.75	137.84	584.17
25	1142.30	5057.06	115.97	513.44
26	1016.00	4701.83	93.77	433.98
27	1071.80	4830.21	89.93	405.30
28	1109.20	4817.54	84.61	367.48
29	882.90	4010.74	61.22	278.13

RESULTS OF THROMBOEMBOLIC TREATMENT SIMULATION

	BASELINE CASE		INI. IMPROVEMENT CASE		PAR. IMPROVEMENT CASE		OPT. IMPROVEMENT CASE	
MEASURE	MEAN	STAN. DEV.	MEAN	STAN. DEV.	MEAN	STAN. DEV.	MEAN	STAN. DEV.
"AGE"* AT DEATH	17.42	10.98	17.11	11.02	21.64	17.88	30.79	18.17
PROBABILITY OF ENTERING STATE								
HEPARIN	.98		.53		.30		.39	
SURGERY	.34		.22		.28		.26	
UROKINASE	.00		.74		.81		.91	
POST-TREATMENT	.89		.88		.88		.94	
NUMBER OF YEARS IN								
HEPARIN	1.98	1.38	.79	.90	.45	.78	.53	.77
SURGERY	0.42	.64	.25	.50	.31	.53	.33	.59
UROKINASE	0.00	0.00	1.41	1.16	2.18	2.01	2.88	2.00
POST-TREATMENT	12.43	9.16	12.07	9.06	15.71	14.48	23.62	15.19
COST TO PRIVATE INDIVIDUAL($)	12,933.	8442.	14,560	9836.	17,974	14,626	20,021	12,299.

*"AGE" IS YEARS AFTER CONTRACTING PULMONARY EMBOLISM

Baseline Case Pulmonary Embolism Model Run Results

STATE	PROB. OF ENTERING STATE
1	1.000
2	0.877
3	0.280
4	0.0
5	0.847

VARIABLE	MEAN	STANDARD DEVIATION
AGE DEATH	16.80	11.35
AGE IN S2	1.76	2.93
AGE IN S3	8.86	9.22
AGE IN S4	0.0	0.0
AGE IN S5	2.15	0.40
Z IN S1	2.24	1.22
Z IN S2	2.02	1.07
Z IN S3	1.14	0.35
Z IN S4	0.0	0.0
Z IN S5	2.04	1.13
N/R IN S1	1.37	1.32
N/R IN S2	1.85	1.29
N/R IN S3	0.32	0.55
N/R IN S4	0.0	0.0
N/R IN S5	12.26	9.57
TOT COST	0.0	0.0
TOT DCOST	0.0	0.0
TOT IND C	12238.53	8301.03
TOT IND D	12238.53	8301.03

INDIVIDUAL COSTS

COST AT AGE	MEAN	STANDARD DEVIATION	DISCOUNTED AT 0.0 MEAN	DISCOUNTED AT 0.0 STANDARD DEVIATION
1	4671.33	2085.07	4671.33	2085.07
2	765.87	1962.12	765.87	1962.12
3	79.47	686.99	79.47	686.99
4	386.80	1413.26	386.80	1413.26
5	417.87	1491.90	417.87	1491.90
6	417.87	1491.90	417.87	1491.90
7	457.60	1558.84	457.60	1558.84
8	268.53	1219.36	268.53	1219.36
9	277.20	1211.49	277.20	1211.49
10	258.93	1173.50	258.93	1173.50
11	258.93	1173.50	258.93	1173.50
12	390.00	1425.86	390.00	1425.86
13	258.93	1173.50	258.93	1173.50
14	149.33	905.20	149.33	905.20
15	146.13	884.34	146.13	884.34
16	292.27	1233.40	292.27	1233.40
17	305.07	1291.00	305.07	1291.00
18	335.20	1331.04	335.20	1331.04
19	222.40	1092.65	222.40	1092.65
20	225.60	1109.37	225.60	1109.37
21	155.73	945.50	155.73	945.50
22	210.53	1084.04	210.53	1084.04
23	262.13	1188.99	262.13	1188.99
24	192.27	1040.23	192.27	1040.23
25	177.20	1012.67	177.20	1012.67

Initial Improvement Case Pulmonary Embolism Model Run Results

STATE	PROB. OF ENTERING STATE
1	1.000
2	0.530
3	0.220
4	0.740
5	0.880

VARIABLE	MEAN	STANDARD DEVIATION
AGE DEATH	17.11	11.02
AGE IN S2	4.36	5.57
AGE IN S3	9.50	8.81
AGE IN S4	4.49	6.84
AGE IN S5	2.19	0.40
Z IN S1	2.41	1.25
Z IN S2	1.42	0.60
Z IN S3	1.14	0.35
Z IN S4	1.76	0.81
Z IN S5	2.09	1.10
NYR IN S1	1.59	1.30
NYR IN S2	0.79	0.90
NYR IN S3	0.25	0.50
NYR IN S4	1.41	1.16
NYR IN S5	12.07	9.06
TOT COST	0.0	0.0
TOT DCOST	0.0	0.0
TOT IND C	14356.90	9748.48
TOT IND D	14356.90	9748.48

Initial Improvement Case Pulmonary Embolism Model Run Results (continued)

INDIVIDUAL COSTS

COST AT AGE	MEAN	STANDARD DEVIATION	DISCOUNTED AT 0.0 MEAN	DISCOUNTED AT 0.0 STANDARD DEVIATION
1	5046.10	1977.19	5046.10	1977.19
2	1078.70	2317.42	1078.70	2317.42
3	0.0	0.0	0.0	0.0
4	283.80	1244.46	283.80	1244.46
5	527.10	1688.37	527.10	1688.37
6	477.40	1628.53	477.40	1628.53
7	587.00	1772.27	587.00	1772.27
8	303.20	1328.95	303.20	1328.95
9	358.00	1425.78	358.00	1425.78
10	293.60	1286.97	293.60	1286.97
11	348.20	1387.98	348.20	1387.98
12	582.10	1757.85	582.10	1757.85
13	412.80	1514.43	412.80	1514.43
14	224.10	1104.22	224.10	1104.22
15	54.80	548.00	54.80	548.00
16	343.50	1367.79	343.50	1367.79
17	353.30	1406.17	353.30	1406.17
18	417.50	1532.48	417.50	1532.48
19	243.50	1199.61	243.50	1199.61
20	283.80	1244.46	283.80	1244.46
21	233.90	1152.43	233.90	1152.43
22	179.10	1023.54	179.10	1023.54
23	298.30	1308.59	298.30	1308.59
24	233.90	1152.43	233.90	1152.43
25	307.90	1349.86	307.90	1349.86
26	229.00	1128.59	229.00	1128.59
27	59.70	597.00	59.70	597.00
28	233.90	1152.43	233.90	1152.43
29	362.70	1445.11	362.70	1445.11

Partial Improvement Case Pulmonary Embolism Model Run Results

STATE	PROB. OF ENTERING STATE
1	1.000
2	0.300
3	0.280
4	0.810
5	0.880

VARIABLE	MEAN	STANDARD DEVIATION
AGE DEATH	21.64	17.88
AGE IN S2	8.23	10.68
AGE IN S3	11.25	13.05
AGE IN S4	2.95	5.31
AGE IN S5	2.24	0.59
Z IN S1	2.83	1.86
Z IN S2	1.33	0.55
Z IN S3	1.11	0.31
Z IN S4	2.51	1.65
Z IN S5	2.66	1.86
NYR IN S1	1.99	1.97
NYR IN S2	0.45	0.78
NYR IN S3	0.31	0.53
NYR IN S4	2.18	2.01
NYR IN S5	15.71	14.48
TOT COST	0.0	0.0
TOT DCOST	0.0	0.0
TOT IND C	17477.00	14151.62
TOT IND D	17477.00	14151.62

INDIVIDUAL COSTS

****

COST AT AGE			DISCOUNTED AT 0.0	
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION
1	5038.80	2138.64	5038.80	2138.64
2	1054.40	2266.54	1054.40	2266.54
3	119.20	841.37	119.20	841.37
4	243.50	1199.61	243.50	1199.61
5	482.10	1645.13	482.10	1645.13
6	427.30	1566.35	427.30	1566.35
7	596.80	1800.71	596.80	1800.71
8	238.60	1176.76	238.60	1176.76
9	472.70	1611.74	472.70	1611.74
10	358.20	1424.94	358.20	1424.94
11	417.90	1530.90	417.90	1530.90
12	472.70	1611.74	472.70	1611.74
13	362.70	1445.11	362.70	1445.11
14	0.0	0.0	0.0	0.0
15	119.40	840.01	119.40	840.01
16	174.20	996.34	174.20	996.34
17	288.70	1265.90	288.70	1265.90
18	596.80	1800.71	596.80	1800.71
19	303.20	1328.95	303.20	1328.95
20	298.10	1309.49	298.10	1309.49
21	472.70	1611.74	472.70	1611.74
22	298.50	1307.69	298.50	1307.69
23	119.40	840.01	119.40	840.01
24	179.10	1023.54	179.10	1023.54
25	179.10	1023.54	179.10	1023.54
26	124.10	873.72	124.10	873.72
27	59.70	597.00	59.70	597.00
28	413.00	1513.64	413.00	1513.64
29	358.00	1425.78	358.00	1425.78
30	183.80	1051.10	183.80	1051.10
31	353.30	1406.17	353.30	1406.17
32	59.70	597.00	59.70	597.00
33	229.00	1128.59	229.00	1128.59
34	183.80	1051.10	183.80	1051.10
35	238.80	1175.77	238.80	1175.77
36	179.10	1023.54	179.10	1023.54
37	59.70	597.00	59.70	597.00
38	114.50	806.29	114.50	806.29
39	119.40	840.01	119.40	840.01
40	179.10	1023.54	179.10	1023.54

Optimistic Improvement Case Pulmonary Embolism Treatment Model Run

STATE	PROB. OF ENTERING STATE
1	1.000
2	0.390
3	0.268
4	0.914
5	0.946

VARIABLE	MEAN	STANDARD DEVIATION
AGE DEATH	30.79	18.17
AGE IN S2	13.35	14.48
AGE IN S3	13.64	14.28
AGE IN S4	3.15	6.18
AGE IN S5	2.15	0.42
Z IN S1	3.37	1.90
Z IN S2	1.30	0.57
Z IN S3	1.18	0.42
Z IN S4	2.95	1.69
Z IN S5	3.30	1.84
NYR IN S1	2.43	1.95
NYR IN S2	0.53	0.77
NYR IN S3	0.33	0.59
NYR IN S4	2.88	2.00
NYR IN S5	23.62	15.19
TOT COST	0.0	0.0
TOT DCOST	0.0	0.0
TOT IND C	16963.48	10461.00
TOT IND D	16963.48	10461.00

INDIVIDUAL COSTS

COST AT AGE	MEAN	STANDARD DEVIATION	DISCOUNTED AT 0.0 MEAN	DISCOUNTED AT 0.0 STANDARD DEVIATION
1	4321.96	1194.91	4321.96	1194.91
2	706.96	1781.29	706.96	1781.29
3	57.16	528.80	57.16	528.80
4	414.48	1304.11	414.48	1304.11
5	379.76	1294.56	379.76	1294.56
6	382.64	1304.50	382.64	1304.50
7	426.80	1326.67	426.80	1326.67
8	305.68	1151.24	305.68	1151.24
9	314.20	1139.54	314.20	1139.54
10	342.84	1214.08	342.84	1214.08
11	403.44	1324.01	403.44	1324.01
12	336.28	1210.30	336.28	1210.30
13	462.80	1376.01	462.80	1376.01
14	219.08	967.57	219.08	967.57
15	287.76	1138.60	287.76	1138.60
16	299.36	1122.37	299.36	1122.37
17	393.00	1341.10	393.00	1341.10
18	339.60	1182.52	339.60	1182.52
19	279.36	1077.58	279.36	1077.58
20	235.56	1067.45	235.56	1067.45
21	318.00	1177.87	318.00	1177.87
22	292.80	1118.02	292.80	1118.02
23	279.12	1103.25	279.12	1103.25
24	257.16	1074.23	257.16	1074.23
25	360.20	1219.83	360.20	1219.83
26	272.56	1098.71	272.56	1098.71
27	178.84	887.59	178.84	887.59
28	230.60	1021.37	230.60	1021.37
29	206.56	953.00	206.56	953.00
30	185.16	924.66	185.16	924.66
31	242.32	1055.18	242.32	1055.18
32	253.36	1031.83	253.36	1031.83
33	145.72	813.14	145.72	813.14
34	164.80	837.98	164.80	837.98
35	182.64	936.85	182.64	936.85
36	160.32	872.10	160.32	872.10
37	178.84	887.59	178.84	887.59
38	150.32	841.79	150.32	841.79
39	110.52	679.95	110.52	679.95
40	192.88	934.37	192.88	934.37

APPENDIX C

Patient and Government Cost Breakdown

C.2

PUBLIC SECTOR COSTS

DIALYSIS	First Year	
	80% of Hospital costs after 3 months	$13,500.00
	80% of Doctors' fees	1,700.00
	20% of patients on welfare	1,000.00
		$16,200.00
	Subsequent Years	
	80% of Hospital costs	$18,000.00
	80% of Doctors' fees	2,300.00
	20% of patients on welfare	1,000.00
		$21,300.00
TRANSPLANT	First Year	
	80% of Transplant operation (see transplant cost breakdown)	$13,000.00
	Subsequent Years	-0-
DEATHS		-0-

PRIVATE SECTOR COSTS

DIALYSIS

First Year

Center dialysis cost-$17,000 times 70% = (see Center Dialysis Cost Breakdown)	$11,900
Home Dialysis- 18,450 times 30% = (see Home Dialysis Cost Breakdown)	5,535
Average	$17,435
minus income (see income breakdown)	2,200
	$15,235
Rounded =	$15,250/year

Subsequent Years

Center dialysis cost $11,850 x 70% =	$ 8,295
Home dialysis cost $8,450 x 30% =	2,535
	$10,830
minus income	3,750
	$ 7,080
Rounded =	$ 7,100/year

TRANSPLANT

First Year

20% of average operation cost plus other incurred costs	$9,250
minus income	2,800
	$6,450
Rounded =	$6,500

Subsequent Years

Costs	$5,100
minus income	5,600
	-$ 500

DEATH

Estimated Burial Costs	$2,500

CENTER DIALYSIS COST BREAKDOWN ($)

	1st Year	2nd Year
Surgery for connection	500	0
Counseling (50% assuming $1500/year)	750	150
Changes in diet	200	200
Job loss	4800	3000
Retraining	500	0
Tutoring	150	150
Diet supplements	250	250
Moving expenses	250	0
Spouse or family job loss or reduction	1000	750
Transportation costs	750	750
Dialysis		
3 month initial period	1300	-
Medicare coverage (80%)	4500	6000
M.D.		
3 month initial period	750	-
Medicare coverage (80%)	430	600
	17,000	11,850

HOME DIALYSIS COST BREAKDOWN ($)

	1st Year	Subsequent Years
Loss of spouse work	500	500
Chair	250	-
Plumbing	400	-
Water	600	600
Utilities	100	100
Training	4000	
M.D.	800	
Machine	4000	
Maintenance	300	300
Lab	350	350
Hospital Backup	3000	3000
Counseling	500	350
Diet changes	200	200
Job loss	1000	1000
Retraining	500	
Tutoring	100	100
Diet supplements	250	250
Spouse or family job loss	1000	1000
M.D.	600	600
	18,450	8,450

COSTS ($)

TRANSPLANT	1st Year	Post Transplant Years
From living person (30% of total x $14,000)		
From cadaver (70% of total x $12,800)		
Average cost of operation to patient (20% of total cost)	2600	-
Work loss	1800	-
Donor work loss	1300	-
Medication and M.D.s	1500	3500
Diet changes	200	200
Counseling	500	300
Tutoring	100	100
Diet Supplements	250	-
Job decrease (too weak, cannot continue old skill)	1000	1000
	9,250	5,100

INCOME

Assumptions

* Yearly average income estimated at $10,500.00
* 75% of the male population are of income age.
* 65% of the female population are of income age.
* 50% of the female population of income age are in the labor market.
* Children do not have incomes.
* Children are designated as those persons under age twenty.
* 5% of ESRD patients are children.

First Year Dialysis	$2200/year
Continued Dialysis	$3750/year
First Year Transplant	$2800/year
Post Transplant	$5600/year
Death	$0/year

Estimated Costs of Alternative Treatment

Regimes for Pulmonary Embolism

ITEM	Costs in Dollars			
	Heparin	Surgery & Heparin	Urokinase & Heparin	
			Normal	Optimistic
Hospital Room				
. Intensive Care				
@ $400./day	5 days .00	4 days .00	4 days $1600.00	2 days $ 800.00
. Medium Care @ $140./day	9 days $1260.00	10 days $1400.00		
. Semi-Private @ $110./day	-	2 days $220.00	10 days $1100.00	12 days $1320.00
Medication				
. Urokinase	-	-	1 day @ $2000./day $2000.00	1 day @ $200.00/day $200.00
. Heparin	$20.00	$20.00		
Physician				
. Surgeon	-	$1900.00	-	-
. Internist	$1500.00	$500.00	$1000.00	$1000.00
Misc.				
. Misc. Tests & X-Rays	$200.00	$200.00	$200.00	$200.00
. Lung Scans	$600.00	$600.00	$600.00	$600.00
TOTAL	$5580.00	$6440.00	$5970.00	$4140.00

ECON *Corporate Headquarters:*

Princeton, New Jersey
Telephone 609-924-8778

Western Office:

San Jose, California
Telephone 408-249-6364