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Renal Homotransplantation

PART I

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LATE IN THE LEGISLATIVE SESSION of 1972 the H.R.1 Bill amending Medicare-Medicaid was passed by Congress and signed into law by the President. The last provision of the act had a unique effect in that it "socialized" a common human disorder, chronic renal disease. Henceforth, according to the letter of this law, most victims of end-stage kidney disease, after 3 months of renal dialysis, can be treated under federal fiscal sponsorship by renal homotransplantation.

The H.R.1 legislation will give further impetus to the development of a field that has bloomed overnight on its own scientific merit. Consequently, this monograph may be timely as new transplantation teams are formed to meet a predictably increasing demand. We will try to compress our own experience, which spans more than a decade and more than 500 transplantations, and from it draw conclusions for future guidance. To meet these objectives we have undertaken an up-to-date evaluation of all patients in whom operation was performed before July, 1972. Follow-ups have been made current to September, 1973.

Based on this experience, a number of important and often controversial issues will be examined, including variations in immunosuppressive treatment with special reference to antilymphocyte globulin (ALG) and cyclophosphamide, technical innovations and special surgical situations, the role of tissue typing, hyperacute rejection, organ procurement and preservation, the problem of bone disease and hyperparathyroidism after transplantation, the timing and results of retransplantation, and recent changes in the interpretation of histopathologic changes in the homografts.

EARLY TRIALS

The specialty of organ transplantation is the most recently developed of the surgical disciplines, and is one that as a practical venture was considered highly improbable even 15 years ago.[24] The observations that changed this point of view were made in most instances by clinicians who used the kidney homograft as their main experimental model in dogs and as their first clinical application. The principles delineated with the kidney were later applied, essentially without change, to the transplantation of other organs, including the liver, heart and lung. In spite of the glamour of these latter efforts, the simpler kidney transplant still serves as the standard by which management policies involving

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immunosuppression, tissue typing and other matters can be evaluated most precisely.

The first known attempts at clinical kidney transplantation by vascular anastomoses were made without immunosuppression between 1906 and 1923 with sheep,[167] pig,[103] goat[103] and subhuman primate[215, 266] donors. None of the organs functioned, and the human recipients died from a few hours to 9 days after transplantation.

The first renal *homotransplantation* was reported in 1936 by Voronoy[271] who transplanted a kidney from a cadaver donor of B+ blood type to a recipient of O+ blood type in violation of what are now well-accepted rules of tissue transfer (Table 1)[235] (see section on hyperacute rejection). Nevertheless, a few drops of initial urinary excretion were observed. The patient's death 48 hours after transplantation was attributed to a blood transfusion reaction.

In the next 20 years sporadic additional trials were made without the benefit of effective immunosuppression, as recounted 10 years ago by Goodwin and Martin[70] and more recently by Groth[71] for the purpose of recording historic landmarks. By 1951, Küss *et al.*[128] and other members of the French school of surgery[54, 55, 222] had virtually standardized the procedure of kidney transplantation to the iliac fossa, anastomosing the renal to the pelvic vessels of the recipient in much the same way as is practiced today. Despite the lack of success with these early patients, other cases were soon reported from Chicago,[129, 130] Boston,[99, 100] Paris,[151] Toronto,[156] London[104] and Cleveland.[122]

By the middle of the 1950s, the total number of attempts at human renal homotransplantation had reached approximately 30 without any immunosuppression at all, or with adrenocorticotropic hormone (ACTH) or cortisone in a few patients of Küss *et al.*,[128] Dubost *et al.*[54, 55] and Hume *et al.*[100] Most of the homografts never had significant function, and those that did initially, usually underwent prompt rejec-

TABLE 1.—DIRECTION OF ACCEPTABLE MISMATCHED TISSUE TRANSFER*

O to non-O	Safe
Rh− to Rh+	Safe
Rh+ to Rh−	Relatively Safe
A to non-A	Dangerous
B to non-B	Dangerous
AB to non-AB	Dangerous

*The immunologic explanation for these rules is given in the section on hyperacute rejection. O is universal donor. AB is universal recipient.

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tion, as was reported particularly clearly by Michon *et al.*[151] There were three more or less clear exceptions to this generalization. Renal homografts inserted by Lawler,[129, 130] Gordon Murray[156] and Hume[100] and their colleagues were said to have excreted urine for several months before being rejected slowly. The life of Hume's patient probably was increased thereby by several months. The unexpectedly prolonged survival of kidneys in untreated recipients has been explained since by the loss of immunologic reactivity that has been shown to accompany uremia.[44, 112, 155]

An intermediate era in clinical renal transplantation was begun in 1958 by Joseph Murray and his associates[159] at the Peter Bent Brigham Hospital with the use of total body irradiation as the primary means of immunosuppression. In the following 4 years, between 30 and 40 renal recipients were treated primarily in this way, although in a few instances adjuvant therapy was added later with immunosuppressive agents such as 6-mercaptopurine. Almost all of these trials ended in the early death of the recipient, with the few notable exceptions recorded by Merrill,[150] Hamburger,[84, 85] Küss[125–127] and Shackman[214] and their associates. Within 3 years, all but 2 of the patients were dead. Both of the exceptions, who were treated in Boston and Paris in 1958, were given kidneys from fraternal twins; they are still alive and are celebrating their fifteenth post-transplantation anniversaries in the summer and fall of 1974.[79, 80, 157]

The most productive era of clinical transplantation began in 1962/1963, and it is this period and the subsequent decade with which this monograph will be concerned. One factor contributing to the transplant "explosion" was the introduction of primary pharmacologic immunosuppression with the thiopurine compounds, 6-mercaptopurine and its imidazole derivative, azathioprine. These agents were developed by Dr. George H. Hitchings and his colleagues at Burroughs Wellcome and Company, Inc., Tuckahoe, New York, and found by them to inhibit hemagglutinin formation in mice challenged with heterologous red blood cells.[58, 90] Later, the effect of 6-mercaptopurine and azathioprine in ameliorating rodent skin graft and canine kidney rejection was reported by Schwartz and Dameshek[218] and Calne,[27 28] respectively. As recounted by Groth,[71] a number of patients in Europe and the United States were given one or the other of the mercaptopurine drugs between 1959 and 1962, usually with a fatal outcome. However, 2 French recipients survived for prolonged periods of time. One who lived for 17 months was treated in 1960 by Küss and his colleagues[126, 127] with 6-mercaptopurine after initial total body irradiation, and the other was managed similarly by Hamburger and associates[83] in January, 1962. Hamburger's patient, whose donor was a cousin, is still alive and is the

longest surviving non-twin recipient in the world.[79, 80] Murray *et al.*[158] reported the first patient in whom prolonged survival was achieved under primary immunosuppression with azathioprine alone; this recipient of a cadaver kidney lived for almost 2 years.[161] However, even well into 1962, there was little evidence to indicate that drug therapy would yield results substantially better than those obtained with total body irradiation.

Such improvements would await the administration of drugs in combination (see later sections). The most important agent in such pharmacologic cocktails has been prednisone and, as will be shown, it is the steroid rather than the 6-mercaptopurine or azathioprine component of combination drug therapy that has proved to be the only truly indispensable element without which transplantation would not be practical. The experimental basis for the use of steroids to mitigate first-set rejection had been laid a decade earlier by Billingham, Krohn and Medawar[18] with prompt confirmation by others.[29, 124, 148, 154, 234] Concerning second-set rejection, it was demonstrated by Krohn[123] as early as 1954 that cortisone acetate given to rabbits could abolish even a pre-existing state of sensitivity induced by full-thickness skin homografts.

The other main immunosuppressants that have been used in drug combinations for whole-organ recipients are heterologous ALG and cyclophosphamide. The widespread use of these agents came later in the story of clinical transplantation and will be discussed in a subsequent section.

DOUBLE DRUG THERAPY

So far, attention has been focused upon some of the early clinical trials of immunosuppression with total body irradiation, steroids and the mercaptopurine drugs. With each of these agents, and for that matter with cyclophosphamide or heterologous ALG used alone, laboratory research has shown that a protracted and healthy life can be obtained for some canine kidney recipients. However, the consistency with which really long-term survival could be achieved was (and is) poor for the obvious reason that complete control of rejection usually was not possible with a single agent. Since the same kind of treatment failure was observed regularly in almost all of the early patients, there was little encouragement at first to undertake major clinical trials of renal transplantation.

The most important development that made immunosuppression practical was the discovery of how azathioprine and prednisone could be used together advantageously. There were virtually no existing laboratory data to indicate that the benefit of this now universally accepted combination of agents would be as great as it proved to be. Indeed, the

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first publication on experiments in animals[141] was a belated confirmation of the far more convincing observations already made in man.[244]

It is difficult even in retrospect to ascribe priority for azathioprine-steroid therapy to any single authority or transplantation group. What is clear is that by late 1962 the two drugs were being used together at our center[244] and by Hume *et al.*[98] at the Medical College of Virginia with great enthusiasm about their synergism in the prevention or reversal of renal homograft rejection. Murray[161] and Woodruff[288] and their colleagues also reported giving steroids to some of their patients in less regular and less well-defined regimens. Since then, the double drug program of azathioprine and prednisone has become standard therapy throughout the world. Some authorities do not believe that further changes in this regimen (such as the addition of ALG) are necessary.

The Timing of Azathioprine-Steroid Therapy

At our center double drug treatment has been provided in two ways. In both, azathioprine was started shortly before operation and continued indefinitely thereafter, generally in the maximum doses thought to be possible without causing leukopenia. Prednisone was used either prophylactically, beginning on the day before or the day of operation, or it was withheld until the onset of a clinically evident rejection. From our own experience, the technics and drawbacks of both approaches were analyzed several years ago.[235] In retrospect, the most important advantage of withholding steroids until graft repudiation clearly had started was that the features of rejection and host-graft adaptation as well as the influence of drug therapy on these processes could be delineated with some precision. The greatest disadvantage was that the rejections that developed under treatment with azathioprine alone were sometimes very severe and difficult to reverse with delayed steroid therapy. It was found that their incidence and severity were reduced if prednisone was given from the beginning.[235] Consequently, it has been our policy since December, 1963, to treat virtually all recipients of organ homografts with both drugs from the outset.

In 1967, Kountz and Cohn[120] reported that azathioprine and prednisone delivered suddenly into the arterial supply of renal homografts had an increased protective effect on the organs as compared to that obtained with oral or intravenous administration. The steroid amounts were very large, and it soon became obvious that this dose factor rather than the route of administration was the most important therapeutic influence. Subsequently, many centers have reported that by giving large intermittent doses (up to 2 gm) of corticosteroid, the daily maintenance steroid requirements can be reduced.[35, 236, 265, 289]

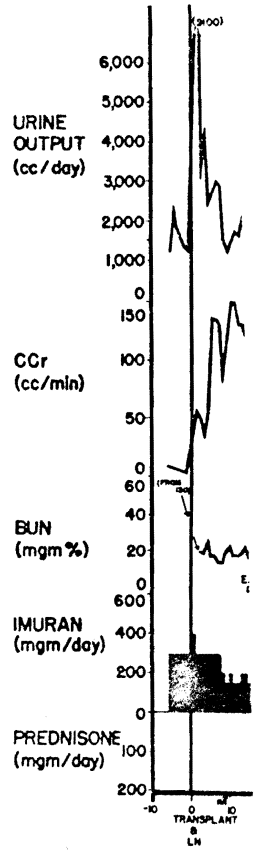
The Reversal of Rejection

The use of the double drug programs promptly led to one of the most important contributions of clinicians: the demonstration that rejection is a highly reversible process. This concept had not emerged from the skin graft experiments upon which the foundations of transplantation biology were largely based, nor was it evident in the first trials of either canine or human renal homotransplantation.

In retrospect, it is probable that the Boston and Paris fraternal twins mentioned earlier both passed through rejection crises. The events in Hamburger's case[85] were the clearest. For almost 3 weeks after operation the transplanted kidney functioned perfectly. Fever, azotemia and proteinuria then developed, but within a 10-day period these symptoms receded without the institution of any specific therapy. Hamburger ascribed the changes to the spontaneous reversal of an immunologic crisis.

Evaluation of the course in Merrill's case[150] was made difficult by complicating circumstances. Although immediate good renal function was obtained also, within a few weeks fever and a rise in BUN level were seen, but at the same time the patient's own kidneys had cortical and perinephric abscesses. After nephrectomies and drainage had been carried out, the deterioration was reversed and Merrill concluded that "the oliguria and nitrogen retention . . . were clearly associated with an episode of infection." Eight months later, a biopsy of the homograft revealed mononuclear cell invasion and other morphologic evidence of chronic rejection. Although function was stable and essentially normal, additional total body irradiation was given as well as a course of adrenal corticosteroids. At the time that these observations were reported, Merrill and his associates believed that a rejection had been "aborted" thereby. In commenting on the significance and the earlier timing of events in Hamburger's case, Merrill expressed doubt that rejection had occurred in the French patient, saying that "it seems highly unlikely . . . that in a partially tolerant patient, rejection would begin at the time at which it might be expected for the non-tolerant person, only to abort spontaneously."

The first suggestion that rejection is a highly controllable and reversible phenomenon came from our own observations in 10 patients treated in late 1962 and early 1963.[244] In 7 patients, clear-cut rejection of variable intensity occurred from 4–34 days after operation (Fig. 1), leading in one case to anuria. In each instance the process was reversed by the addition of massive doses of prednisone to the pre-existing azathioprine therapy (Fig. 1). Three of these 7 patents are still alive more than a decade later and are now among the longest-living recipients of non-twin homografts in the world. After the remarkable effectiveness



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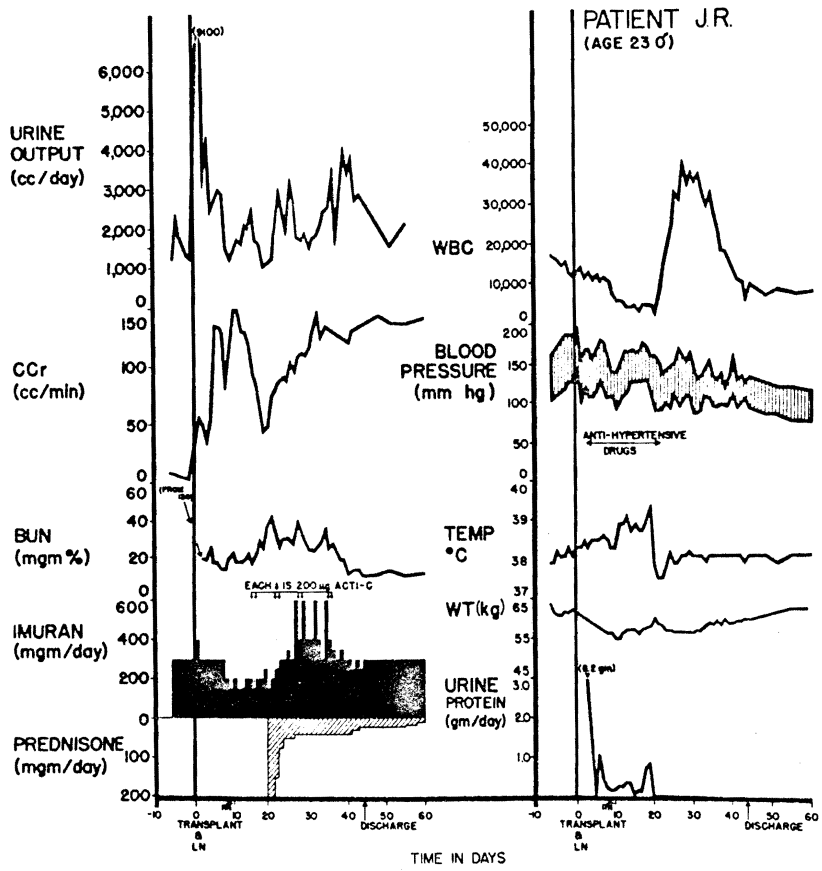

FIG. 1.—Classical rejection crisis in a patient from Series I treated initially with azathioprine (Imuran) alone. Deterioration of renal function began 19 days after transplantation. All stigmata of rejection were present except for acute hypertension and weight gain, which were successfully prevented by medical treatment. With the addition of prednisone the rejection crisis swiftly resolved. *Acti-C*, Actinomycin-C; *LN*, left nephrectomy at time of transplantation; *RN*, right nephrectomy. (From Starzl, T. E., *et al.*[244])

of steroid therapy in this situation had been established from our own experience, but before our findings were published, it was learned that the same kind of rejection reversal with steroids had been achieved by Goodwin and his associates[69] in a young woman whose other main drug was cyclophosphamide and who ultimately died of sepsis 144 days after receiving a maternal homograft.

It was realized also almost from the beginning[235] that a reduction in

homograft blood flow is an integral component of rejection crises and that the pharmacologically induced reversal is accompanied by relief of organ ischemia. Both conclusions have been supported by animal experiments.[66, 201, 206]

Graft "Acceptance"

The reversibility of rejection was only one of the features that established the clinical feasibility of organ transplantation. The quantities of adrenal corticosteroids necessary to achieve reversal were often extremely large and too toxic to be compatible with long survival of the recipient if continued indefinitely. Fortunately, another event of equal practical importance transpired coincidentally with or shortly after the reversal of rejection. The need for intensive immunosuppressive therapy usually diminished with the passage of time both in patients who did and those who did not pass through a clinically evident rejection. Thus, the patient whose course is depicted in Figure 1 had returned within 5 months after transplantation to treatment only with azathioprine, the drug that initially had not prevented the onset of a moderately severe rejection. An ultimate, similar reduction in drug requirement is seen today in almost all new cases although it is known now that there are but few occasions when steroid therapy may be stopped completely. Even so, it is probable that some patients eventually could have *all* therapy discontinued. In our laboratory, dogs that were given treatment with immunosuppressants for only the first 4 months after receipt of life-sustaining liver or renal homografts from nonrelated mongrel donors are living almost 10 years later.[235, 236]

Although it has been well established that a homograft may come to be more or less tolerated in its new host, the explanation for the privileged status is by no means clear, perhaps because more than one immunologic pathway may be involved.

Specific immunologic tolerance.—Probably, the continuous presence of a transplanted organ in a host being treated with immunosuppressive therapy often leads to a selective loss of responsiveness to the antigens of the homograft (tolerance). The evidence that chemotherapy can be used for the induction of narrow-range tolerance is unequivocal, as has been summarized by Schwartz.[217, 219] Experimentally, azathioprine, 6-mercaptopurine, amethopterin, cyclophosphamide and even total body irradiation can be used to promote specific tolerance, provided the antigen in question is administered in an appropriate dose and in close temporal approximation to the immunosuppressive treatment.

One of the theories that has been advanced to explain the specific effect of chemotherapy under these circumstances is depicted in Fig-

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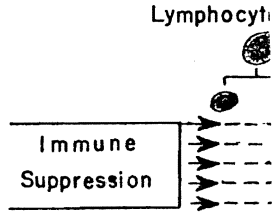
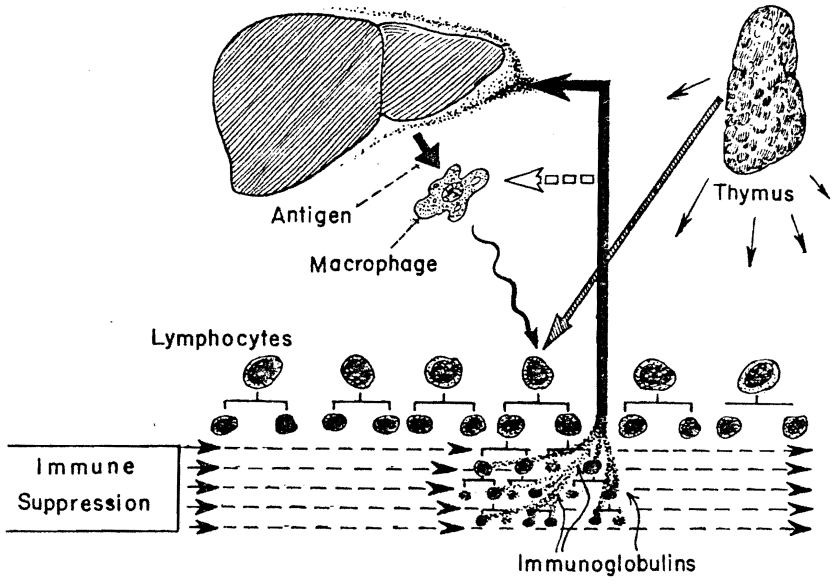


ure 2.[217, 219, 235, 236] The drawing suggests that a clone of lymphocytes that presumably have an active metabolism as the result of stimulation by antigen should be differentially susceptible to killing by antimetabolites. That such an effect could be attained without the need to induce leukopenia implies that specific abrogation of the host immune response is achievable under the conditions of clinical transplantation even though nonspecific immunosuppressive agents are employed.

The concept of "clone stripping" in the scheme of Figure 2 is consistent with the cyclic phenomena that occur characteristically after whole-organ transplantation in treated recipients. But whether and with what frequency human recipients of renal homografts actually establish tolerance to their donor tissue has not been established securely. One reason has been the potential risk that could attend some of the testing, such as skin transplantation, required to prove this possibility. In dogs this has been said to precipitate the rejection of pre-

FIG. 2.—Hypothetical mechanisms by which nonspecific immunosuppression may lead to selective abrogation of the host immune response. Special susceptibility to these agents of a fraction of the lymphoid population could lead to exhaustion of a clone and, hence, tolerance. Since maintenance of such cell lines even in adult life is apparently thymic-dependent in experimental animals, thymectomy would be expected to aid the process; this appears to be true in rodents, but the effect of thymus removal in man has not been shown to be an overriding factor. A possible protective role is shown also of immunoglobulins elaborated by the replicating cells. Conceivably, the antibodies could act at several sites. See text for discussion. (From Starzl, T. E.[236])



viously well-established canine renal grafts.[162] However, Amos and Bach[4] have performed mixed lymphocyte culture examinations from the peripheral blood of a number of the recipients in our hospital and their donors 2–4 years after transplantation. In some patients in whom clear donor-recipient histocompatibilities were detectable by serologic typing, they found that the recipient lymphocytes no longer underwent blast transformation when exposed to killed donor white cells, although they reacted vigorously to third-party lymphocytes.[4] The findings, which were interpreted as indicating specific acquired immunologic tolerance, have been confirmed in patients studied in other centers,[12, 227] but the frequency of this happy occurrence is not known.

ENHANCEMENT.—It was shown by Kaliss[107] that homografted tissue in tumor systems may be protected by the presence of certain kinds of antigraft antibodies. It is conceivable that by a feedback mechanism of protective blocking antibodies or antigen-antibody complexes, the same thing occurs under the conditions of whole-organ transplantation. The process could be envisioned as shown in Figure 2, whereby antigraft immunoglobulins synthesized by the activated clone either shield the target tissue from killer lymphoid cells (local enhancement) or prevent the immune processes from proceeding normally at some more distant site (central enhancement).[20, 63, 282]

COMBINATION MECHANISMS.—Of course, it is unnecessary to characterize graft acceptance with a single explanation, whether this be narrow range tolerance, the action of blocking antibodies (enhancement) or some additional but less formally stated possibility(ies). Traditionally, the two immunologic mechanisms of tolerance and enhancement have been separated very strictly from each other. The justification for this recently has been summarized brilliantly by Medawar,[147] who at the same time pointed out that an "either-or" attitude was not necessary to explain graft survival under a wide range of experimental circumstances, especially if a state of *partial* tolerance were involved.

There is no doubt that the conditions for successful renal transplantation are complex and vary from case to case. An unstable situation of partial tolerance is probably common, with significant inactivation of the cell lines involved in cell-bound immunologic response but with retention of some antibody responses as depicted in Figure 2. How this might be achieved presumably would depend upon the fortuitous choosing of the right dose, aggregation form and administration route of the transplant antigens, to say nothing of the immunosuppressive treatment. Although such factors can be demonstrated readily to be instrumental in inbred animal strains, they can be studied only irregularly and at random in outbred animal populations, including man.

Recent publications from Seattle by Pierce[184] and Quadracci,[198] working with the Hellströms and Marchioro, have offered hope of dis-

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entangling the complex and obviously dynamic processes of human homograft acceptance in individual patients. Using the cell inhibition assay of Hellström and Hellström,[87] Pierce and Quadracci demonstrated that blood lymphoid cells capable of exerting a cytotoxic effect against donor target cells were very common early after transplantation but often were accompanied by serum-blocking factors (antibodies?) that could cancel the expected harmful effect. By the end of the first year, in successful cases the reactive lymphocytes tended to disappear as one might expect with the gradual induction of tolerance. However, the findings were highly variable from case to case and at different times in the same recipient.

The Durability of "Accepted" Human Homografts after Double Drug Therapy

Updated reports about patients provided with renal homografts early in the so-called modern era of organ transplantation are still of vital current interest since these are the only data from which an idea of the long-term prognosis of more recently treated and still surviving patients can be obtained. Consequently, a series of 64 consecutive patients treated in Denver by our group with azathioprine-prednisone therapy between the autumn of 1962 and March, 1964, is particularly useful. This was the first series in which a large number of patients were brought through the first few postoperative months successfully. Those from the original group who are still alive now have follow-ups of 9½ to almost 11 years.

There were 46 recipients of consanguineous kidneys from 23 siblings, 20 parents, one aunt, one uncle and one cousin, and 18 recipients of nonrelated kidneys donated by healthy volunteers. In 45 patients azathioprine was started alone (Fig. 1); with the appearance of clinically obvious rejection, prednisone was added in 43 of these 45 patients. In the other 19 recipients both drugs were administered from the outset.

Typing procedures were not available when this series was compiled. Consequently, the donor-recipient matching was not done by any kind of immunologic guidelines except for the avoidance in all patients (after Case 23) of the kind of red blood cell type incompatibility that can lead to hyperacute rejection (Table 1). Parenthetically, one of our earliest patients, an A+ type recipient, is still alive with perfect graft function 10 years and 8 months after transplantation from a B+ type donor, a combination that no longer would be used.

All of the recipients had splenectomy. The first 8 (of whom 4 are still living) had pretransplantation thymectomy. Nine additional patients had thymectomy 8½–17 months after transplantation in the hope of reducing the need for immunosuppression. Five of the 9 recipi-

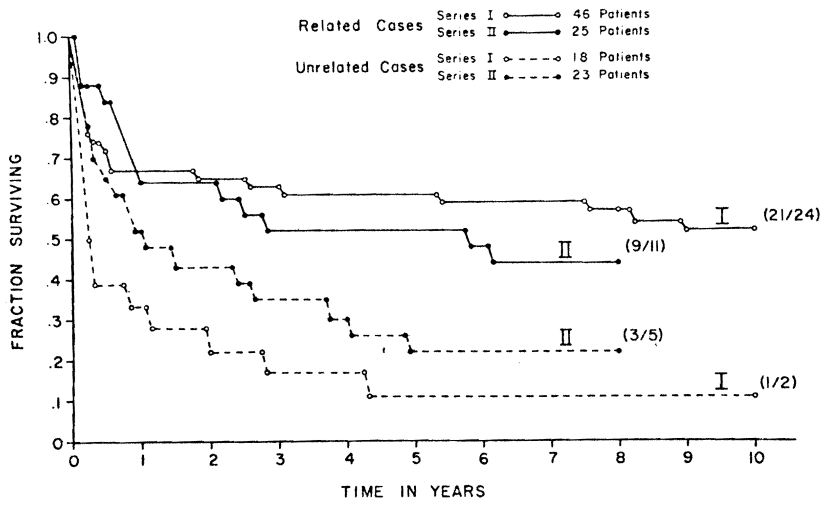

FIG. 3.—The life survival curves of 112 recipients treated between November, 1962, and April, 1966, with the double drug program of azathioprine and prednisone. Series I was compiled between November, 1962, and March, 1964, so the potential follow-ups are 9½ to almost 11 years. Series II was compiled from October, 1964, to April, 1966, permitting follow-ups of 7½–9 years. All of the nonrelated donors in Series I were volunteers. Of the 23 nonrelated donors of Series II, 17 were volunteers; the other 6 were cadavers. The main difference between Series I and II was that prospective HL-A typing was attempted in Series II. At the end of each curve, the denominator shows the number of patients still alive. The numerator indicates the number of original kidneys still functioning. Only one of the surviving patients is on dialysis (a member of unrelated Series II). The other recipients whose kidneys have failed have had successful retransplantation, usually under one of the triple drug treatment regimens that included ALG.

ents are still alive but 3 of them have undergone retransplantation. Although thymectomy may have a significant effect in human beings, as will be discussed later, it is no longer performed in our center.

SURVIVAL AFTER 46 RELATED TRANSPLANTATIONS.—After a heavy mortality (33%) in the first 6 months, subsequent deaths have been uncommon (Fig. 3). Of the 31 recipients who survived a half year, 29 lived for 3 years, 28 for 5 years, and 24 (52%) are still alive after 9½ to almost 11 years. None is now on dialysis, and 21 of the 24 have function of their original grafts; the other 3 had retransplantations 5½, 5¾, and 7 years after the first procedure. The secondary kidneys have functioned subsequently for 5⅓ and 4¾ years in the first 2 of these retransplanted recipients. The third one is now living on his fifth kidney. The problem of retransplantation will be considered in a later section.

The outcome was not influenced strikingly by the nature of the donor relationship (parent, sibling or other) (Table 2). The parent-

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TABLE 2.—THE INFLUENCE OF CONSANGUINITY UPON SURVIVAL IN 46 CASES OF RELATED TRANSPLANTATION AFTER 9½ TO 10⅝ YEARS

DONOR	1 YEAR		3 YEARS		5 YEARS		NOW	
	Patient	Graft	Patient	Graft	Patient	Graft	Patient	Graft
20 Parents	14	14	14	14	14 (70%)	14 (70%)	13 (65%)*	10 (50%)*
23 Siblings	14	14	12	12	11 (48%)	11 (48%)	8 (35%)	8 (35%)
3 Aunt, uncle or cousin	3	3	3	3	3 (100%)	3 (100%)	3 (100%)	3 (100%)

*Retransplantation was carried out after 5½, 5¾ and 7 years.

to-offspring results were amazingly stable in terms of recipient survival. At the end of 6 months, 14 (70%) of 20 recipients were alive. By 9½–11 years there were still 13 (65%) alive, although 3 of these survived by virtue of retransplantation. Also of interest was the fact that all of the 3 distantly related renal grafts (aunt, uncle and cousin) were providing superb function nearly a decade after their insertion.

The causes of mortality in the first 5-year follow-up of this series have been reported exhaustively.[235, 247] They usually involved infection, renal failure or both (see Fig. 7). Therefore, only the four deaths in the second 5 years will be mentioned. Two patients with adequate renal function 8¼ and 9 years post-transplantation died of chronic aggressive hepatitis of several years' duration; one was Australia antigen positive. A third patient had a fatal myocardial infarction after 7⅓ years, and the fourth patient had a technically unsuccessful retransplantation in the sixth year and then committed suicide by refusing to be placed back on hemodialysis.

Half of the original series of related kidney recipients are entering or already have entered into the second decade of their convalescence.

SURVIVAL AFTER 18 UNRELATED TRANSPLANTATIONS.—Two thirds of the recipients died in the first year, and the mortality rose until only 2 patients were left at the 5-year mark (Fig. 3). These 2 are still alive after 9½ and 9⅔ years, but in one instance a second homograft from the mother has supported life for the last 6 years of the total survival.

The poorer results in nonrelated transplantation would have been discouraging were it not for the great progress made in many centers, including our own, with cadaver transplantation (see later section) since the spring of 1964, when this series was completed.

GRAFT FUNCTION AND IMMUNOSUPPRESSION.—Table 3 shows the average renal function in September, 1972, of the 22 survivors whose first and only homografts had functioned at that time for 8½ to nearly 10 years. The data have not changed substantially since then. The immunosuppression given chronically to those patients also is listed. The average daily doses of prednisone are small enough to avoid a Cushing's facies.

Arterial hypertension is an almost universal finding in the immediate posttransplantation period and even for several years afterward.[235, 247] This problem has tended to diminish with longer follow-up, and none of the 22 patients with original homografts has significant hypertension.

At the time that the foregoing data were collected, the 4 patients who were (and still are) living after retransplantation had less favorable functional results, with follow-ups after retransplantation of 2¾–7 years. In September, 1972, their BUN levels were 39 ± 18.5 mg/100 ml, and their creatinine clearances were 60 ± 33 ml/min. One of the latter recipients is severely hypertensive.

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LD 39	
LD 42	
LD 49	
LD 51	
LD 52	
LD 53	
LD 55	
LD 58	
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LD 63†	
Mean ± SD of 22 original grafts	

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TABLE 3.—AVERAGE RENAL FUNCTION AND IMMUNOSUPPRESSION IN 22 RECIPIENTS SURVIVING 9½–11 YEARS AFTER TRANSPLANTATION FROM LIVING DONORS AND WITH CONTINUING FUNCTION OF THE ORIGINAL HOMOGRAFT*

PATIENT	BUN (mg/100 ml)	SERUM CREATININE (mg/100 ml)	CREATININE CLEARANCE (ml/min)	AZATHIOPRINE (mg/day)	PREDNISONE (mg/day)
LD 2	16	1.7	70	100	0
LD 3	11	1.1	130	150	0
LD 6	20	1.3	105	200	10
LD 12	18	1.4	70	100	15
LD 13	19	1.4	90	87.5	7.5
LD 14	10	0.9	120	200	0
LD 17	9	0.8	70	100	2.5
LD 22	17	0.8	90	137.5	10
LD 25	22	1.6	80	50	10
LD 33	12	1.2	90	125	0
LD 34	31	1.5	60	50	0
LD 37	11	1.0	94	150	15
LD 39	17	1.0	80	125	10
LD 42	18	1.1	75	125	7.5
LD 49	25	1.1	70	87.5	5
LD 51	21	1.3	85	125	10
LD 52	17	0.8	110	150	5
LD 53	25	1.6	55	100	5
LD 55	27	1.4	40	150	20
LD 58	16	1.4	65	137.5	10
LD 60	46	3.3	40	87.5	20
LD 63†	27	1.4	80	125	15
Mean ± SD of 22 original grafts	19.8 ± 8.3	1.3 ± 0.5	80.4 ± 22.9	121.0 ± 38.8	8.1 ± 6.3

*The data were compiled in September, 1972, but have not changed significantly since then. Four additional patients in this 1962–1964 series are still alive but are living on their second to fifth grafts. See text for renal function of the latter patients.
†Surviving recipient of living unrelated renal homograft.

The degree of rehabilitation in the group has been truly remarkable. All who were adults at the time of transplantation have returned to some kind of full-time work. Of the 12 survivors who were younger than 18 years (range 3–17 years) at the time of the original operation, all have returned to school. By September, 1972, when a full social follow-up was organized,[75] half had graduated from college, 8 supported themselves fully in adult work and 9 had married. The only patient who had spent an excessive amount of time in the hospital was a child, first treated at the age of 3, whose original homograft failed and who subsequently required four retransplantations. He is now 13 years old and is stunted in growth. His prognosis for reaching emo-

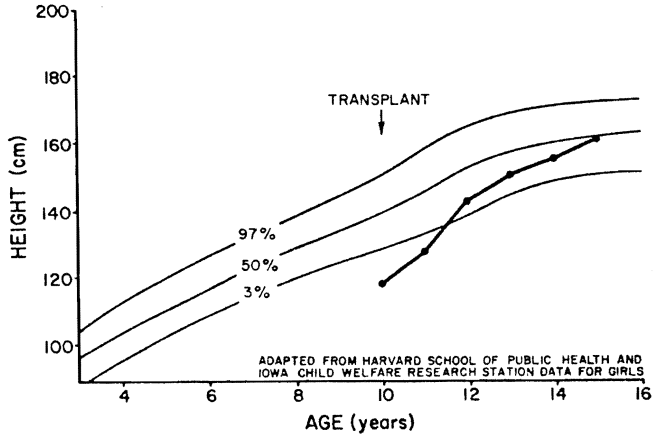
tional and physical maturity is doubtful although his present condition is highly satisfactory.

At the time of this original series potential recipients were screened with great care to rule out those with possible important psychiatric problems. Because of this it is not surprising to find exceptional emotional stability among those who were accepted and who are still surviving. Excellent adjustments have been made in spite of serious early postoperative complications such as aseptic necrosis of one or both femoral heads in 3 of the adolescents. These 3 patients have learned to walk adequately in spite of their handicaps. Many of the young patients were stunted in growth before and after their transplantations but have had catch-up growth spurts late in their teens (Fig. 4).

Nine of the 64 patients in the original series had had children of their own by September, 1972, 3 by 2 female recipients, and 10 by 7 male recipients. One of the offspring had a meningomyelocele that required operative correction; no other birth defects have been recorded. It is of interest that all of the children issuing from this transplant population came from the 26 recipients still surviving. Thus, no orphans have been created so far by the premature death in Series I of a transplant patient.

It is fair to say that no new difficulties ever were encountered in our extensive subsequent experience that had not been defined by the time the foregoing series was closed out in March, 1964. A number of these

FIG. 4.—The height percentile growth curve in a 10-year-old girl who was far below the third percentile at the time of renal homotransplantation. After operation, steroids were tapered gradually. She did not reach the fiftieth height percentile until the fifth year after transplantation. She is now 20 years old and a college student. (From Pediatrics, 47:548, 1971).



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problems will be discussed in a later section, including special technical surgical hazards, requirements of retransplantation and the effect of chronic immunosuppression in increasing the risk of cancer.

Further Experience with the Double Drug Regimen

When the original series of patients on double drugs was completed in March, 1964, a 6-month moratorium was called for two purposes. First, we felt obliged to establish the general pattern of the life survival curve before undertaking a new series of renal transplantations. During the moratorium it became clear that very important prolongation of recipient life would be obtained, thereby justifying further trials.

Second, we hoped to find a better means of biologic selection of the donor than the essentially random method that had been necessary up to this time. A collaboration was established with Dr. Paul Terasaki of Los Angeles, from which eventually came the first prospective trial of HL-A typing.[262] When clinical activities were resumed in October, 1964, which continued until April, 1966, an effort was made in almost every case of this Series II to find the most HL-A compatible donor from available volunteers. For the consanguineous transplantations the selectivity usually was limited, and in a number of instances there was only one possible organ volunteer. This made it difficult to upgrade substantially the average matches in comparison to those achieved before by chance, as judged by a retrospective study of surviving patients from Series I. In contrast, the first 17 recipients of nonrelated kidneys had their donors selected with considerably increased discrimination by HL-A matching of from a few to as many as almost 100 penal volunteers. The last 6 patients in the unrelated Series II received unmatched cadaver organs.

It was a great disappointment that the results in Series II were so little affected by prospective HL-A typing, a subject to which we will return. Now, with a follow-up of from 7½ to almost 9 years, the life survival curve after consanguineous transplantation is actually poorer than that with the randomly selected donors of Series I (Fig. 3). Only 11 of the 25 related recipients are still alive, 9 with continuing function of their first grafts. To compensate, there has been a slight improvement in the life survival curve after nonrelated transplantation (Fig. 3). However, in both groups the actual changes in results of the 1964–1966 versus the 1962–1964 era were not statistically significant.

It is possible, especially in related cases, that the deterioration of results in Series II was due to relaxation of the very stringent requirements for admission to the program that were enforced at the beginning. Thus, more patients at high risk were accepted.

TRIPLE DRUG THERAPY INCLUDING ALG

The justification for adding further therapeutic adjuncts to azathioprine and prednisone was that the patient mortality or kidney loss rate appeared, at least in our hands, already to have reached an irreducible minimum by the spring of 1964 when Series II was completed. As just recounted, the results in the ensuing 2 years (1964–1966) of Series II had not been improved substantially in spite of the increased experience acquired.

This experience resulted in a change in timing but not in the ultimate incidence of failure. During the learning period, when azathioprine and prednisone first were used together, there were a number of deaths from drug toxicity during the early postoperative period. Many of these fatalities were due to bone marrow depression caused by overdoses of azathioprine. A common course was that good initial kidney function was obtained from the homograft, a severe rejection crisis then supervened with a secondary return of uremia, and leukopenia and lethal sepsis followed shortly thereafter.[235] At least part of the explanation was thought to be that the renal pathway of detoxification of azathioprine had been lost to a variable degree as a consequence of rejection. The practice was developed of considerably reducing the azathioprine doses under these circumstances or after poor initial function of cadaveric homografts had been observed. Bach and Dardenne,[9] in subsequent studies, could find no good evidence that poor renal function changes the proper dose of azathioprine, but in spite of their interesting publication we have continued to exercise great restraint in the azathioprine doses prescribed during secondary renal failure. With this cautious attitude, practiced at our center for almost 10 years, the complication of bone marrow depression has been largely eliminated.

Avoidance of the hazards of chronic steroid therapy was less simple. Indeed, the side-effects of prednisone seemed even more numerous and severe with the increased conservatism in azathioprine dosage. In many cases of both Series I and II, continued function of the transplanted kidneys proved to be dependent upon the chronic administration of unacceptably large quantities of prednisone. The delayed complications that often followed ranged from the exceedingly troublesome to the lethal. They included cosmetic deformity, bone demineralization, muscle wasting, arrest of growth in infants, fatty infiltration of the liver, pancreatitis and gastrointestinal ulceration and hemorrhage. Most serious, however, was the resulting susceptibility to infection with microorganisms of all types.

If the consequent infections were due to common pathogenic bacteria, usually they could be treated successfully with properly chosen antibiotics. Very often, however, they were caused by fungi, protozoa or viruses for which specific therapy was not available. The manifesta-

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A difficult therapeutic dilemma often was posed by the foregoing situation with either intrafamilial or cadaveric transplantation, but far more commonly after the latter. On the one hand, life was threatened by reduced or failing function of the homograft, and on the other, by the immunosuppressive measures taken to prevent further deterioration or complete loss of the graft. One of the great lessons learned in the field of renal transplantation has been that there are very material benefits of retransplantation with or without removal of the first homograft. An alternative approach would be to deliver more effective and less toxic early postoperative immunosuppressive therapy during that critical time when graft acceptance is hoped for. It was with this objective that heterologous ALG was added as a third agent in almost all clinical cases after May, 1966.

The Therapeutic Schedule

The fascinating history of antilymphocyte serum (ALS) and its globulin fraction (ALG) has been recapitulated in a recent text.[236] The first investigators to demonstrate the ability of ALS therapy to mitigate skin homograft rejection were Waksman, Arbouys and Arnason,[272] who in 1961 observed a weak but statistically significant effect in guinea pigs. The subsequent investigations of Woodruff and Anderson[287] catalyzed widespread interest in such antisera by demonstrating a striking protection of homografts in rats treated with ALS alone or in combination with thoracic duct drainage. Within 2 years, antisera of comparable or greater potency for use in mice or rats were developed by many other investigators. By 1966, a beneficial effect of ALS after whole-organ transplantation had been demonstrated in our laboratory and elsewhere in mongrel dogs. These intermediate steps in large animals were necessary to determine the most effective and least toxic therapeutic schedules and to evolve practical technics of administration acceptable for use in man. This kind of information was sought in dogs by use of heterologous ALS raised in horses, sheep or rabbits. The regimen of ALG that was used in man eventually was guided by the following conclusions that emerged from these large animal experiments[236]: (1) ALG has potent but imperfect immunosuppressive qualities when used alone. (2) With continued administration of the heterologous serum derivatives there is a highly significant risk from a variety of foreign protein reactions including anaphylaxis. (3) ALG can be used effectively and probably with increased safety in combination with other drugs.

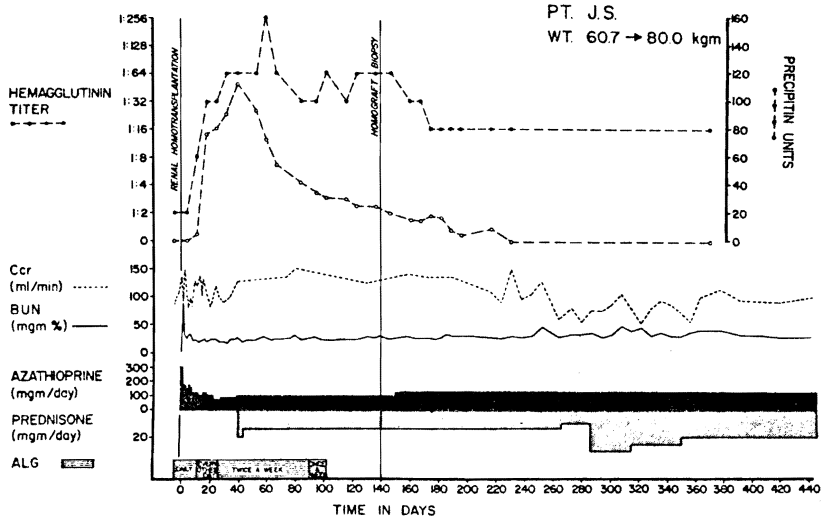
Each of these factors contributed to the initial decision to employ heterologous ALG as an adjuvant agent combined with azathioprine

and prednisone and to limit its use to the first 4 postoperative months. It was hoped that the predictability and safety with which homograft rejection could be prevented would be improved thereby and that the hazards of immunologic reactions to the serum product would be reduced in accordance with the efficient level of immunosuppression to which all three agents would contribute.

TREATMENT PROGRAM IN THE FIRST CASES.—The way in which this policy decision was translated into the treatment program[236, 242, 248] is shown in Figure 5. Daily intramuscular injections of ammonium-sulfate-precipitated ALG prepared from horse serum were started several days before operation, continued for the first 10–14 days afterward and then progressively reduced to every other day, twice a week and once a week in the ensuing 3½ months. Azathioprine was begun on the day of operation and continued indefinitely. Prednisone therapy was either instituted immediately or, in a few cases, withheld until onset of rejection or the appearance of serologic evidence of antibody formation against the injected ALG (Fig. 5).

In these first cases the dose of the immune globulin for adults was

FIG. 5.—The postoperative course of a patient who received ALG before and for the first 3½ months after renal homotransplantation. The donor was an older brother. There was no early rejection. Prednisone therapy was started 40 days postoperatively because of high rises in the serologic titers that indicated a host response against the injected ALG and warned against a possible anaphylactic reaction. By our present policy steroid therapy would be started at the same time as the ALG. Note the insidious onset of late rejection after cessation of globulin therapy. This was treated by increasing the maintenance dose of steroids. (From Surg. Gynecol. Obstet. 126:1023, 1968).



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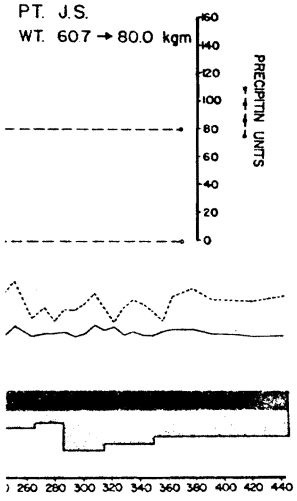

usually 4 ml. The injectate had leukoagglutinin and lymphocytotoxicity titers of 1:4,000 to 1:16,000 and a protein content of 4.6 to 9:3 gm/100 ml. Significant lymphopenia was not always produced. Usually, the fraction of lymphocytes in the peripheral smear was reduced, but a leukocytosis also occurred, and the total peripheral lymphocyte count was relatively unchanged. Nevertheless, a striking immunosuppressive effect was detectable during the pretransplantation period when no other immunosuppressants had been started. Many of the recipients had positive skin tests to tuberculin, histoplasmin or other allergens. These became negative when the patient was retested 48–72 hours after the institution of globulin therapy, indicating that the ALG prevented expression of previously established delayed hypersensitivity.

ADJUSTMENTS OF TREATMENT PROGRAM IN SUBSEQUENT CASES.—ALG has now been used at the University of Colorado for more than 7 years. In a few cases and for special indications the raw antiserum has been obtained from rabbits or goats; however, the usual source of ALG in our program has been the horse. From 1966 to 1971, the animals were chronically immunized with splenic lymphocytes obtained from human cadavers. Beginning in 1971, the cultured lymphoblasts introduced by Najarian and his colleagues[166] were used for the antigen, thereby permitting a much more standard product[72] to be raised by acute immunization.

At present, the schedule of ALG recommended for our patients differs only in a few details from that originally introduced. The last 4- to 6-week period, during which the injections were given once or twice a week, has been eliminated, so the usual duration of globulin therapy now is about 2 months. The antilymphoblast globulin now employed is made up to a standard concentration of 5 gm% rather than the previous wide range of protein content being permitted. With Groth's schedule of immunization[72] antiwhite cell (leukoagglutinin and lymphocytotoxicity) titers as well as rosette inhibition titers of 1:8,000 to 1:32,000 are predictably obtainable.

CLINICAL RESULTS

FIRST TRIALS.—Beginning in June, 1966, when ALG was introduced clinically, and continuing to the spring of 1968, a total of 77 patients were treated with renal transplantation (Series III, Fig. 6). The donors for 60 of these recipients were related family members. The other 17 kidneys were taken from cadavers, usually under conditions of brain death rather than cessation of cardiac activity. Except for some sibling cases, the results of HL-A matching were no longer followed in donor selection, which consequently reverted to a nearly

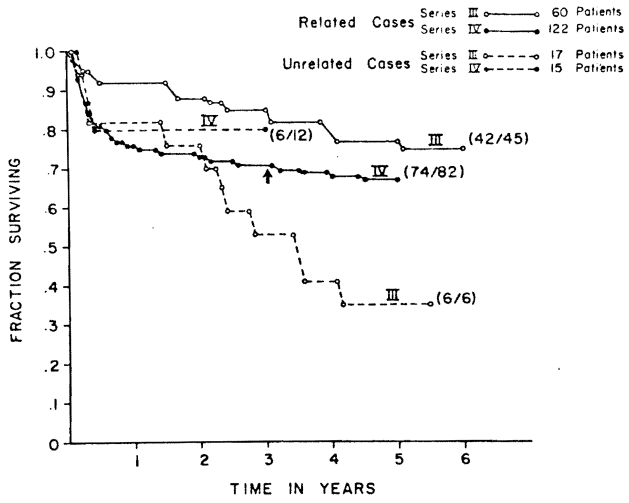

FIG. 6.—The life survival curves of 214 patients treated between June, 1966, and March, 1971, with the triple drug program of azathioprine, prednisone and heterologous ALG. All of the nonrelated donors were cadavers. Since Series III was completed by the spring of 1968, a minimal potential follow-up of 5½ years is available for the 51 surviving recipients. Series IV was completed by March, 1971, permitting a minimum potential follow-up in these patients of about 3 years. Thus, the life survival curves in the related cases of Series IV from the point of the arrow to the fifth year is the best that could be achieved provided no further deaths occur in the final 2-year interval. This latter life survival curve is the only one either in this illustration or in Figure 3 that is not essentially complete as depicted.

The main distinction between Series III and IV was that recipient selection was liberalized greatly in the later period, so the previous contraindications of age, concomitant systemic disease and certain kinds of renal or urinary tract disease were largely removed. The numerator, which indicates the number of original kidneys still functioning, and the denominator, which indicates the number of patients still alive, at the end of the curves have the same significance as in Figure 3. Only 1 of the 145 patients who are still alive is presently on hemodialysis; 128 have continuing function of their original grafts and the other 16 have been retransplanted successfully.

random process. The results from this series have been reported on several occasions, most recently in 1970.[247] In September, 1973, there were follow-ups in the remaining patients ranging from almost 5½ to more than 7 years.

Observations of the 60 related cases of Series III have supported the attitude that renal transplantation no longer can be considered an experimental clinical procedure. Of the 60 recipients the survivals are: 1 year—55 (92%), 2 years—53 (88%), 3 years—51 (85%), 4 years—47 (78%) and 5 years—46 (77%). At the present time, 45

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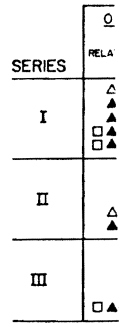

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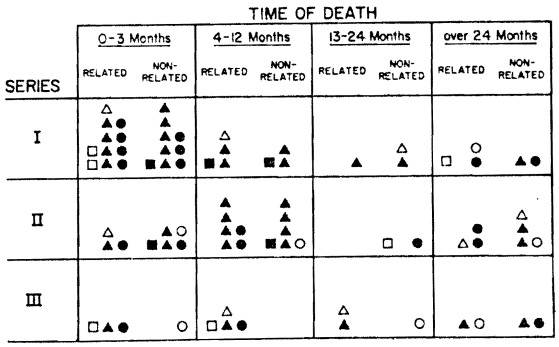
(75%) of the patients are living 5½ years or more postoperatively. Furthermore, 42 of the 45 surviving patients (70% of the original 60) still have function of their first transplants. These results constitute an improvement over our 1962–1966 experience in that there were more kidneys and more patients left after *5½–7 years* than had remained at the end of the *first year* in either Series I or II.

The results were also improved substantially in the 17 unrelated (cadaveric) organ recipients of Series III. There were 14 (82%) and 13 (76%) of the patients still alive at the end of the first and second post-transplantation years. However, unlike the situation after consanguineous transplantation, the losses continued at a brisk rate through the third, fourth and fifth post-transplantation years. By the end of 5 years there were only 6 survivors (35%). All 6 still have life-sustaining function of their original homografts.

Although the mortality was lower, the causes of death in the triple drug, ALG-treated patients of Series III were not very different from those encountered in the double drug era of Series I and II. In the spring of 1970, the data from all of the unsuccessful cases were examined. At that time, 79 of the 189 patients who made up the three series had died, 40 after receiving related kidneys and 39 after receiving nonrelated organs. Autopsies were performed in all but 2. In reviewing the causes of the 79 deaths, a specific notation was made in every case about the roles of renal insufficiency and infection in the fatal outcome. Two associations were obvious. First, 68 of the 79 patients had less than normal (42 examples) or failed (26 examples) renal function in the interval before death (Fig. 7). Second, a major infectious compli-

FIG. 7.—The contribution of imperfect or failed renal function and of infections to the deaths of 79 patients. The shading of symbols indicates that infection either caused or was a major contributor to death. The *squares* indicate excellent premortem renal function, the *triangles* indicate subnormal but life-supporting premortem renal function and the *circles* indicate that the homografts had failed. (From Starzl, T. E., *et al.*: Ann. Surg. 172:437, 1970).



cation was present in 58 (73%) of the patients (Fig. 7). As discussed earlier, the most difficult therapeutic dilemma was posed by the coexistence of variable degrees of renal impairment in conjunction with sepsis. In 53 (70%) of the deaths the combination of imperfect (or failed) homograft function and infection was present.

The timing of death differed in the three periods of our experience. In Series I the mortality was heavily concentrated in the first 3 months (Figs. 3 and 7), largely due to a tendency to administer doses of azathioprine that caused bone marrow depression, especially when renal impairment was present. In Series II this error was avoided. However, the mortality from infection was not prevented but only postponed to the 4- to 12-month post-transplantation period (Figs. 3 and 7). With the more balanced form of immunosuppression used in Series III the deaths became rather evenly distributed throughout the first 2 years (Figs. 6 and 7). Half of the patients in the last series had significant infection at the time of death, compared to 80% and 76% in Series I and II.

The locations of the infections were highly variable, but the most common were the lung (31 cases), the central nervous system (5 brain abscesses and 3 meningitides), the transplant wound (8) and the peritoneal cavity (4). The infecting microorganisms were frequently multiple, but it was usually possible to determine the dominant agent. Deaths in the first 3 months were due mainly to well-known bacteria such as *Pseudomonas aeruginosa, Escherichia coli* and *Staphylococcus aureus* (Table 4). After the early post-transplantation period, nonbacterial (fungal, protozoan or viral) infection played a major role (Table 4). Between the fourth and twelfth months after transplantation *Pneumocystis carinii* accounted for 5 deaths, and fungal infections killed an additional 5 patients. After 4 months 4 patients died from viral causes alone, 3 with viral hepatitis and the fourth with panintestinal varicella. Multi-organ cytomegalic inclusion disease was found in many patients, often in association with *Pneumocystis carinii.*

There were 2 deaths in the early postoperative period from acute pancreatitis. Pulmonary emboli were the cause of death in 3 patients (after 3, 18½ and 28½ months) and contributed to the death of at least 10 others. Two recipients aged 37 and 41 died of myocardial infarction 2½ and 4⅓ years post-transplantation. Reticulum cell sarcoma accounted for 2 late deaths. Other causes of mortality in single cases included suicide, inanition, stroke and jejunal necrosis.

The foregoing list of complications, which spans our total experience up until 3 years ago, has been presented in detail for two reasons. First, it provides a realistic cross-section of the hazards of major surgery under immunosuppressive therapy with or without recurrence of uremia. Second, it indicates that the problems caused by immuno-

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TABLE 4.—PATHOGENIC ORGANISMS INVOLVED IN THE DEATHS OF 79 PATIENTS*

	Number of Patients Dying of Infection at		
	0–3 Months	4–12 Months	Over 12 Months
BACTERIAL			
Staphylococcus aureus	3	4	2
Hemolytic *Streptococcus*	4	0	0
Listeria monocytogenes	0	1	0
Diplococcus pneumoniae	1	0	0
Escherichia coli	8	1	2
Pseudomonas aeruginosa	12	8	5
Klebsiella aerobacter	4	1	2
Proteus mirabilis	3	0	0
Paracolon species	1	0	0
VIRAL			
Hepatitis	0	1	2
Cytomegalic inclusion disease	3	1	2
Varicella	0	0	1
PROTOZOAN			
Pneumocystis carinii	1	8	1
FUNGAL			
Aspergillus fumigatus	2	3	2
Candida albicans and *C. stellatoidea*	4	2	1
Nocardia	0	2	0
Histoplasmosis	0	1	0
Cryptococcus	0	0	1

*Some patients died with 2–3 types of microorganisms. For each patient the full spectrum of clinically significant microbiologic data has been entered into the table.

suppression are apt to be troublesome and of the same general kind with a wide range of regimens. Thus, no single agent or combinaton of agents now in use can be viewed as a panacea.

LATER CASES.—From March, 1968, until March, 1971, 137 fresh cases were added to the drug combination trial of azathioprine, prednisone and ALG, creating a Series IV with present follow-ups ranging from 2½–5½ years. The donors for 122 of the patients were blood relatives, and the organs for the other 15 were taken from cadavers. The small number of new cadaveric cases was because most of the available cadaver kidneys were being used to carry out retransplantations upon recipients whose first grafts were failing or had failed. This special subject will be discussed later. HL-A typing was not a major factor in donor-recipient matching except for A-matched siblings.

There were some features of Series IV that distinguished it from Series III. First, a number of the criteria by which patients formerly were excluded from treatment by transplantation had been progressively eroded; thus, there were increasing numbers of recipients over the age of 45 years who had diseases of other organ systems, including the heart, or who for other reasons such as prior malignancy, diabetes mellitus or systemic lupus erythematosis previously would have been considered excessively high risks. Second, there was a change in the ALG used midway through Series IV from that raised with immunization by cadaveric spleen cells to that raised with immunization by lymphoblasts. Finally, the number of surgeons and physicians operating upon and taking care of the growing colony of transplantation patients increased. To some extent the degree of personal attention that could be given to every patient by a small and highly experienced team was lost, with a consequent greater dependence upon therapeutic formulas.

The results in the related donor component of Series IV were less favorable than in Series III. The life-survival curves in Series IV are complete to almost 3 years. At 3 years the patient survival is 71%, compared to 82% in Series III. It is certain that a disparity in results of approximately the same magnitude will persist through at least the fifth year (Fig. 6).

So far, the results in a small series of cadaveric transplantations in Series IV have been superior in terms of patient survival. Twelve (80%) of the 15 recipients are still alive with follow-ups exceeding 3 years in 11 of the patients and 2¾ years in the twelfth. The reason for the high patient survival was our readiness to carry out retransplantation with or without removal of the first homograft, as has been strongly advised by Hume[97] and Kountz[118] and their associates. Only 6 of the 12 remaining patients have continued function of their original homografts. However, none of the other 6 is on dialysis since all have undergone successful retransplantation.

The Importance of ALG and Other Questions

In December, 1971, and late April, 1972, two working conferences on the clinical use of ALG were convened—the first in San Diego and the second in Bad Soden, Germany. The discussions and formal papers from the European workshop have been published[220] and are available for those who wish to peruse the details from which the following summary has been drawn.

First, it was disconcerting to realize from these two meetings the extent to which many central and practical questions about ALG had

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yet to be answered. Some of these questions have been clarified at least partially but others have not.

There is probably not an appropriately informed, responsible scientist in the world who does not concede that ALG is a potent immunosuppressive agent in man; but that is not the question perplexing clinicians interested in renal transplantation. Rather, the issue is whether or not ALG fills some unique role that cannot be met equally well by the clever manipulation of other agents such as steroids, azathioprine and cyclophosphamide. Opinions about this vary even today. At the Bad Soden conference, testimony about the value of ALG in renal transplantation was given from 13 centers. Representatives from eight thought ALG was valuable, but four clinicians did not believe that their results were improved by it, and one European surgeon thought they actually might have worsened. The only controlled study of ALG in cadaveric renal transplantation yet performed[224] was brought up to date by Dr. Ross Sheil of Australia. His patients, who received a 2-month course of goat ALG in addition to maintenance therapy with azathioprine and prednisone, fared better than those who did not get ALG. However, the differences were not overwhelming. Consequently, this small series, important and wisely planned as it was, must now have corroboration. Although we ourselves have resisted thus far the compilation of a control series without ALG because of our conviction of its value, we would support strongly anyone wishing to carry out such a controlled study and are now considering this possibility ourselves.

The question of indispensability of ALG must be settled because of the tremendous investment of personnel and material resources required to make ALG available for human use. We have heard of examples in which the cost of ALG accounted for half of the financial investment in the treatment of a renal recipient. The expertise required to ensure a supply is considerable. These efforts and expenses will be worthwhile only if tangible and substantial benefits are demonstrable.

In addition to the labor of procuring ALG there are potential dangers in its administration. Anaphylaxis, which has led to several deaths (including two at our institution), is the most terrifying side-effect, but there are others, including injection site pain and thrombocytopenia. Injury to the homograft itself by the development of serum-sickness nephritis has been reported, but we have not seen this. The University of Minnesota group has reported serious thrombotic complications with a high titer ALG given intravenously at their center and elsewhere. Apparently these thrombotic calamities were caused by cross-reactions of the antiwhite cell antibodies with recipient platelets.

If the results of future controlled clinical trials prove to be positive,

it will be an enormous stimulus for commercial drug companies to go into production, and the consumer cost should then fall. Even if highly successful clinical transplantation trials are carried out, major problems of standardization will remain. There are four exceptionally sensitive points that must be clarified: (1) the best animal in which to raise ALS, (2) the most effective immunization schedule, (3) the correct antigen and (4) the in vitro and in vivo technics for evaluating the effectiveness of the product.

The choice of an animal probably is not a crucial factor provided certain rules are followed.[286, 220] The schedule of immunization also is not critical except that if the course is short and standard, the ultimate product is apt to be relatively the same from animal to animal. In horses in our laboratory Groth *et al.*[72] have shown that the use of 5 or 6 accurately timed pulses with large doses of lymphoblasts almost always gives an essentially identical response curve.

The third question—the best antigen source—is still open for discussion. The thymocyte has a number of advocates in spite of the demonstration of Ono *et al.*[170] that a variety of lymphoid organs are about equal in their ability to raise potent ALG. From the viewpoint of convenience and purity a strong contender is the cultured lymphoblast, which, as far as we know, represents a pure β-cell population. Within the next few months we plan to begin a controlled study comparing horse ALG raised with thymocyte membranes to that raised with cultured lymphoblasts.

As to the fourth point, there has been a gradual acceptance of at least three in vitro tests. Even a year ago there were flat denials that the leukoagglutinin and lymphocytotoxicity titers had any correlation with immunosuppressive effect, although it was commonly asserted that correlations were good with the rosette inhibition test of Bach *et al.*[10] At the Bad Soden meeting good correlations were reported with all three of these tests as well as with several new ones. With this kind of information it should be possible to establish dose schedules for ALG that would make its use as a traditional drug possible.

In reviewing our experience of the last decade it is obvious that ALG is not an absolutely indispensable drug without which clinical transplantation would be impossible; nor, for that matter, is azathioprine, which can be replaced by cyclophosphamide. The only agents that occupy this role are the adrenal corticosteroids, of which prednisone has been used most widely. Without the adrenal corticosteroids we believe that the management and reversal of rejection would be so seldom achievable that the clinical discipline of renal transplantation would vanish.

It is in this context that ALG must be evaluated. We have always considered it an adjuvant immunosuppressant that is of the greatest

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value for short-term use during the often difficult early postoperative period when the issue of graft acceptance or failure is decided most commonly. When viewed in this way, we have been convinced that ALG is an important part of our therapeutic armamentarium and has improved not only survival but also the quality of convalescence.

TRIPLE DRUG THERAPY INCLUDING CYCLOPHOSPHAMIDE

During the 9 years starting in 1962, only three major immunosuppressants were used extensively for whole-organ transplantation: azathioprine, prednisone and heterologous ALG. None of these agents is sufficiently potent to permit consistent success when used alone in human beings. Consequently, the drugs have been administered in the double combination of azathioprine and prednisone or the more recent triple combination of all three agents. Since March, 1971, we have had extensive experience with a fourth major immunosuppressive drug, cyclophosphamide (Cytoxan®), which we have given instead of azathioprine to most recipients of a primary transplantation for a variable portion of the early postoperative period.[238, 240, 249]

EARLY BACKGROUND

In retrospect, it is surprising that cyclophosphamide has played such a trivial role in the transplantation of whole human organs, since the drug has been known for more than a decade to possess strong immunosuppressive properties.[140, 250, 254] Moreover, the animal research supporting this contention has been reviewed and updated frequently.[16, 21, 62, 64, 106, 173, 211] Virtually all of the encouraging laboratory investigations were done in mice, rats or other rodents or in rabbits. Unfortunately, when cyclophosphamide was tested in the dog renal or intestinal transplantation model as an intermediate step to clinical application, either no prolongation of graft survival was obtained or else the effect was minor.[196, 200, 292] It may be suggested now that the dampening influence of the discouraging canine experiments was based upon a species difference that made the dog an inappropriate animal to evaluate cyclophosphamide for human immunosuppression.

Despite the experience in dogs there has been evidence in man supporting the propriety of testing cyclophosphamide for clinical whole-organ transplantation. Some of this information came from efforts to promote tolerance to bone marrow grafts, as proposed by Santos and colleagues[210, 213] and subsequently carried out by several other workers. Prodigious doses of cyclophosphamide (45–100 mg/kg/day) were given, but only for a few days, in close temporal approximation

to infusion of homologous bone marrow. Although such efforts represent an essentially different therapeutic approach from ours, it is worth emphasizing that Santos's data on several immunosuppressive drugs have indicated that, in man, cyclophosphamide is superior to most other agents and is at least equal to azathioprine.[210, 212]

In the early days of renal transplantation, immunosuppression with cyclophosphamide was tried in a few cases. Almost 10 years ago, Goodwin *et al.*[69] treated a renal recipient with cyclophosphamide plus prednisone; good kidney function was maintained during much of the 144 days of post-transplantation life. Shortly afterward, Parsons,[175] Fox[62] and others reported 4 patients with cadaveric renal transplantation in whom cyclophosphamide was given as the sole therapy. One patient died after a technical surgical accident, and a second died from infection after 33 days. The other 2 recipients lived for 8 and 23 months, respectively, a feat that in our experience can be achieved only rarely with azathioprine or any other single agent after renal transplantation from a nonrelative.[235] However, in a follow-up of these 2 patients and 4 more who survived for only a few days, Parsons *et al.* pessimistically advised against further clinical trials of cyclophosphamide.[174]

It is regrettable that these early efforts at renal transplantation under cyclophosphamide therapy were made when the conditions were not more propitious. Specifically, it was then believed that the deliberate production of leukopenia was desirable, whereas now we hold such a policy to be dangerous and unnecessary. Moreover, as already implied, the importance of combination drug therapy was not yet fully appreciated. In our own trial cyclophosphamide was used with two other potent immunosuppressants, prednisone and ALG, and against a background of considerable experience with multiple drug treatment.

The Colorado Trials

With consanguineous transplantation, administration of cyclophosphamide, prednisone and horse antilymphocyte ALG was started several days before operation and continued afterward, as in the triple drug regimen described earlier (Figs. 8 and 9). The first patients in this study were treated with cyclophosphamide for many months, after which a change was made eventually in almost every case to maintenance therapy with azathioprine (Fig. 8). In contrast, patients treated in the last portion of the study, to be reported below, had a shorter course of cyclophosphamide therapy (1–2 months) before being switched to azathioprine (Fig. 9). The results were essentially the same with either variation. The dose of cyclophosphamide (in mg/kg) was usually one half to two thirds of that later used for azathioprine in

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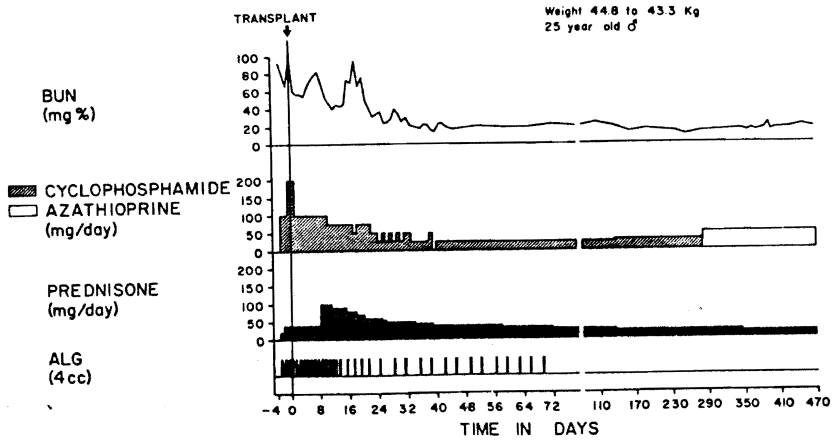


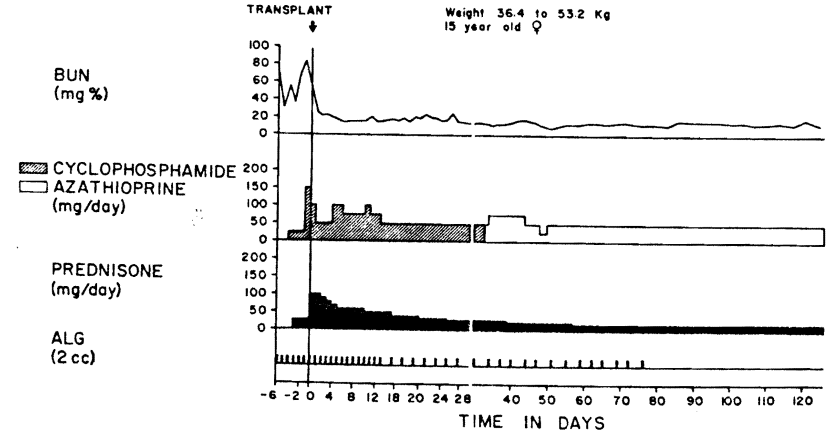
FIG. 8.—The chronic use of cyclophosphamide in conjunction with prednisone and early ALG in the recipient of a parental renal homograft. Treatment was changed to azathioprine after 10 months with an increase in the mg/day dose. The patient has a perfect result after 2½ years. (From Starzl, T. E., *et al.*[238])

the same patient. With both of these potentially radiomimetic agents an effort was made to avoid leukopenia.

Therapy after cadaveric transplantation was similar to that after consanguineous transplantation, but immunosuppressive pretreatment was not feasible.

RESULTS AFTER RELATED TRANSPLANTATION.—For the 44 recipi-

FIG. 9.—The use of cyclophosphamide for the first postoperative month with subsequent azathioprine treatment. The result is excellent after 2 years. (From Starzl, T. E., *et al.*[238])



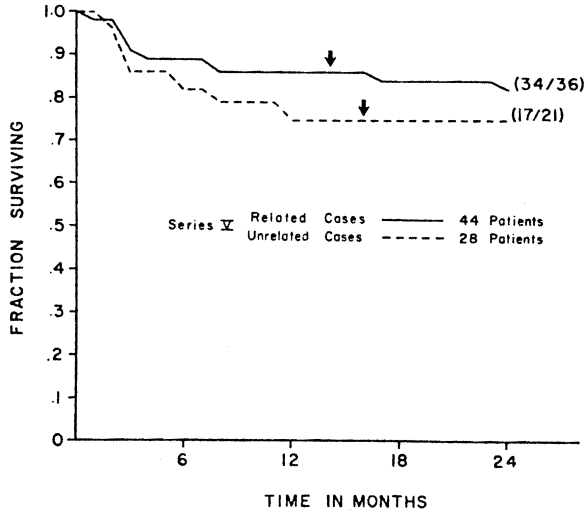
ents the donors included 24 siblings (9 HL-A double haplotype identical), 17 parents, one aunt, one cousin and one grandmother. Except in sibling cases, the HL-A matching was not taken into account in the donor selection. The patients were treated from March, 1971, to July 10, 1972, assuring a minimum follow-up of 14 months and a maximum observation period of 2½ years.

The life survival curve in this Series V is shown in Figure 10. Of these related recipients 36 (82%) are alive and 34 (77%) still have function of their original grafts. The results were approximately the same as had been achieved in the last with similar case material and azathioprine as the primary cytotoxic drug.

RESULTS AFTER CADAVERIC TRANSPLANTATION.—After 16–30 months, 21 (75%) of the 28 recipients are alive and 17 (61%) still have life-supporting function of their first cadaveric kidney (Fig. 10). The results were comparable to those obtained earlier with the original triple drug program that did not contain cyclophosphamide.

DELAYED CYCLOPHOSPHAMIDE THERAPY.—In addition to the foregoing experience with new cases, observations have been made with late substitution of cyclophosphamide for azathioprine. This was done

FIG. 10.—Life survival curves of 72 patients submitted to primary renal transplantation under the triple drug program of cyclophosphamide, prednisone and ALG shown in Figures 8 and 9. A month or more postoperatively, cyclophosphamide usually was replaced by azathioprine for chronic maintenance therapy. All recipients have follow-ups of at least the duration indicated by the *arrows*. All unrelated organs were cadaveric. The numerators and denominators at the end of the curves have the same significance as in Figures 3 and 6. Note that the time scale (abscissa) is different from those in Figures 3 and 6.



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in 49 renal recipients from 1½–94 months postoperatively.[249] In 11 patients hepatotoxicity or other side-effects of azathioprine, including drug fever, were suspected. Nine more patients were switched to cyclophosphamide because of the serologic diagnosis of chronic Australia antigenemia even though abnormalities in liver function were either minimal or absent. The switch in therapy in the other 29 patients was made in the hope of eventually maintaining graft function with smaller dosages of prednisone. Consequently, reductions in the daily quantities of steroids usually were made shortly after the institution of cyclophosphamide.

In replacing azathioprine with cyclophosphamide, the same precautions were taken as when cyclophosphamide was used from the beginning. Frequent white blood cell counts were obtained, and appropriate dosage adjustments were made with any indication of impending leukopenia. It was found possible to maintain the typical patient on a per-kilogram dosage of cyclophosphamide one half to two thirds of that previously tolerated for azathioprine.

The details of this substitution trial have been reported.[249] Since the ALG injections usually had been stopped earlier, the drug switch in most patients was made when the only other immunosuppressive agent being used was prednisone. After the drug change the clinical course usually was not obviously different from that preceding the substitution. In a few instances in which hepatic dysfunction or fever were present, these abnormalites receded. The studies demonstrated once more, and in a very straightforward way, that cyclophosphamide is an immunosuppressant with a potency, safety and therapeutic role similar to that of azathioprine, at least for short-term therapy.

Practical and Theoretic Implications

The remarkably comparable effectiveness of cyclophosphamide and azathioprine under the aforementioned general conditions of clinical testing is of some theoretic interest since they belong to different chemical families and because their pharmacologic actions are thought to be dissimilar. Yet, the events of rejection, its reversibility and eventually the feasibility in many instances of lightening maintenance immunosuppression have not been perceptibly different in the two drugs. It remains to be seen whether or not switching agents will have real benefits that might be realized if, for example, the depletion of sensitized immunocompetent cells were made more complete thereby. At the moment this remains a possibility for which there is as yet no solid evidence.

At our center we continue to use cyclophosphamide as our first cytotoxic drug, changing to azathioprine after 1–2 months. However, the essentially similar results after renal transplantation under primary

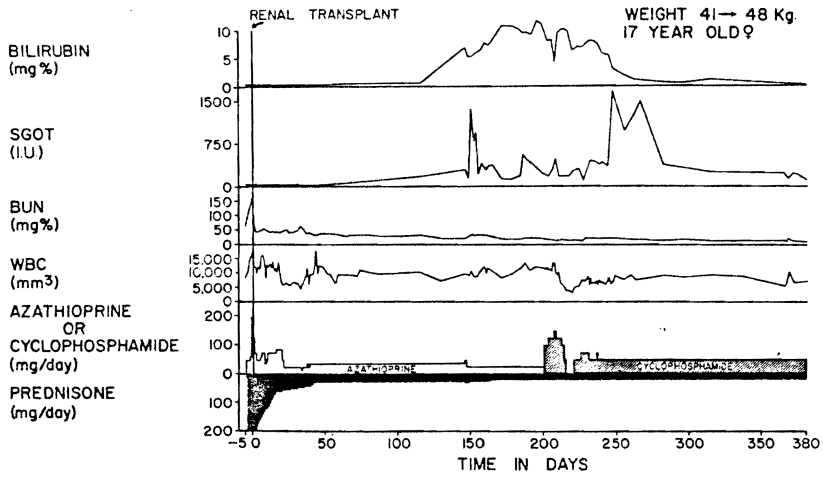

FIG. 11.—The course of a 17-year-old girl in whom azathioprine was stopped because of the suspicion of hepatotoxicity and fever. Multiple Australia antigen tests for serum hepatitis were negative. Note the recession of jaundice after the substitution of cyclophosphamide for azathioprine. More than a year later, azathioprine was reinstituted with recurrence of the manifestations of the same toxicity which receded again under cyclophosphamide. *BUN*, blood urea nitrogen level. *SGOT*, serum glutamic oxalacetic transaminase in international units. *WBC*, white blood cell count. (From Starzl, T. E., *et al.*[249]).

cyclophosphamide, as opposed to azathioprine therapy, will not be a strong inducement for other groups to change their present regimen of azathioprine management except for special indications. Even though we have treated patients daily with cyclophosphamide for as long as 2½ years, we prefer to switch to azathioprine eventually for maintenance, based on our experience of this drug's remarkable safety in many patients over the span of a decade.

However, one special indication for use of cyclophosphamide chronically, instead of azathioprine, is the suspicion of specific toxicity of the latter agent. In several of our patients derangements in liver function were improved thereby, and in a few others unexplained high fever has disappeared within a few days. The patient whose course is shown in Figure 11 had liver function abnormalities and fever, both of which receded with substitution of cyclophosphamide for azathioprine. More than a year later, a switch back to azathioprine was made with recurrence of these symptoms, which once again reversed under cyclophosphamide.

Because of its relative freedom from causing hepatotoxicity, we tend to use cyclophosphamide for somewhat longer periods for our liver transplant recipients.[238]

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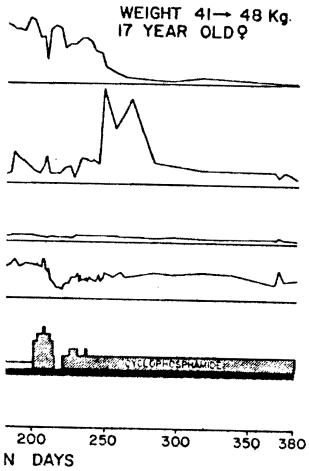

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HL-A typing was one of the principal research interests of the Colorado transplantation team, in collaboration with Dr. Paul Terasaki of Los Angeles, in the mid-1960s. Unfortunately, the evaluation of human histocompatibility matching in renal transplant recipients has not been possible with anything like the precision of a controlled laboratory experiment. One reason was that varying degrees of patient presensitization may occur to antigens present in the eventual organ donor. The consequence of this unfavorable condition may be an accelerated or even a hyperacute rejection in spite of an apparently good histocompatibility match. The following remarks will summarize what has been learned of this disastrous complication and the mechanisms leading to its development.

The Role of Preformed Antibodies

ABO INCOMPATIBILITY.—The first clear examples of hyperacute rejection of renal homografts were observed in patients who had received kidneys from ABO blood group incompatible donors.[235] An effective blood flow to some of these transplants was not restored when the vascular anastomoses were opened. Angiography demonstrated the small vessels of the excised kidneys to be closed and, histopathologically, the arterioles and capillaries were plugged with formed blood elements, particularly erythrocytes (see section on pathology).

A rational, although partial, immunologic explanation was available since the blood group substances that allow red cells to be typed are found also in other tissues, including the kidneys.[91, 255] Consequently, if the kidney of an A, B or AB donor were placed in a patient whose serum contained naturally occurring anti-A and/or anti-B isoagglutinins (e.g., a recipient with O blood type who would have both kinds of isoagglutinins), these antibodies might be predicted to bind with the renal red cell antigens. Serologic studies in some of our patients showed that falls in systemic isoagglutinin titers actually occurred,[235] suggesting their depletion by such an antigen-antibody reaction. Subsequent authors have reached similar conclusions about the role of red cell isoagglutinins in precipitating accelerated rejections.[225]

PRESENSITIZATION.—Hyperacute rejection in the presence of red cell group compatibility has been seen with increasing frequency, and, in fact, this kind of rejection has become a major cause of acute homograft loss in many transplantation centers. The first case was described by Terasaki and associates[257] in a patient whose serum contained lymphocytotoxic antibodies that killed donor cells. The recipient apparently had been immunized accidentally to white cells that shared histocompatibility antigens with the eventual renal donor. This concept

of presensitization has been supported indirectly by the high rate of hyperacute rejection with retransplantation in patients whose first homografts were rejected and who presumably were immunized thereby to some antigens also present in the second graft.

Subsequently, Kissmeyer-Nielsen and his associates[114] and many other authors[39, 163, 231, 241, 261, 276, 278] have confirmed the adverse implications of preformed antidonor antibodies as detected with several technics. The methods most commonly employed have measured lymphocytotoxins and leukoagglutinins, but the most sensitive examination has been said by Williams *et al.*[276] and Klassen and Milgrom[117] to be the mixed agglutination test. In our laboratories[231] deliberate sensitization of dogs by repeated skin grafts led to the formation of a variety of antibodies, each with antidonor reactivity. However, the titer of these antibodies is not well correlated with the rapidity of rejection of a kidney from the skin donor. Moreover, it has been emphasized in reports of clinical cases[237, 241] that hyperacute rejection may occur even though antidonor antibodies in the recipient serum cannot be found with any currently available technic, including the mixed agglutination method. Under these circumstances it has been necessary to assume that an immediate, albeit undiscernible, immunologic reaction is the initiating event in the destructive process that follows.

Vascular Occlusion by Formed Blood Elements and Coagulation

One view of hyperacute rejection might be that antidonor antibodies destroy renal homografts by their direct nephrotoxicity or toxic effects on vascular endothelium. However, the process is not this simple even though clearance of the antibodies by the stricken organ can be demonstrated easily.[19, 231, 237]

The evidence has been growing for several years that coagulation changes are an integral feature of the hyperacute rejection caused by preformed antibodies in the presensitized canine model[231] as well as in man.[237] In dogs receiving multiple skin grafts from the eventual organ donor, the subsequently transplanted kidney, spleen or liver always consumed clotting factors, platelets and other formed blood elements locally. One of the objectives of these animal investigations was to see whether or not transplantation of consecutive organs from the same donor would mitigate the rejection of the second graft. It was found that the second transplant was protected briefly, possibly by the prior depletion of humoral antibodies, clotting factors, formed blood elements or possibly all of these. In time, however, the final organ suffered the same fate as the first one.

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All of the sensitized canine recipients in the above study[231] developed evidence of local consumption of clotting factors. In addition, a minority of animals also had profound systemic coagulation changes that were like those of disseminated intravascular coagulation (DIC). The same kind of observation has been made in patients after renal homotransplantation with a subsequent severe or even fatal bleeding diathesis.[163, 237] Thus, although the clotting aberrations of hyperacute rejection usually are confined to the graft insofar as can be measured, there is now little reason to doubt that profound systemic changes may follow.

White cells, platelets and red cells also are cleared by hyperacutely rejecting homografts and form a morphologically prominent component of the vascular plugs.[19, 231, 237] Williams *et al.*[278] were the first to draw attention to the dramatic appearance of polymorphonuclear leukocytes (PMN) in such kidneys. Their observations, which since have been confirmed, were made possible by systematically doing biopsies of homografts about 1 hour after revascularization. In some instances the PMNs appeared before any other histopathologic findings were evident. That the participation of these cells in the ultimate destruction was not immunologically specific was illustrated by the canine experiments of Clark[34] and Robertshaw[204] and their associates that showed that autologous PMNs were effective intermediaries of hyperacute rejection. The recent studies of cat-to-dog lung xenografts by Cook *et al.*[40] have shown how the vascular plugging in hyperacute rejection may proceed, at least in this model, with red cells before the aggregation of white cells.

Therapeutic Possibilities

Although the factors contributing to hyperacute rejection (especially presensitization) have been well defined, the precise mechanism of the destructive process remains obscure. In particular, the interlocking pathogenetic relationships of antibodies, formed blood elements and clotting factors have not been well defined. However, because of the existence of these interrelationships, two general lines of therapy have been investigated. First, attempts have been made with a variety of anticoagulants to interfere with the coagulation process. Second, efforts have been made to deplete the preformed antibodies or to prevent their action with use of complement inhibitors or organ pretreatment with digested antidonor immunoglobulin.[42]

All therapeutic trials so far in human beings with presensitization states have failed. Hyperacute rejection remains one of the unsolved problems in the field of renal transplantation.

HL-A TISSUE TYPING

After having completed a survey of our clinical experience, it now will be useful to describe our investigations of HL-A tissue typing. The use of these technics for their possible value in more rational donor-recipient pairing occupied our attention soon after the inception of the Colorado transplantation program, and our interest has continued until the present time. However, by the time Series III had been completed, it was already apparent that the initial great expectations of simple HL-A typing were not going to be realized.

The only ground rule that was followed for donor-recipient immunologic matching during the compilation of Series I during 1962–1964 was avoidance of the red blood cell incompatibilities summarized in Table 1. By the spring of 1964, considerable interest had developed in the serologic detection of lymphocyte antigens[258] as a measure of histocompatibility determinants in the kind of matching that since has been widely employed.[3, 30, 31, 43, 46, 116, 119, 256, 259, 260, 268] Patients who had died by this time obviously could not be studied, but matching could be carried out retrospectively upon the nearly 40 recipients still surviving from Series I and their donors.[243] Subsequently, tissue typing almost always was carried out in advance of operation. At all times the reagents used for typing were lymphocytotoxin-rich human isoimmune antisera obtained from persons who had been sensitized, accidentally or deliberately, to white cell antigens.

The cytolysis of test lymphocytes by such antisera indicated the presence of the same or a similar antigen to that which originally had sensitized the serum donor. Failure of such a reaction implied the absence of the antigen. When the lymphocytes of both donor and recipient reacted the same to a given antiserum, *identity* of that antigen was said to be present. The absence in a donor of an antigen that was present in a recipient was defined as *compatibility*. When an antigen was found in the donor lymphocytes but not in those of the recipient, a *mismatch* existed. Identity of antigens was preferable, compatibility was the next most satisfactory condition and the least desirable was an overt mismatch.

The number of antisera used for a single typing has been as large as 200. Even when human typing was first performed, it was appreciated that many of the antisera in the total panel measured the same or similar lymphocyte antigens. Between 1963 and 1968, Terasaki and other workers in this field, by direct testing and by computer technics, classified those antisera according to their specificity of action. In this way it eventually became possible to define human lymphocyte HL-A antigens against which groups of antisera reacted.[43, 256]

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after the definition of these HL-A groups, it was necessary to convert the year-to-year data into uniform terminology. This was done in December, 1969, and January, 1970, by re-analyzing the results obtained with the original antisera in the cases of Series I–III and converting the findings into HL-A designations. It was possible to define at least eight antigenic groups, and at the time of the most completely studied later cases, 11 groups (*phenotypes*) could be identified.

With the definition of antigen phenotype groups a histocompatibility grade (A-E) could be given. An A match indicated identity of all of the measured donor and recipient HL-A antigen groups. With a B match no incompatibilities were present, but there were one or more examples of non-identity. C, D and E matches were progressively less satisfactory, with frank mismatches of one, two or more antigen groups. Because new HL-A groups were discovered and characterized throughout the 6-year period of analysis, the basis for grading was more complete, and consequently more accurate, at the end of the study than at the beginning.

HL-A Correlations

By 1970, the case material with a reasonable period of follow-up that had become available for analysis from our center consisted of Series I–III. The retrospective typing for Series I was incomplete. For Series II the typing was performed in advance and actually was used systematically as an instrument of donor selection in the first such clinical trial ever attempted.[259] As it became obvious that a quantum improvement in results was not going to be achieved (see Figure 3), less and less credence was given to the typing reports even though these were always available; thus, in Series III the selection was allowed to return to a more or less random process with the exception of sibling cases, in which an A match was still considered a significant advantage.

In late 1969 and the spring of 1970, we and Terasaki undertook a total re-evaluation of the HL-A typing versus the clinical and histopathologic outcome in the Colorado Series I–III.[247] After inter-sibling transplantation the recipients of A-matched kidneys had better average renal function and a slightly increased long-term survival. In addition, the incidence and severity of histopathologic abnormalities in the A-matched sibling transplants were minimal. With parent-to-offspring transplantation or with transplantation between more distant relatives or nonrelated people, no correlation existed between the A–E phenotype matching grades and survival, function or histopathology. These discouraging results were presented to the American Society of Nephrology in December, 1969, and to the American Surgical Association in April, 1970.[247]

At the International Transplantation Society meeting in September, 1970, Terasaki offered the same conclusion of poor HL-A correlation in all but perfectly matched siblings on the basis of more than 1,300 cases compiled from many centers.[152] A storm of protest, mainly from typers of the European community, greeted Terasaki's presentation.[61, 94, 115, 269] However, in the ensuing 3 years, Terasaki's conclusions have become more and more accepted, even by some of his former critics.[113, 169, 180, 267] The consequence has been a dampening of enthusiasm for kidney shipping schemes in which the traffic of preserved cadaveric organs from city to city and center to center was envisioned to be controlled by the results of HL-A typing. Today, the only authority who continues to make unequivocal claims about the value of HL-A matching for unrelated cases is Dausset.[45]

Possible Explanations

From a biologic viewpoint the most significant positive fact from correlation studies was that the designation of an A match endowed a slight advantage in terms of survival and quality of homograft function as well as a highly significant advantage in terms of the histopathologic appearance of the kidneys at varying times postoperatively. In practical fact, the designation of an A match in sibling cases almost always was an indication that both the donor and the recipient had the same two histocompatibility haplotypes, one from each parent, and had, therefore, achieved total identity of the HL-A antigens; for the HL-A chromosome it thus could be said that there was *genotype* as well as *phenotype* identity. These observations supported the conclusions from other skin or renal transplantations studied within families about the relevance of HL-A antigens to histocompatibility.[3, 30, 268]

Several factors could have contributed, perhaps cumulatively, to the failure to find significant relationships between the matching grades and survival, function or histopathology in all other kinds of cases. One such possibility would be "immunologic artefact" caused by the transmission of pre-existing host glomerulonephritis to the transplant (see section of histopathology). Other reasonable speculations could be that (1) the completeness and/or accuracy with which HL-A phenotypes currently can be measured are substantially poorer than is generally realized, (2) variable host immunologic reactivity in different patients[112, 171, 267, 283] was comparable in importance to the antigen match in determining the outcome or (3) host presensitization to antigens present in the homografts jeopardized the outcome in a number of instances but was not always recognized as a factor (see preceding section on hyperacute rejection). The latter two possibilities recently have loomed so large in the perspective of some transplant centers that

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However, the most important reason for the poor correlations may well be the obvious one that the HL-A antigen analysis as presently performed provides a woefully incomplete evaluation of histocompatibility. For example, the HL-A genes might not be the only ones of importance in human histocompatibility matching, but could be situated on the same chromosome as even more important genes. They would then be inherited together within families and thus would serve as meaningful indicators for the selection of A-match sibling transplants but inadequate markers in other genetic situations.[7]

In the search for other means of donor-recipient selection, mixed leukocyte culture (MLC) matching has been evaluated extensively, experimentally and clinically. Good correlation between the intensity of stimulation and transplant survival has been obtained by some[8, 11, 36, 108] but not all[291] observers. "One-way MLC matching" is thought to measure the magnitude of the cellular immunologic response of the recipient against donor cell antigens. The presence of blocking serum factors in the recipient also can be evaluated with MLC.[202, 221] At present, the test is too time consuming—requiring 2 or 3 days for completion—for convenient pre-transplantation evaluation in cadaveric kidney transplantation.

Recently, there has been much discussion suggesting that although the genes controlling HL-A and MLC reactivity in human beings are on the same chromosome, they are distinct and not necessarily parallel in their manifestations.[7] In experimental rodent models the nature of the major histocompatibility complex has been well mapped out. In mice two serologically defined loci on the main histocompatibility chromosome (H-2D and H-2K) are of major importance and are probably comparable to the HL-A loci in man. On the same mouse chromosome there are also other lymphocyte-defined loci of major histocompatibility importance controlling MLC reactivity (such as the Ir locus) situated between the H-2D and H-2K regions. If analogous complexities exist in man, adequate tissue matching apparently will require MLC determination as well as HL-A typing, probably as well as other tests that have yet to be devised. With each such new ramification the potential practical value of tissue typing will be diminished, particularly in cadaver cases, since the statistical probability of achieving a good match by all criteria will be progressively less. At the moment, the single most discriminating predictor of success or failure would appear to be the MLC. Consequently, development of a rapid MLC test will

provide a potentially valuable tool for recipient selection in cadaveric cases.

Our Present Policies

When familial donors are being screened, priority is given to a sibling with an A match, and an effort is made by genetic mapping of other family members to establish that the A match represents a genotype, as distinguished from a phenotype, identity. In all other familial combinations the quality of the HL-A match no longer is given major consideration. Rather, the decision about who is to be the donor is made on social, vocational or general medical grounds. Similarly, cadaveric organs are distributed to recipients on the basis of ABO type and need, rather than by the results of a search for an HL-A match. If all other conditions were equal, we still would give an organ to a recipient with a good HL-A match versus a poor one, but such a choice rarely presents itself.

The only absolute immunologic contraindication to either intrafamilial or cadaveric transplantation in our center is the demonstration of preformed antidonor humoral antibodies. If a prospective recipient has antibodies against third-party lymphocytes but not against the lymphocytes of the donor, we proceed even though the risk of failure apparently is increased thereby. We believe that refusal to treat these higher-risk patients will deprive many of effective palliation and will flood dialysis facilities with an unacceptably high proportion of the end-stage uremic population.

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