POLICIES FOR THE TREATMENT OF CHRONIC RENAL FAILURE:
THE QUESTION OF FEASIBILITY

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Methodological Introduction and Some Tentative Conclusions

The large scale treatment of chronic renal failure (CRF) raises policy problems and medico-social dilemmas that are becoming increasingly common in many sectors of modern medical care. Medical research and technological advances, symbolized by artificial dialysis and kidney transplantation, make it possible to prolong the lives of thousands of patients who would otherwise die in a few weeks or months.

But only a minority of CRF patients can be restored to a normal life, at least for some years. Most of the lives that are saved are really "half lives," full of pain and anxiety, that can be maintained only at an extraordinary cost to the community. From the point of view of the health planner, medical progress, short of a real breakthrough, can aggravate the problem, by increasing the stock of chronic patients.

Here, as in other cases, modern medicine's technical capabilities have outstripped its resources and the ability of governments to face the social and ethical issues involved. It would be wrong to think that financial limitations are the only, or even the most important, constraints facing the different decision makers (health manager, physician, patient) in this case. Actually, the relaxation of financial constraints, would make other constraints, e.g. the supply of cadaver kidneys, even more binding.

Up to the present time, treatment of chronic uremic patients, by dialysis or by transplantation, has been largely reserved to the fifteen to sixty years age group; but it is estimated that about 75% of all such patients are older than sixty years. A situation where social security, or similar institutional arrangements, would cover all the permanently disabled regardless of age, would produce not only an enormously increased demand of medical services, but even a qualitative change in problems of patient care and rehabilitation. This is precisely the situation toward which several countries, including the United States, are now moving. Cost-effectiveness calculations and policy recommendations made in a period when patients were carefully screened (see section 3, below) lose much of their significance in the new context.

It is the purpose of the present report to discuss the
feasibility of a policy that would provide full treatment to
all "medically suitable" CRF patients. This is done by inves-
tigating the constraints set by the present level of scientific
and technical knowledge, by institutional factors, and by
resource limitations. My conclusion (a tentative one, since
the numerical implications of the model developed in the last
part of this paper have not yet been fully explored) is that
such a policy is infeasible under present conditions, more a
medical utopia than a public program capable of actual imple-
mentation. Some form of patient selection would take place,
under the cover of medical suitability; and it may be argued
that a disguised form of rationing is less desirable, both on
efficiency and on equity grounds, than one which frankly
recognizes the existence of the constraints.

Some advocates of a comprehensive policy for chronic renal
disease have placed their hopes in transplantation as the op-
timal form of treatment, and in home dialysis as a sort of
second-best solution. Large scale transplantation would have
to rely largely on cadaver kidneys, but it seems highly un-
likely that all the medical, logistical, and legal problems
involved in the procurement, storage, and utilization of the
organs can be solved in the near future.

Home dialysis is considerably cheaper than institutional
dialysis, and it can improve the quality of life of the patient
in several important respects. However, its superiority, in
terms of survival rates, has never been satisfactorily esta-
blished, and increasing experience with its long-term problems
has somewhat dampened the initial enthusiasms. If it is true
that "home dialysis should be restricted to patients who are
well motivated, can return to work, are intelligent, have a
stable and supportive spouse, and are middle or upper middle
income bracket" (De Palma [13]), the proportion of patients
that are suitable candidates for this mode of treatment cannot
be very large. Different authors have given estimates of 10%
(Leach [28]), 20% (De Palma [13]), and less than 40% (Schupak
[45]), of all patients that are medically suitable for dialysis.
One writer who had given an estimate of 70% in 1970, had lower-
ed that value to 35% two years later, presumably on the basis
of more extensive experience (Friedman and Kountz [16]).
According to the United States National Dialysis Registry, of
the 7,305 patients known to be on dialysis as of January 1, 1973,
37% were on home dialysis. As a national average this is quite
high (considerably higher than that of most European countries,
with the notable exception of Great Britain), and in view of
the arguments to be presented below, see in particular section
2.4, it may be doubted that such a proportion can be maintained
in the long run (in fact, it was 41% in 1972).

Another school of thought, acknowledging the impossibility
of treating large numbers of CRF patients by present methods,
maintains that prevention offers the only hope of significantly

alleviating the problem of chronic renal disease; see especially A Report to the Surgeon General by the U.S. Department of Health, Education, and Welfare [50]. Unfortunately, so little is known about the natural histories of the diseases which most commonly lead to a condition of chronic uremia, that the entire population must be taken as the population at risk. Hence, high costs and great uncertainties about the results, rule out any massive preventive program at the present time; although early diagnosis and treatment of particular groups at risk appear to be cost-effective program components, especially if carried out in conjunction with other types of screening.

In sum, the only form of treatment available, now and in the near future, to most CRF patients is institutional dialysis, with its high costs and limited rehabilitation capabilities. In the following pages, the different constraints briefly discussed in this introduction, are examined in greater detail, and a model is developed which enables us to estimate the case load of dialysis patients, in the short or medium term, and in a steady state situation. Numerical applications of the model will be reported in a separate paper.

One final point should be made here, in order to avoid misunderstandings of the methodology used in this study (for a more detailed discussion of the general methodological issues involved, see Majone [34]). The emphasis on feasibility considerations, on the constraints and uncertainties surrounding a policy problem, should not be interpreted as a defeatist attitude on the part of the analyst. Just as it is the essence of the scientific method to submit theories and hypotheses to the most stringent logical and empirical tests, so, I would argue, it is the professional duty of the policy analyst to examine critically the conditions of feasibility of any proposed course of action. In both cases, criticism does not imply resignation to the complexities of our physical or social environment; on the contrary, it is the necessary premise to better understanding and more incisive action.

I.   Epidemiological Aspects of Chronic Kidney Disease

1.1.   Natural History

Chronic renal failure is defined as a disease process which involves a slowly progressive loss of nephrons, frequently accompanied by vascular narrowing, with clinically irreversible impairment of kidney function. Once a patient reaches the irreversible state, he dies in a few months, unless he is treated by dialysis or transplantation.

Very little is known about the natural histories of the diseases that may progress to CRF. Of the most frequent pathological diagnoses in patients dying with chronic uremia from primary kidney disease, i.e. chronic pyelonephritis, chronic

glomerulonephritis, and polycystic disease of the kidney, the first two are asymptomatic for many years. As for poly-cystic disease of the kidney, this is apparently a hereditary condition whose pattern of inheritance is that of a recessive character in the infantile form, and of a predominant trait in adults.

Great uncertainty also surrounds the causal connections between renal failure and other pathological conditions. For instance, a recent longitudinal study covering a period of eight years for a group of 8,641 original examinees (Perlman et al. [40]), suggests only a limited relationship of urinary-tract infections to renal failure. Hypertension was found in no more than the expected frequency for the population at large, despite its common association with renal disease.

In fact, the probability of transition to a state of CRF is unknown even in the case of persons who have had an acute renal disease, such as acute pyelonephritis or glomerulo-nephritis.

1.2. Feasibility of Prevention

The present state of knowledge concerning the natural history of the disease sets severe constraints on preventive programs. In the words of the Committe on Chronic Renal Disease (Gottschalk [19]), "consideration of prevention of chronic uremia is complicated by the uncertain relationship of the various acute and chronic diseases of the kidney and urinary tract to the end-stage kidney which produces the syn-drome of chronic uremia." More specifically, the Committee has taken the position that "it is impossible to predict what effect a massive program aimed at the early diagnosis and treatment of urinary tract infection would have on the inci-dence of chronic uremia," and that "problems relating to the prevention of chronic glomerulonephritis are in the nature of investigative issues and a massive prophylactive program aimed at the prevention of chronic uremia by the early diagnosis and treatment of streptococcal sore throats is not a reasonable proposal at this time."

Also the Report to the Surgeon General of the U.S. Department of Health, Education, and Welfare [50], although more hopeful than the Gottschalk Committee about the possi-bility of significantly diminishing the annual reservoir of patients with irreversible renal failure through a vigorous program of screening, had to admit that "in the area of hyper-sensitivity diseases involving the kidney there appears to be no promising mode of attack in sight except for the launching of a systematic research effort."

But while a general policy of prevention seems to be out of the question at the present time, recent epidemiological research suggests that preventive programs for limited sections of the population at risk may be feasible and reasonably cost-effective. One possible target group is that of the relatives of chronic uremic patients. In a study conducted at the University of Minnesota Hospitals (Spanos et al. [47]), the families of 200 patients awaiting renal transplantation, were examined for evidence of renal disease. If was found that 22% of the families of patients with renal failure had a history of renal failure in other members, a very much higher prevalence than that observed in the population at large. Intensive examination of 209 potential related donors suggested that apparently healthy, symptom-free relatives of CRF patients have an extremely high frequency of underlying renal disease.

Several studies of bacteriuria have shown that hospital patients, diabetics, pregnant women, and school girls have a significantly greater frequency of asymptomatic bacteriuria than control populations (Brumfitt and Reeves [9]). It has been calculated that a prevention program directed at these target groups could reduce mortality due to kidney disease by 1%, mostly through the possibility of successful treatment of acute pyelonephritis, before severe tissue damage has occurred (U.S. Department of Health, Education, and Welfare [50]). Since the costs of a detection test (such as a Greiss test), a confirmatory test (urine culture, colony count, sensitivity test), and treatment are not too high (perhaps $20 for patients already under physicians' care), it appears that among all possible community prevention programs for the reduction of the frequency of chronic renal disease, those concerned with bacteriuria and pyelonephritis in children, pregnant women, and diabetics are the most cost-effective. However, given our limited knowledge about the relation between bacteriuria and chronic renal disease, the effectiveness, in absolute terms, of all such programs may very well be questioned.

1.3. Incidence

Incidence and prevalence of CRF can be estimated by direct surveys, by examination of hospital admission rates, from the incidence and prevalence of individual renal diseases and, most commonly, from mortality statistics. Unfortunately, the uncertainty about the natural history of the CRF condition, strongly affects the reliability of these estimates. All the indicated methods of estimation have disadvantages but, on balance, mortality statistics are the least unreliable source of information. In general, such statistics will lead to underestimates of true incidence and prevalence, since they do not indicate those who died from another disease where CRF was related as a significant factor, or those with CRF who died from other causes, especially cardiovascular. On the other hand, they may list deaths from genitourinary conditions which

were not severe or chronic enough to qualify as CRF. For instance, the U.S. National Health Survey groups kidney disease together with other diseases under the single category heading of Genitourinary Disorders. But the proportion of genitourinary disorders which leads to chronic uremia is unknown, and will vary with the breadth of definition adopted for this group of diseases. Moreover, one cannot assume that nephritis and nephrosis represent the same proportion of reported genitourinary disorders as they do of genitourinary deaths, since the case-fatalities rates are different. The fact that different countries group the categories defined by the International Statistical Classification of Causes of Death (ISCD) in different ways, also creates problems, especially for international comparisons.

In addition, since the CRF patient dies in a few months, unless treated by dialysis or transplantation, the distinction between prevalence (stock) and incidence (flow) is rather ambiguous here, especially for data collected before these forms of treatment had a significant impact on the total numbers of chronic renal patients. This has caused a certain confusion in the literature: for instance, McCormick and Navarro [32] interpret, in terms of prevalence, the estimates of incidence worked out by the Gottschalk Report.

The preceding remarks are probably sufficient to explain why current estimates of the incidence of chronic uremia vary, between twenty and forty patients per 100,000 population, some estimates being as high as 200/100,000 (Dr. Traeger, Lyon) and 533/100,000 (Dr. Alwall, Sweden). The weight of evidence favors values in the 20-25/100,000 range. Such values have been obtained from American and European mortality statistics, and in many cases have been validated by surveys and examination of morbidity rates. Thus, according to data collected by the Research Triangle Institute (U.S. Department of Health, Education, and Welfare [50]), about 50,000 people die as a result of uremia each year in the United States. The corresponding rate of about 25/100,000 has been considered rather conservative by some authorities. On the other hand, the crude death rate from primary kidney disease in the United States in 1969 was 14.3/100,000. When one adds appropriate precentages of the deaths due to other diseases involving the kidney (e.g. hypertensive deaths with arterioral nephrosclerosis, corresponding to ISCD code numbers 442 and 446), the incidence rate approaches the value of 20/100,000.

A mail survey of all doctors practicing in the Southeast Hospital Board of Scotland, carried out by the Scottish Home and Health Department in 1968-69, gave a rate of nineteen CRF patients per 100,000 population (McCormick and Navarro [32]).

An incidence rate of 18/100,000 was determined by a study of Israeli morbidity data during the two year period 1965-66 (Modan et al. [37]). This certainly underestimates the

incidence in the entire population, since only patients whose age did not exceed sixty years were counted; but the error is partly compensated by the fact that in the Israeli study, the condition of CRF was quantified in terms of blood urea (BU), the level being set at 60 mg%, against the 100 mg% level used in the Scottish study.

1.4. Incidence of Patients Requiring Treatment

For the purpose of the present discussion, knowledge of the number of terminal renal patients who might benefit from treatment by intermittent dialysis, with or without transplantation, is even more important than that of general incidence rates. However, estimates of "needs" vary even more widely, being influenced by the availability of facilities and manpower, by the age groups considered, and by the admission criteria adopted by the different dialysis and transplant units. The following table presents a synoptic view of recent estimates. It is an expanded and slightly modified version of Table 1 in Platt [41].

The quantitative significance of the age restriction in defining suitability for treatment of CRF patients can be better appreciated after we examine their age distribution. In forecasting future requirements, one should also keep in mind that the prevention of early deaths from diabetes and other diseases will increase the number of persons going into renal failure.

1.5. Demographic and Socioeconomic Characteristics

Knowledge of these characteristics is essential in determining the most suitable form of treatment for CRF patients. For instance, socioeconomic conditions may preclude the possibility of home dialysis; very young patients are usually unable to submit to the strict discipline of chronic dialysis, and for this and other medical reasons (e.g. growth) they are the most natural candidates for transplantation; persons living alone must rely on institutional care to a much greater extent than other patients, and so on.

Available data (McCormick and Navarro [32]; Perlman et al. [40]) show that, by comparison with the population at large, the CRF population does not differ significantly with regard to sex distribution; but many more men receive transplants (and, probably, also dialysis treatment) than women.

Given the chronic nature of the disease, one would expect that the CRF population differs significantly from the general population with respect to the age distribution. This is indeed the case, and Table 2, taken from McCormick and Navarro [32], points this out quite clearly.

Table 1. Estimates of the incidence of patients requiring treatment for chronic renal failure.

Author	Site of study, publication date	Method used	Age group to be treated	New patients per million population
Gottschalk	USA, 1967	Mortality data.	15-54	35
Lipworth	San Francisco, 1968	Mortality data, hospital records for one-third sample of city population over two year period.	15-64	26
Sheil et al.	Australia, 1969	Patient care: 190 patients treated for a two-year period from a population of 2,000,000.	15-55	45-50
Hallan and Harris	USA, 1970	Expert opinion, mortality data.	15-54	32-42
Branch et al.	Wales, 1970	Hospital lab data and physician survey for 120,000 people over three-year period.	15-50	28
Baltzan and Baltzan	Saskatchewan, 1971	Patient care: 105 patients treated over 5 $\frac{3}{4}$-year period.	5-65	19
Branch et al.	Wales, 1971	Patient care: 56 patients treated in one year from population of 2,600,000.	15-55	25-30

Table 1 (continued)

Friedlander	Baltimore, 1971	Death certificates.	15-54 15-60	49-102 63-151
Pendreigh et al.	Scotland, 1972	Physician survey, hospital records, death certificates.	0-54 0-64	38 52
McGeown	Northern Ireland, 1972	Physician survey, hospital data for a three-year period.	5-55 5-60	33 38
Rosenheim	UK, 1972	Survey of patients in dialysis-transplant units between Jan. 1, 1967 and May 1, 1970. Review of literature.	0 to 55-60	23-39
McCormick and Navarro	Scotland, 1973	Physician survey in Southeast region of Scotland between July 1, 1968 and June 30, 1969. BU level used: $\geq$ 100 mg%.	15-55 16-65	35 40
Modan et al.	Israel, 1973	Hospital lab data and hospital records for all CRF patients (BU $\geq$ 60 mg%), 60 years of age or younger, over a two-year period 1965-1966.	15-60	57.4 (in 1965) 58.0 (in 1966)

Table 2. Comparison of at-risk and CRF populations of
southeastern region of Scotland by age, 1968.

Age Group (years)	Population at risk		C R F (n = 218) Transplant		Dialysis		Other		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
0-14	293,200	25	2	1	0	0	7	3	9	4
15-24	175,700	15	2	1	3	1	13	6	18	8
25-34	140,400	12	1	1	2	1	9	4	12	6
35-44	140,100	12	1	1	5	2	29	13	35	16
45-54	142,500	12	0	0	2	1	43	20	45	21
55-64	140,000	12	0	0	0	0	42	19	42	19
65-74	93,800	8	0	0	0	0	38	17	38	17
75+	49,700	4	0	0	0	0	19	9	19	9
Total	1,175,400	100	6	4	12	5	200	91	218	100

Source: McCormick and Navarro [32].

A median age of forty-five years for chronic uremic
patients has often been suggested. The Scottish data indi-
cate a somewhat higher value for this parameter, and the mor-
tality figures collected by the Research Triangle Institute
(U.S. Department of Health, Education, and Welfare [50]) show
an even more skewed distribution: of the 50,000 yearly deaths
due to uremia in the United States, 79% are in the age group
above fifty-five, 19% in the fifteen to fifty-four age group,
and 2% in the age group zero to fourteen. The fact that most
persons in whom renal failure develops are elderly has far-
reaching policy implications. As the comparative data of
Table 1 imply, age limits have traditionally played a crucial
role in the definition of criteria for admission to treatment
of CRF patients. But recent institutional changes, especially
in the Social Security legislation of many countries, tend to
weaken, or even to abolish, such constraints. Since older
patients are generally unsuited for transplantation, it is to
be expected that the patient load for dialysis centers will
greatly increase in the near future, even if the proportion
of medically qualified patients is smaller in the older age
groups. For further discussion of this point, see section
3 below.

Published information on socioeconomic characteristics
of CRF patients is quite limited. Statistics such as those
published by the Kidney Transplant Registry or by the European
Dialysis and Transplant Association, being largely research
oriented, do not include occupational data, nor descriptive
information indicative of social class. McCormick and Navarro
[32] have found that CRF was underrepresented in the category
of white collar workers and skilled laborers, corresponding
to the standard British Social Classes II and III (this group
represents 65% of the population at risk, but only 39% of the
CRF population). However, given the high proportion (24%)
of patients for which incomplete or no information on socio-
economic characteristics could be obtained, these findings
have only limited significance.

In countries that are not racially homogeneous, the
racial composition of the population may also be an important
factor in calculating treatment requirements. In the United
States, for instance, total mortality from renal disease is,
according to U.S. Vital Statistics (1968), 43.8/100,000 for
nonwhites, against a rate of about 25/100,000 for the white
population. Mortality from hypersensitivity diseases, includ-
ing chronic glomerulonephritis, in 1967 was 4/100,000 in whites
and 9.6/100,000 in nonwhites. Friedlander's analysis of the
data for Baltimore, where 47% of the population is composed
of nonwhites, makes the significance of the racial factor
quite obvious (Friedlander [15]). His estimates, shown in
Table 1, are much higher, and present a greater spread, than
any other published data; they probably reflect an underlying
bimodal distribution.

II. Treatment Modalities

For a patient with irreversible kidney damage, two life-saving therapies are available: intermittent (hemo- or peritoneal) dialysis and transplantation. Conservative management, through drugs, diet, etc. is not really an alternative form of treatment for such patients, but can significantly contribute to the success of the other therapies. For dialysis, the main options are home or institutional treatment; in transplantation, there may be a choice between the use of an organ coming from a living or from a cadaver donor.

2.1. Hemodialysis

Extracorporeal dialysis is the older form of treatment. J.J. Abel, L.G. Rowntree, and B.B. Turner used it on animals over sixty years ago. Neither cellophane, the material commonly used today for the semipermeable membrane through which dialysis takes place, nor heparin, an anticoagulant, were known at that time.

The first use of hemodialysis in humans (Dr. W.J. Kolff in the Netherlands, 1944) marked the availability of cellulose acetate membranes in tube form, and of heparin as an artificially produced anticoagulant. However, hemodialysis entered in common use in the treatment of chronic renal failure only in 1960-1961, with the introduction of the arteriovenous (AV) shunt.

The dialysis systems in current use consist of a fluid preparation unit, and the dialyzer itself. Numerous monitors and fail-safe devices are incorporated in most dialysis machines.

Artificial dialysis takes place by circulating blood on one side of a cellophane membrane, while the other side is bathed by a salt solution. The accumulated toxic products diffuse out of the blood, and the concentration and total amount of water and salts in the body fluids is adjusted by appropriate alteration in the composition of the bath fluid (dialysate). Dialysis is generally performed two or three times a week, each dialysis treatment lasting from six to sixteen hours.

Present artificial kidneys only partially replace a normally functioning kidney, except in relation to electrolytes and acid base. The difficulty of matching the performance of a healthy human kidney can be appreciated by considering that each kidney contains about a million filtration units, the glomeruli. Blood passes to a glomerulus and an ultrafiltrate is formed. This passes down the tubule which modifies it to produce urine. The glomerulus is an extremely permeable filter. A substance with molecular weight of 5,000, e.g. inulin, is cleared from the blood as fast as creatinine,

with a molecular weight of 113. The relative inefficiency of
the artificial dialyzer is indicated by the fact that its
clearance (ml/min) at a molecular weight of 5,000, may be in-
ferior to that of a diseased kidney with a glomerular filtra-
tion rate of 2 ml/min, or about one-fiftieth of the normal
value (Coles [12]). With present equipment, clearance can be
improved only be increasing surface area or treatment time,
and there are definite limits to both. Moreover, normal
kidneys perform important functions other than filtration and
reabsorption. For instance, they produce several hormones,
and convert vitamin D into its active form. The latter fact
explains the close connection between renal failure and sub-
sequent bone disease (osteodystrophy).

2.2. Peritoneal Dialysis

This form of dialysis exploits the fact that the human
peritoneum, with a surface of between 1.5 and 2 m^2 (consider-
ably greater than that of any of the hemodialyzers of today),
behaves as an inert, semipermeable membrane. The technique
of peritoneal dialysis is essentially a simple matter of ab-
dominal paracentesis, and is usually performed at the bed side.
After ensuring that the bladder is empty, a nylon catheter
with a removable central stylet is introduced into the peri-
toneal cavity. Either one or two liters of dialysis fluids
are then instilled during each exchange, which normally lasts
one hour (total treatment time varies between twelve and
thirty hours).

The use of peritoneal dialysis on humans precedes hemo-
dialysis. Ganter used it in Germany in 1923 for acute renal
failure, and the technique was introduced in the United States
twenty years later, again for treatment of acute cases. But
problems of infection, particularly peritonitis, of fluid and
electrolyte imbalance, and technical complications (including
the production of a sterile infusion fluid for use with this
type of equipment), represented major stumbling blocks for
several decades.

The outlook for peritoneal dialysis improved substantially
when, in 1959, Maxwell, Boen and co-workers devised a completely
closed automated sterile supply system to replace the open
system with multiple one-liter bottles, and used repeated punc-
tures instead of a constant indwelling catheter. The advent
of biologically inert silicone-rubber catheters has also in-
creased interest in the possibilities of long-term peritoneal
dialysis for CRF treatment. Tenckhoff et al. [49] have ana-
lyzed ten years' experience with peritoneal dialysis in sixty-
nine patients whose ages ranged from three to seventy-eight
years. Most patients were dialyzed three times a week (three-
fourths of the 11,921 dialyses performed in total were done
at home), for twelve hours overnight. Of the sixty-nine
patients, thirty performed 3,166 dialyses with a single episode

of peritonitis; the remaining patients had seventy-three peri-
toneal infections (0.6% of all dialyses performed). There
were no peritonitis deaths.

Not all workers have obtained such good results, but peri-
toneal dialysis is increasingly becoming an interesting alter-
native even for chronic treatment, especially for particular
groups of patients such as: small children, in whom blood
access is difficult; patients who have lost all blood access
for hemodialysis; patients living alone and for whom unattended
hemodialysis would be hazardous; patients who are intellectually
incapable of dealing with the complicated techniques of hemo-
dialysis; and patients for whom facilities for hospital-based
dialysis are not available, particularly those awaiting trans-
plantation or retransplantation.

The majority of expert opinion considers it unlikely that
regular peritoneal dialysis will ever prove preferable to main-
tenance hemodialysis (Miller and Tassistro [36]; Henry Jones
[23]; but in view of the expected level of demand for dialysis
treatment, no possibility should be rejected without a sub-
stantial body of up-to-date evidence. The results recently
obtained with peritoneal dialysis make randomized control
trials ethically acceptable. Table 3 compares, in qualitative
terms, the major advantages and disadvantages of the two forms
of dialysis treatment.

Table 3. Comparison of hemo- and
           peritoneal dialysis.

	Advantages	Disadvantages
Hemodialysis	- Shorter duration of treatment	- Danger of bleeding through use of anticoagulants
	- Reliable elimination of metabolic waste products	- Heavy demand on the circulatory system
	- Can be used also in cases of stomach operations and in-flammation of the peritoneum	- Greater technical complication of the equipment; greater demand on staff attention
Peritoneal	- Small danger of bleeding	- Longer duration of treatment
	- Limited demands on circulatory system	- Proteins loss
	- No need of artificial vessels	- Danger of peritoneal infection
	- Possibility of drain-ing larger amounts of water	- Greater patient discomfort
	- Greater simplicity of the equipment and lower costs	

2.3. Technical Innovations

A number of recent developments in equipment and clinical techniques show promise of being able to increase substantially the effectiveness of dialysis treatment in the near future.

Much effort has been spent in the attempt to reduce dialyzing time, and in many cases it has proved possible to reduce dialyzing time from thirty to about eighteen hours a week, with significant benefits for the rehabilitation prospects of the patients. Further reductions could probably be obtained, for instance by connecting several dialyzers in series (Coles [12]), but there are physiological limits to the speed with which the organism can adapt to sudden changes in plasma composition.

In the opinion of many experts, the most exciting innovation in recent years has been the development of sorption-based hemodialysis systems (Bultitude and Gower [10]; T.M.S. Chang [11]; The Lancet, August 24, 1974). This started with the work of Dr. H. Yatzidis, in the early 1960's, showing that activated charcoal absorbed creatinine. Professor T.M.S. Chang has designed a microcapsule artificial kidney, in which the patient's blood flows through a bed of 300 g. of microcapsules of activated charcoal, contained in a cylindrical chamber, 8 cm. high and 10 cm. in diameter; it then returns through an air and clot trap to the system circulation. No blood pump is needed for patients with AV shunts. So far, fifteen chronic patients have been treated, three of them for more than six months each. The results indicate that, so far as the relief of uremic symptoms and the general feeling of well-being in the patient are concerned, two hours of this treatment are as effective as six hours of treatment with a more conventional hemodialyzer. However, a few problems, such as the removal of water, still exist.

The trend toward smaller disposable dialyzers is continuing. A truly portable, miniaturized kidney machine, using cartridges for the dialysate, would represent a very important advance, but a real breakthrough in this direction is not yet in sight.

2.4. Home Dialysis

The organization of dialysis treatment in the home of CRF patients, has become an important component of dialysis programs in a number of countries. In England and Wales, the Department of Health and Social Security has adopted the policy that CRF patients should be treated initially by hemodialysis at a hospital, acting as a regional renal unit, and subsequently be discharged from the hospital, either with a successful transplant or as a trained home-dialysis patient (Grant and Whelpton [20]). Even patients who receive successful kidney transplants have been supported for varying periods by home dialysis. Of the 1,500 patients being treated by hemodialysis

in the United Kingdom, as of January 1973, nearly 900 (60%) were on home treatment.

In the United States, the proportion of patients on home dialysis varies from almost 100% in the State of Washington, to 33% in New York State and 20% in Massachusetts (part of this variation is explained by institutional factors: in some states, major insurance policies cover center but not home dialysis). About 37% of the 7,305 patients on chronic hemodialysis reported to the U.S. National Dialysis Registry as of January 1, 1973 were being treated at home.

If one were to extrapolate the present trend toward increasing reliance on the home treatment, it would indeed appear that institutional dialysis is bound to be reduced to a rather minor role in the service of research, training, and transplantation. But the success of a large program of home dialysis depends on a number of factors, many of which are outside the control of the health authorities. With increasing experience, these difficulties become more and more apparent.

The patient and his official helper, usually the spouse, must be trained so that he may be able to treat himself and to take care of the machine. Given the level of technical complexity of hemodialysis equipment, successful training requires a certain level of intelligence, and considerable pedagogical skills on the part of the nursing and technical staff.

A room in the patient's home must be set aside for this purpose, after the necessary alterations have been made. Alternative arrangements are necessary if suitable space inside the house is not available. The possibility which has been suggested, of installing a mobile unit outside the house (Grant and Whelpton [20]), is often infeasible in an urban setting.

A team of technicians must be organized to control the first home dialysis, ensure that the patient has a sufficient stock of the necessary materials (intravenous fluids, tubing, eparin, etc.), maintain the machine in good working condition, and provide other emergency services. The number of required technicians varies widely with geographical dispersion of the patients, nature of the terrain, road and traffic conditions, and the weather.

A telephone line connecting the patient with the renal unit is absolutely necessary, and the possibility of bringing him back to the unit, in case of serious technical or medical complications, must be arranged under all possible circumstances. Contingency plans must also be worked out to meet such eventualities as restrictions in electricity supplies caused by industrial action, power failure, extreme weather conditions, natural catastrophes, fire, and so on.

Even under normal circumstances, patients occasionally have to return to the dialysis unit for a variety of reasons. Back up rates of 5% to 8% have been reported, when external shunts were used (Platt [41]). Thus, about twenty home patients will keep one center bed in constant use.

The benefits of home dialysis, when it is feasible, are of course quite substantial. They are economic (see below, section 3); medical (reduced danger of infections, especially hepatitis); psychological (greater self-reliance of the patient and possibility of choosing preferred periods of treatments; but problems arising out of fears of machine failure, lack of sleep, family tensions, etc. have been reported by Blagg et al. [6] and by Gordon [18], among others); and logistical (reduced travel time for the patient). Mortality statistics do not reveal any clear-cut superiority, in terms of survival rates, of either home or institutional dialysis. The differences that have been reported can be explained both in terms of selection bias, the patients selected for home treatment being usually those with better prognoses, and of the fact that the high initial mortality has already occurred in the hospital centers where the patients are being trained for home dialysis.

Experience with other organizational forms, in particular the satellite centers, is still too limited to justify even a tentative assessment. Undoubtedly, the strong research orientation still prevailing in most hospital units, has not stimulated the search for organizational structures that are adequate for the task of providing large-scale dialysis services.

2.5. Transplantation

This is the second major form of treatment of CRF. Kidney transplantation has made great progress since the "black years," back in the 1950's, described by the former surgeon-in-chief at Peter Bent Brigham Hospital in Boston (Moore [38]): "Several of the patients operated on for kidney transplantation at Peter Bent Brigham Hospital during the 'black years' between the introduction of whole body radiation and the discovery of immunosuppressive chemotherapy were admitted with no kidneys whatsoever . . . . Repeated dialysis was then in an infant stage, and any concept of maintaining a person for weeks, months, or even years under dialysis alone was simply out of the question . . . . [T]he outlook without operation was nil, and standards for acceptability of operation were therefore lowered to give the patient at least some chance for recovery. In many of these early desperate attempts, experiences were gained which later made it possible to raise the standards of acceptability for other patients with less urgent situations."

An important step forward was represented by the first
successful transplantation between a nonidentical donor and
recipient, performed by Dr. J. Murray in 1958 (the patient
lived for five years). But in 1963, the general situation
still presented "a dismal picture of repeated failures and
only an occasional success" (Starzl [48]).

The process of systematic assessment of the progressively
improving results of kidney transplantation was greatly facil-
itated by the creation, of the Human Kidney Transplant Registry
in 1963 in Boston. Data from institutions in North America,
Europe, Australia, and Japan were collected and analyzed on
a yearly basis. The present Registry, the direct descendant
of the first Boston Registry, operates under sponsorship of
the American College of Surgeons, and receives funding from
several institutes of the National Institutes of Health. In
1972, 246 institutions reported to the Registry, 135 from
North America and 111 from other centers abroad, particularly
in Europe and Australia. The 11th [14] Report of the Registry
includes data relating to 12,389 renal transplants, comprising
experience from 1951 through 1972 (11,264 first transplants,
1,019 second transplants, and 106 third and subsequent grafts).
A notable innovation of the 11th Report is its reference to
five-year figures on survival and duration of function.

The kidneys used for transplantation come either from a
living donor (usually a parent or sibling), or from a cadaver.
In the early years of kidney transplantation, transplants from
living, nonrelated donors were relatively frequent. Today,
such donors are generally considered unacceptable, both on
ethical and on medical grounds, since all available statistics
indicate that the changes of success are higher with cadaver
than with living nonrelated donors (see below).

Medical efforts in recent years have been concentrated
on ways of obtaining better donor-recipient matching, especially
through careful tissue typing, and on post-operative treatment
using benign immunosuppressant drugs, such as azathioprine.
Other methods to reduce the immune response (e.g. antilymphocyte
serum and extracorporeal irradiation of the blood) are still
in the experimental stage.

It has been estimated that about 16% of all the patients
who annualy die from end-stage uremia are ideally suited for
transplantation (Department of Health, Education, and Welfare
[50]). However, there are currently a number of major obstacles
to greater use of renal transplantation from living donors. The
use of living related donors raises serious moral questions,
since the risks for the donor involve not only the possibility
of future renal failure, but also hypertension and its associ-
ated cardiovascular disorders. At any rate, such donors can
provide only a limited number of kidneys.

2.6. The Use of Cadaver Kidneys

For these reasons, and with the improvement in transplan-
tation therapy, nonliving donors are rapidly becoming the most
important source of organs. This trend has been strongly rein-
forced by the finding that a second, or even a third, trans-
plant is possible (and that sometimes the second transplant
is much better tolerated than the first); and by more exten-
sive use of artificial dialysis to support the recipient during
the phase of acute renal failure, due to the tubular necrosis
which may immediately follow transplantation of a cadaver kid-
ney.

The 11th Report of the Human Renal Transplant Registry
[14] indicates that 63.4% of all renal grafts reported to
the registry were from cadaver donors. This figure is heavily
modified by United States experience, where only 52.6% of
the grafts came from this source. In Europe, the proportion
of organs from nonliving donors rises to 78.8%, and in
Australasia to 98.3%.

But, again, any direct extrapolation from these data is
unjustified, as long as a number of medical, logistical, and
legal problems remain unsolved. Among the medical problems
are those of better histocompatibility matching, development
of new methods of immunosuppression and induction of tolerance
at birth or in the adult. Techniques of assessment of cadaver
kidneys for transplantation are still in their infancy.
Whether in situ perfusion is desirable and what is the nature
of the ideal perfusate is still controversial; but evidence
is accumulating that it may be possible, by perfusion, to
identify those cadaver kidneys which will never function
(Baxby et al. [4]).

The main logistical problems are those of preservation
and transportation. Renal preservation can be divided into
four different types (Belzer [5]): simple hypothermic storage
for up to ten hours; short-term preservation for up to three
days; intermediate-term preservation for two to three weeks;
long-term preservation for months or years. Using methods of
continuous pulsatile perfusion, it has proved possible to
store kidneys for an average of twenty-nine hours (University
of California, San Francisco), and kidneys have been success-
fully transplanted after storage periods of up to three days.
Thus, short-term preservation provides enough time to make
transplantation of cadaver kidneys a semielective procedure,
except for the crucial period in which donor nephrectomy
takes place. This means, in particular, that there is suffi-
cient time to perform viability testing before transplantation,
and that a sudden influx of a large number of cadaver organs
to a transplant center can be managed even by a small team.

However, the advantages of short-term preservation over simple hypothermic storage do not show up in the respective survival rates, since the extra time made available has not allowed, so far, improvement of donor-recipient matching by current methods of tissue typing. Only with intermediate-term storage will the more time-consuming methods of donor-recipient matching, such as mixed lymphocyte culture, become practical.

Ideally, the kidney to be used in a transplant operation should be obtained from the so-called heart-beating cadaver, to avoid warm ischemia. Nephrectomy must be performed within one hour of death, and possibly sooner, and this is where the legal problems arise. In the absence of laws permitting an individual to bequeath any organ after his death, the consent of next of kin must be obtained. The recent decision by the surgeons of Addenbrooke's Hospital in Cambridge, England, to discontinue kidney transplants (Jones [24]), arose from a disagreement with the Cambridge coroner over securing written permission from bereaved relatives.

When the coroner insists upon written permission from the relatives before removal of the organs, many surgeons feel that they have no alternative but to abandon transplantation for the time being, since to use organs whose usefulness has been substantially reduced by long delay, can only harm a team's reputation by greatly lessening the probability of success.

In every country, transplant teams are now experiencing an acute shortage of cadaver kidneys, in spite of the fact that the pool of potential donors probably exceeds half the population. In 1972 the British Department of Health and Social Security introduced a kidney donor card scheme (Ascott [1]). So far, the scheme has not had a great deal of impact on the supply of organs; at any rate, the existence of a card does not guarantee that kidneys will be removed at death, especially if the card is not readily apparant among the donor's immediate possessions.

2.7. Survival Rates

In discussing survival rates, one has to distinguish between patient survival and kidney survival, since the failure of a tranplanted kidney does not necessarily mean patient death. Data summarizing experience from 12,389 renal transplants performed from 1951 to 1972 are given in Table 4, taken from the 11th Report of the Human Renal Transplant Registry. The data for the four-year period 1967-1970 are also presented in graphical form to make the comparisons clearer (Figures 1-4.)

Table 4.

Patient Survival and Transplant Function of First Transplant

Year of Transplant	Sample Size	One Year		Two Years		Three Years		Four Years		Five Years	
		% Alive	% Functional	% Alive	% Functional	% Alive	% Functional	% Alive	% Functional	% Alive	% Functional
Sibling 1951-1966	243	68.5	64.1	62.2	57.3	58.5	53.1	56.1	49.3	54.1	46.2
1967	144	84.6	78.4	77.7	71.3	72.9	66.2	66.3	59.5	63.0	55.6
1968	193	89.0	81.3	83.8	75.5	81.4	72.3	77.6	66.2	71.4	59.4
1969	210	82.5	76.2	78.2	71.3	76.9	68.4	73.7	65.6	...	...
1970	259	87.1	82.5	85.0	79.1	82.5	73.3	...	...	...	...
1971	364	85.8	73.8	81.7	69.6	...	...	...	...	...	...
1972	202	87.4	74.0	...	...	...	...	...	...	...	...
Parent 1951-1966	403	61.2	56.4	56.6	50.2	52.9	45.4	51.0	42.7	50.4	40.7
1967	148	74.9	72.2	69.1	63.9	64.6	58.4	63.0	55.5	60.8	51.7
1968	201	79.2	72.5	75.2	67.3	71.0	61.0	66.5	52.8	66.5	51.4
1969	213	80.8	71.7	75.3	65.0	70.6	59.3	67.4	55.3	...	...
1970	246	84.9	74.2	80.5	68.6	79.2	63.2	...	...	...	...
1971	292	86.6	72.9	82.4	67.7	...	...	...	...	...	...
1972	155	81.7	76.4	...	...	...	...	...	...	...	...
Cadaver 1951-1966	683	42.0	35.6	34.0	27.8	28.7	22.3	25.9	19.5	23.2	16.3
1967	395	56.0	45.3	49.1	38.7	44.7	33.9	40.3	29.1	39.3	26.6
1968	641	58.3	47.5	51.3	40.3	46.1	34.9	44.1	32.2	42.6	29.4
1969	839	66.2	54.9	59.9	47.7	55.2	42.0	53.6	39.7	...	...
1970	1,083	70.2	56.1	64.1	47.2	60.6	42.3	...	...	...	...
1971	1,390	69.6	52.8	64.7	46.6	...	...	...	...	...	...
1972	669	71.8	45.4	...	...	...	...	...	...	...	...

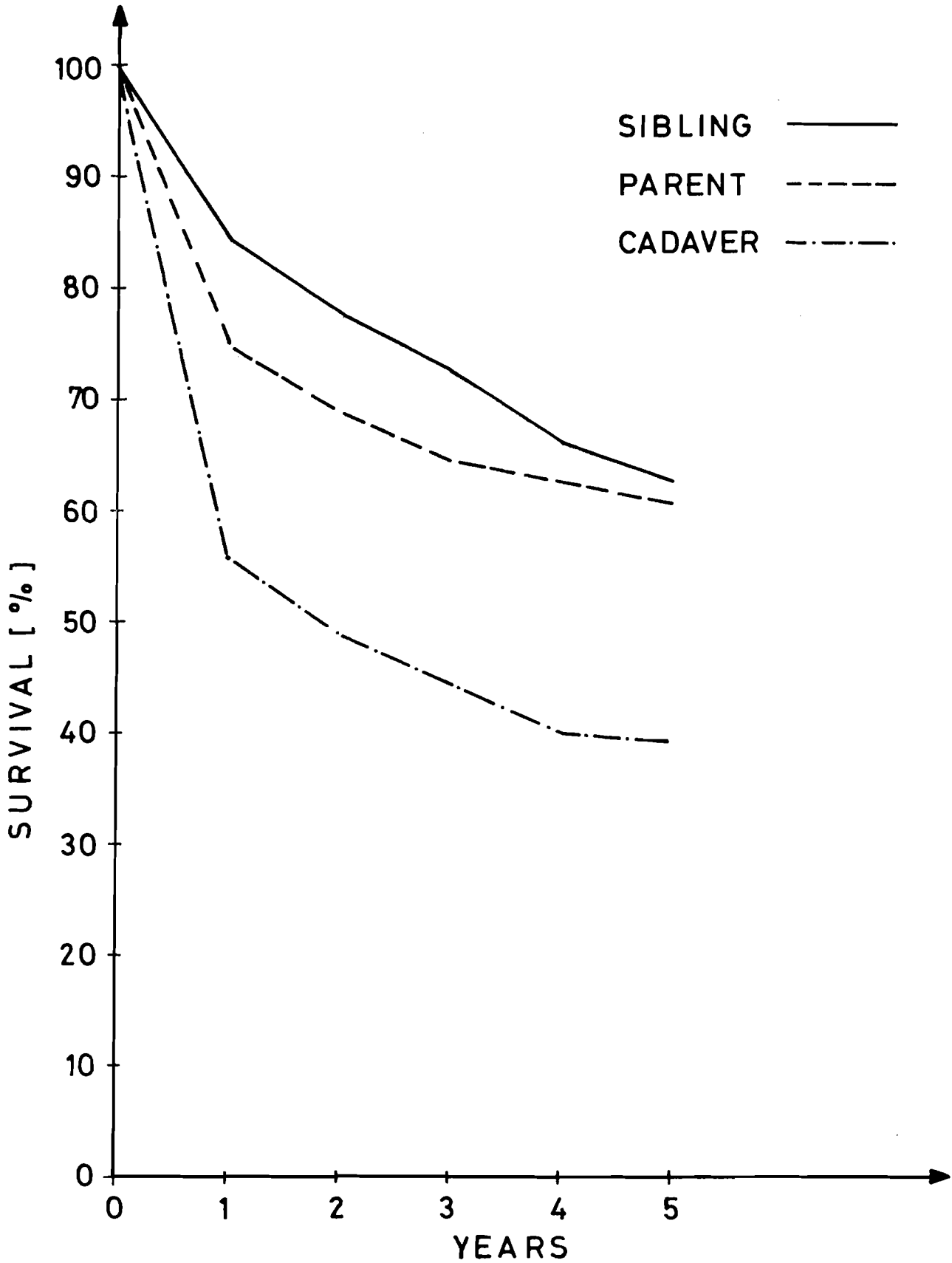Source: 11th Report of the Human Renal Transplant Registry [14].

FIGURE 1. PATIENT SURVIVAL CURVES FOR RECIPIENTS
OF SIBLING, PARENT AND CADAVER ALLOGRAFT.
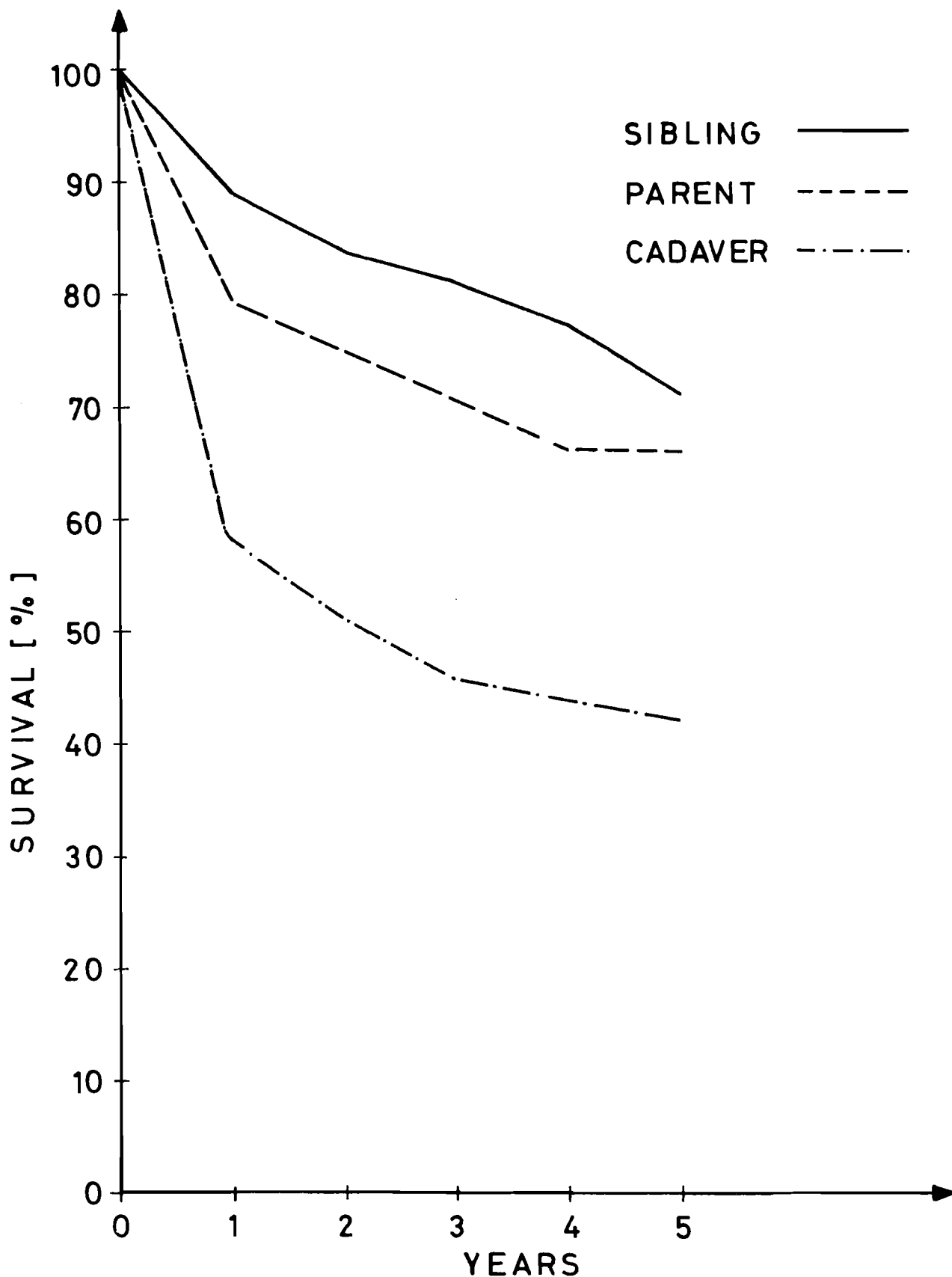YEAR OF FIRST TRANSPLANT 1967.

FIGURE 2. PATIENT SURVIVAL CURVES FOR RECIPIENTS
OF SIBLING, PARENT AND CADAVER ALLOGRAFT
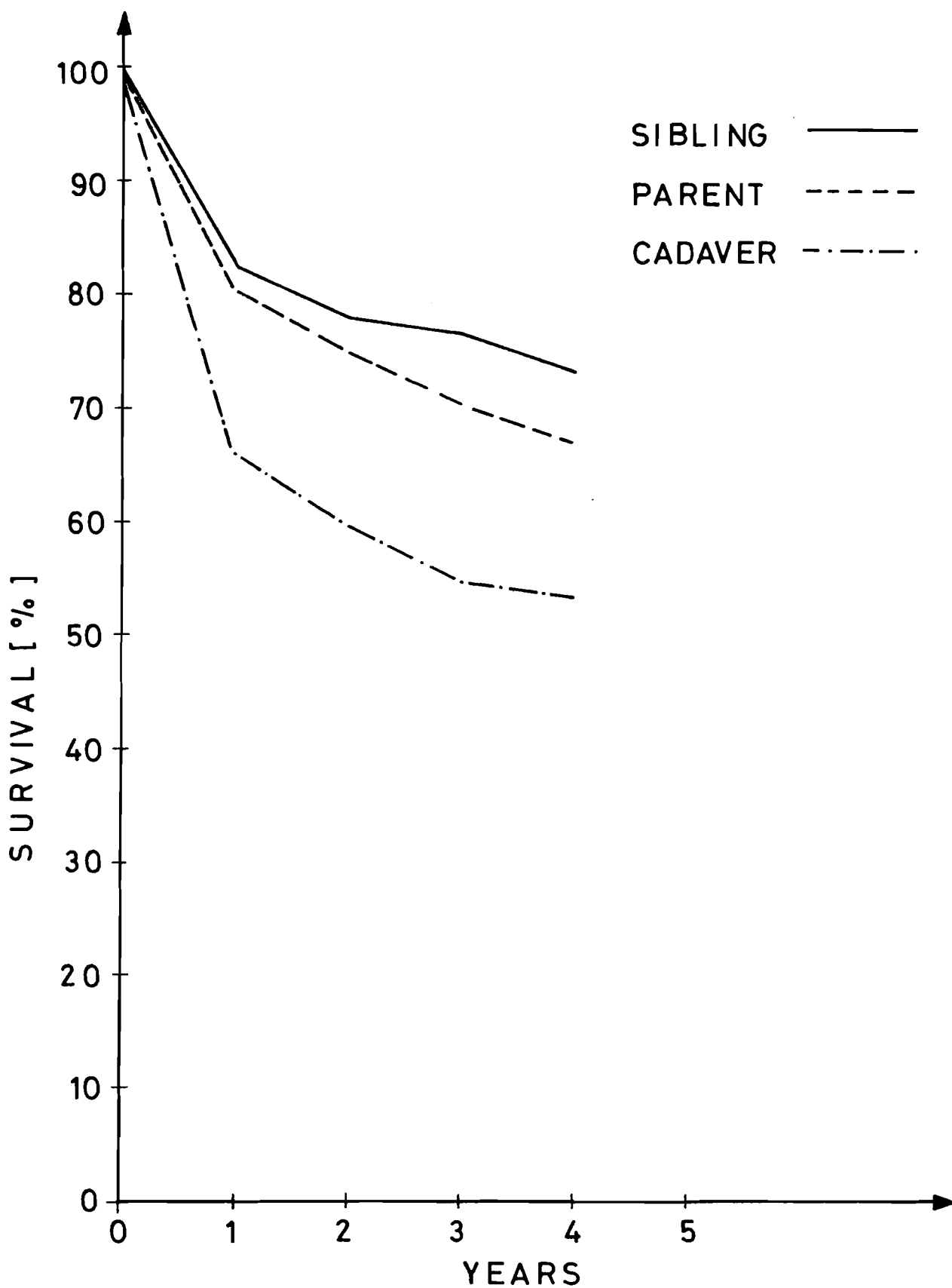YEAR OF FIRST TRANSPLANT 1968.

FIGURE 3. PATIENT SURVIVAL CURVES FOR RECIPIENTS
OF SIBLING, PARENT AND CADAVER ALLOGRAFT.
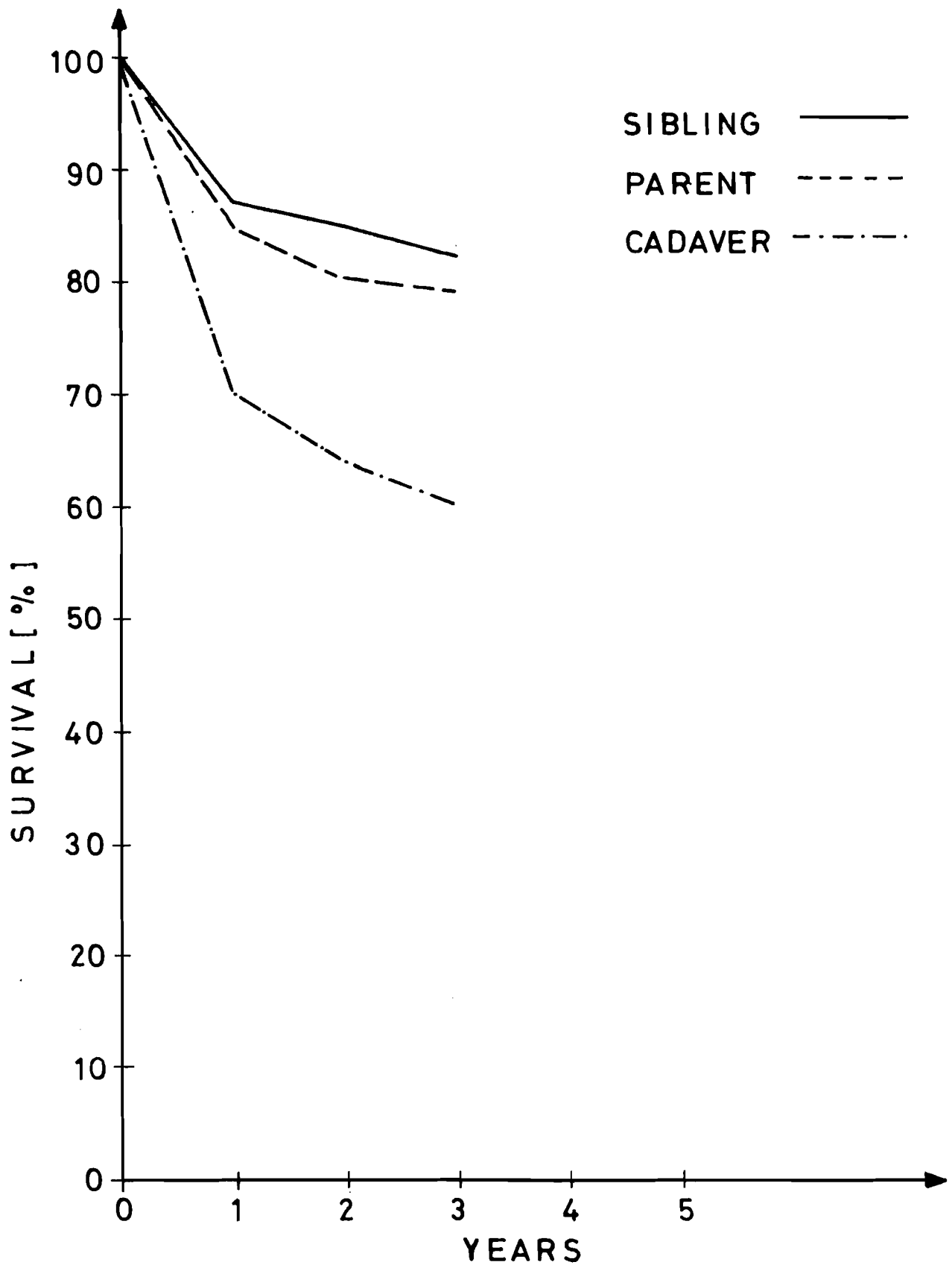YEAR OF FIRST TRANSPLANT 1969.

FIGURE 4. PATIENT SURVIVAL CURVES FOR RECIPIENTS OF SIBLING, PARENT AND CADAVER ALLOGRAFT. YEAR OF FIRST TRANSPLANT 1970.

A thorough statistical analysis of these and related data must be deferred to a subsequent paper. However, it is quite clear from the information collected here that the differences between allograft survival curves for recipients of parental and of sibling transplants are not statistically significant. The same is true for the patient survival curves of recipients of parental and of sibling transplants, whereas the differences between the recipients of cadaver kidneys and the recipients of organs from living related donors are significant for both allograft and patient survival curves.

Naturally, the data reported by the registry are highly aggregated, and conclusions based on them must be interpreted with care. Our inferences, however, are supported by other, independent studies analyzing the experiences of individual transplant centers over a number of years. For example, Lowrie et al [31], discuss the results of the transplant and dialysis program of the Peter Bent Brigham Hospital in Boston, for the eight-year period 1964-1971, and reach the same conclusions concerning the differences among survival rates in the three classes of patients. Also the absolute values of the survival rates are in good agreement with those reported by the Registry.

Another conclusion of the Boston study is that dialysis patients (home dialysis) exhibit survival curves similar to those of recipients of transplants from living, related donors, but show significantly higher survival rates than recipients of cadaver allografts. This finding agrees with the data of the 1972 U.S. National Dialysis Registry, which found survival rates at one and two years, of 90% and 80%, respectively, for all dialysis patients. These values should be compared with the transplant survival rates for 1971 given in Table 4.

A further interesting question is whether the organizational characteristics of the transplantation centers, and in particular their size, has any influence on the survival rates. Information on this point would be useful in determining the optimal size of transplantation centers, and methods of allocation of organs from kidney banks.

Let us define, with the Transplant Registry, a small (large) center as one performing less than (at least) twenty-five transplantations per year. Considering only data from United States centers, we find that in 1965, the one-year survival rate for large centers was 54%, significantly higher than the 36% rate of the small centers. However, if we stratify the population of recipients according to the origin of the organ (sibling, patient, cadaver), it turns out that the difference is significant only for cadaveric and for parent

donors, but not for sibling donors (one-year survival rates: 68% for large centers, 65% for small centers).

In subsequent years, the overall differences are less pronounced: in 1969 the one-year survival rate for large centers was 78%, against 74% for small centers; in 1970, 82% and 78%; and in 1971, 83% and 77%, respectively. Disaggregated data for the later years were not available to check how much of the difference could be ascribed to the type of donor.

III. Economic Costs and Mechanisms of Financing

As the title of this section suggests, the economic costs of medical treatment cannot be meaningfully assessed independent of the mechanisms of financing, and of other institutional factors. Contrary opinions (Klarman et al. [27]) are, I believe, incorrect and the case of CRF shows clearly why this is so.

A situation in which the costs of artificial dialysis and transplantation are covered by private health insurance, voluntary contributions, and a variety of public sources (e.g. Veterans Administration, State Medicaid programs, Medicare and Federal research funds, in the United States) differs quantitatively and qualitatively from one in which such costs are covered by social security.

Because patient selection based on criteria other than strictly medical ones is virtually impossible under social security arrangements, a substantial and constantly increasing proportion of the CRF patients being treated would be composed of elderly patients (see section 1.5 above). In fact, even a limited relaxation of age limits can have a significant impact on patient caseload. For instance, the sudden jump in the estimate of CRF patient caseload in the State of Washington, from seventeen per million in 1969 to thirty-five per million in 1971, can probably be explained in this way.

Few patients in the older age group (sixty years and above) can undergo transplantation. On the other hand, with improvement in dialysis techniques, old age (and perhaps even young age, say two to fourteen years) can no longer be considered a crucial factor in determining medical suitability (Meadow et al. [35]; Ghautous [17]). Thus, the vast majority of elderly CRF patients would be treated by dialysis (in the hospital, moreover, since home dialysis would be impossible for most of them).

Because the aged patient requires more care, the burden on hospital facilities and on the staff will increase significantly; rehabilitation problems will be much more severe. Present difficulties in attracting a sufficient number of nephrologists and other medical personnel to dialysis centers

(Platt [41]), would be compounded in a situation in which a majority of the patients are elderly.

The effects of the mechanism of financing can be felt in many other ways. For instance, under Section 299-I of the Social Security Amendments of 1972 (so-called HR-1), costs of dialysis or transplantation in the United States are reimbursable only after the first ninety days of care. This creates an incentive to delay transplantation, while the patient waits on dialysis for three months. The most favorable moment for transplantation may thus be lost, because of "holding dialysis" which could induce sensitization to antigens in transfused blood (Friedman and Kountz [16]).

In discussing home dialysis (section 2.4), I have already mentioned how some insurance policies cover hospital, but not home dialysis, thus significantly affecting the mix of the two modes of treatment, and the overall cost of CRF. The same restriction appeared in several of the State Medicaid programs in the United States (Platt [41]).

To estimate the economic cost of CRF, one must take into consideration, among other factors, the indirect costs of morbidity, defined as the difference between predisease earnings and earnings during the course of the disease. This component of cost may then be expressed as a percentage of predisease earnings, and calculations have been made on the basis of a 25% loss in income (Hallan and Harris [22]). However, under a system of social security or social insurance, it may be advantageous for the chronic dialysis patient, especially if he is married, to give up his job altogether in order to receive an invalid pension.

Thus, no meaningful cost estimates can be derived, without taking into consideration financing mechanisms and other institutional aspects of the problem. For this reason, not to mention the distortions introduced by recent inflation and soaring costs, published cost figures for hospital and home dialysis and for transplantation must be interpreted with great care.

Using data collected by the Gottschalk Committee, the following estimates have been calculated (Klarman et al. [27]).

Table 5. Present value of expenditures and life years gained
          per member of cohort embarking on transplantation
          and on center and home dialysis (discount rate: 6%).

Modality	Present Value of Expenditures	Life Years Gained	Cost/Life Year
Dialysis	$ 104,000	9	$ 11,600
Center	104,000	9	11,600
Home	38,000	9	4,200
Mean	71,000	9	7,900
Transplantation	44,500	17	2,600
Adjusted for Quality (+ 25% of life years)	44,500	20.5	2,200

The values given in the table correspond to an average
yearly cost of $14,000 for hospital dialysis, $5,000 for home
dialysis, and $13,000 for transplantation. These figures agree
fairly well with those given by Hallan and Harris [22].
British costs calculated at about the same time (Kerr [25]),
put the cost of dialysis per patient at about £2,000 for capi-
tal costs and £1,400 as the yearly running costs. More recent
estimates put the yearly cost of hospital dialysis at $15,000
to $25,000 while the cost of home dialysis has remained at the
$5,000 level (Friedman and Kountz [16]), a revealing indica-
tion of the dynamics of personnel costs. Unpublished figures
for the United Kingdom, expressed in 1972 prices and using a
discount rate of 10%, indicate a cost per patient per annum
of approximately £5,600 for hospital dialysis, and £3,400
(plus an initial cost of £1,300) for the home treatment.

The estimates appearing in Table 5 can be misleading in
yet another sense. The cost-effectiveness ratios given there
point very definitely to transplantation as the optimal policy
for the treatment of CRF. However, in the words of two well-
known medical experts, "The reality facing the treatable
uremic patient in mid-1973 is that his present alternatives
remain either home hemodialysis or outpatient-center hemo-
dialysis" (Friedman and Kountz [16]). The point of general
methodological interest here is that cost-effectivenes or
cost-benefit ratios are of little use to the policy maker if
they are not preceded by a careful exploration of the feasibil-
ity domain, since they can vary quite significantly with the
scale of the program and with the magnitude of the effort re-
quired to overcome presently binding constraints.

IV. Estimating Long-Term Requirements

Since any future program for the treatment of CRF will
have to rely to a large extent on hemodialysis, it is impor-
tant to estimate program requirements under various admission
policies and for different time horizons. The possibilities
of transplantation (and retransplantation) must also be taken
into account since the rate of transplantation is, to a cer-
tain extent, a decision variable and will affect the size of
the dialysis pool.

The model to be discussed in this section has consider-
able flexibility in these respects, and can accommodate differ-
ent hypotheses concerning survival rates, transplantation rates,
admission criteria, and long-term epidemiological and demo-
graphic trends. The population of patients on chronic dialysis
is divided into k strata or states, according to the length
of treatment. A patient is said to be in state S_i if he has
been on dialysis for more than i-1 and no more than i years,
for i = 1,2,...,k-1; S_k is interpreted as "k or more years
on dialysis." Different choices of time units are, of course,
possible. It should be noted that the number of years a
patient is on dialysis has more than a purely temporal conno-
tation, since the passage of time usually implies a steady
deterioration in his physical condition.

A patient in state S_i in a given year can move to state
S_{i+1} in the next year, or he can die, or undergo a transplan-
tation. If the transplant fails, the patient can return to
dialysis, with the possibility of a second transplant later
on.

The states S_i, i = 1,2,...,k, form the nonabsorbing part
of the process. The probability of transition from S_i to S_j
is p_{ij}, and P = $\{p_{ij}\}$ is the corresponding substochastic matrix.
S_L is the absorbing state to which the patient moves when he
leaves dialysis, because of death or transplantation.

R(T) denotes the input to the system at time T. It in-
cludes new CRF patients who are accepted for dialysis, patients
who resume dialysis after their allograft has failed, and
patients transferred from other systems. New patients enter
the system in S_1; transfers are placed in the same state they
occupied in the center of origin. Transplant failures could
be assigned to the state they occupied at the time of trans-
plantation, or perhaps to a later state, to account for the
negative physical effects of the operation and of immunological
suppression, and for the likely deterioration in his psycho-
logical conditions (Baxby et al. [4]).

The new arrivals are distributed among the different non-
absorbing states according to a "recruitment distribution"

$p_o = \{p_{oi}\}$, $\sum_{i=1}^{k} p_{oi} = 1$. All recruits are supposed to join the system at the beginning, and all dead and transplanted patients to leave it at the end of each year. These assumptions are, of course, unrealistic but they will not seriously affect our conclusions, particularly for the long-run results.

A potentially more serious assumption is that of the time-independence of the transition probabilities. However, given the present state of knowledge, it would be extremely difficult to specify how the probabilities might change over time. Because of advances in medical science and in technology, one would expect some improvement in the probabilities of survival. At the same time, the progressive relaxation of the criteria of "medical suitability" has the opposite effect and available data do not allow any firm conclusion as to what the net result might be. Something more can perhaps be said about tne dependence of the transition probabilities on the age group to which the patient belongs. It may be advisable to use different matrices P for different age groups, especially if the elderly form a substantial part of all dialysis patients.

The basic structure of our model can be represented as follows:

		P_{o1}	P_{o2}	P_{ok}
	S_L	S_1	$S_2 \ldots \ldots \ldots S_k$	
S_L	1	0	0 $\ldots \ldots \ldots$ 0	
S_1	P_{1L}	0	$P_{12} \ldots \ldots \ldots$ 0	
S_2	P_{2L}	0	0 $P_{23} \ldots \ldots$ 0	
$\vdots$				
S_k	P_{kL}	0	0 $\ldots \ldots \ldots P_{kk}$	

Let $n_i(T)$ be the number of patients in S_i at time T. The initial distribution of patients in the different nonabsorbing states is given by the vector $\underline{n}(o) = (n_1(o), n_2(o),\ldots,n_k(o))$. The values of $n_i(o)$, $i = 1,\ldots,k$, are assumed to be known. $N(T) = \sum_{i=1}^{k} n_i(T)$ is the total number of dialysis patients at time T. For $T > 0$, the $n_i(T)$ are random variables. Elementary

calculations show that the expected number of patients in S_i at time $T+1$, denoted by $\bar{n}_i(T+1)$, is given by the formula

$$\bar{n}_i(T+1) = \sum_{h=1}^{k} p_{hi}\, \bar{n}_h(T) + R(T+1)\, p_{oi} \ . \tag{1}$$

$R(T)$ is supposed to be known, at least in the mean value sense. Thus, $\bar{n}_i(T)$ can be computed recursively for all T's. Writing (1) in matrix notation:

$$\underset{\sim}{\bar{n}}(T+1) = \underset{\sim}{\bar{n}}(T)\, P + R(T+1)\, \underset{\sim}{p}_o \ , \tag{1a}$$

we find

$$\underset{\sim}{\bar{n}}(T) = \underset{\sim}{n}(0)\, P^T + \underset{\sim}{p}_o [\, \sum_{h=0}^{T-1} R(T-h)\, P^h] \tag{2}$$

where P^o is the unit matrix.

In order to evaluate (2) explicitly, it is necessary to make some assumptions about the functional form of $R(T)$. Two cases are particularly relevant here:

    a) $R(T) = R$ (constant input; for $R = 0$ the model can be used for a cohort analysis);

    b) $R(T) = Rx^T$, $x > 1$ (geometric growth).

In the constant case, (2) becomes

$$\underset{\sim}{\bar{n}}(T) = \underset{\sim}{n}(0)\, P^T + R\underset{\sim}{p}_o (I-P)^{-1} (I-P^T) \ . \tag{3}$$

For the case of geometric growth, the expression is

$$\underset{\sim}{\bar{n}}(T) = \underset{\sim}{n}(0)\, P^T + Rx\underset{\sim}{p}_o (xI-P)^{-1} (x^T I-P^T) \ . \tag{4}$$

Notice that the existence of the inverses $(I-P)^{-1}$ and $(xI-P)^{-1}$ is assured by the fact that the matrix P is substochastic, and hence all its eigenvalues are between 0 and 1. In the particular case under discussion, P is actually upper triangular, and the elements of its main diagonal (its eigenvalues) are all equal to zero, except for p_{kk} which is strictly between 0 and 1.

Particular interest is attached to the asymptotic behavior of the system. For T → ∞, equation (3) becomes

$$\bar{\underset{\sim}{n}}(\infty) = Rp_O(I-P)^{-1} \qquad\qquad (5)$$

while if R(T) → ∞, as in the case of geometric growth, the size of the system will obviously increase beyond all bounds.

By well-known results in the theory of absorbing Markov chains, equation (5) represents a condition of steady state, in which the number of patients entering the system equals the number of those leaving it. It is clear from equation (5) that the initial distribution of patients, $\underset{\sim}{n}(0)$, does not affect the limiting size and structure of the system.

Using methods due to Pollard (Pollard [43]; Bartholomew [3]), one can also calculate the variances and covariances of the numbers of patients in the different states. These methods presuppose that the input to the system is stochastically independent of the movement of patients within the system. This hypothesis is not quite true in our case, since transplant failures going back to dialysis are counted with the new arrivals. However, the dependence is rather weak (of the 12,389 transplants reported by the Transplant Registry in 1973, only 9% were second or third transplants, a slight increase from the 7% value observed in 1967), and it should not seriously affect the analytic results. This question will be investigated in a future paper, where the results of calculations performed under a variety of hypotheses, will also be reported.

I shall conclude this section with a small numerical example, where the following model is assumed:

		1	O	O	O	O
	S_L	S_1	S_2	S_3	S_4	S_5
S_L	1	O	O	O	O	O
S_1	.3	O	.7	O	O	O
S_2	.3	O	O	.7	O	O
S_3	.2	O	O	O	.8	O
S_4	.1	O	O	O	O	.9
S_5	.1	O	O	O	O	.9

The initial distribution of patients need not be specified since I shall examine only the asymptotic results, It is assumed that when transplantation is possible, it will usually be performed within the first two years of dialysis treatment. Suppose that 20,000 CRF patients enter the system each year, to be transplanted or treated by dialysis. This corresponds to 40% of all patients who die of chronic uremia each year in the United States. Since

$$
(I-P)^{-1} = \begin{pmatrix}
1 & .700 & .490 & .392 & 3.528 \\
0 & 1 & .700 & .560 & 5.040 \\
0 & 0 & 1 & .800 & 7.20 \\
0 & 0 & 0 & 1 & 9 \\
0 & 0 & 0 & 0 & 10
\end{pmatrix} ,
$$

equation (5) gives the following steady-state structure:

State	S_1	S_2	S_3	S_4	S_5
Number of Patients	20,000	14,000	9,800	7,840	70,560

.

Under our assumptions, the total number of patients in the system each year will thus be 122,200, of which no more than 12,000 could probably be transplanted. Putting the cost of dialysis, rather conservatively, at $15,000 per patient-year (current prices), the total yearly cost would amount to about $1,650,000,000. If it is assumed that one physician, two nurses and three or four technicians and aides are required for every ten patients on dialysis (U.S. Department of Health, Education, and Welfare [50]), such a program would eventually require 11,000 nephrologists, 22,000 specially trained nurses, and more than 40,000 technicians. These requirements would probably exceed any realistic manpower constraint and would, in any event, lead to severe shortages in other parts of the health care system.

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