phosphorus. The decrease in growth rate is abrupt, and is extremely difficult to detect. The rate of growth changes only slightly during the first 6 days and decreases by less than 20 percent on the following day, but in the next 8 hours it decreases from 80 percent of the maximum rate to 0. Such a mode of growth is considerably different from what might be expected from the logistic growth model.

Other studies have failed to show a change in growth rate with differing concentrations of important nutrients because the concentrations of nutrients are very high (*14*). If the relationship suggested by Monod (*13*) and shown by Golterman *et al.* (*5*) to hold for *Scenedesmus* is valid, then changes in nutrient concentration dramatically alter the rate of growth or photosynthesis only at rather low nutrient concentrations.

There are natural situations in which a type I growth pattern may seem to occur. The study of *Asterionella formosa* over a number of years by Lund (*15*) shows that the reduction in the concentration of silica dissolved in the water coincides with the increase in *A. formosa*, and that each year growth ceases at a silica concentration of about 0.5 mg/liter, with the final yield of *A. formosa* being determined by the concentration of silica. This type of response may be determined by the slow rate of silica turnover or by the fact that silica plays no role in cell metabolism. However, as demonstrated in Fig. 2, it is extremely difficult to detect changes in the rate of growth when the population density is increasing and, consequently, the nutrient concentrations are decreasing rapidly.

It seems certain that changes in the concentration or intensity of most factors that have been identified as limiting to phytoplankton algae cause changes in the growth rate, but not necessarily in the final yield. Experimenters working on eutrophication problems and limiting factors must recognize the basic difference in the two growth patterns and design experiments that will test for changes in growth rate. Workers must be especially careful in interpreting changes in yield as definitive when they are determining whether a particular factor is limiting in nature.

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$$\mu = \hat{\mu}\left(\frac{S}{K_s + S}\right)$$

where μ is the specific growth rate; $\hat{\mu}$ is the maximum growth rate; S is the concentration of the substrate limiting the growth rate; and K_s is the half-saturation constant, equal to the substrate concentration where the specific growth rate is equal to one-half the maximum growth rate.
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Prolonged Survival of Second Human Kidney Transplants

Abstract. *Rejection of kidney transplants in 264 patients, followed by retransplantation from cadaver donors, resulted in a 1-year survival rate of 51 ± 3 percent (rate ± standard error) as compared to 51 ± 1 percent for first transplants. If the first transplant immunizes the patient or is rejected by immunologically responsive patients, second grafts into the same patients would be expected to be rejected at a higher rate. Only those reject who reject first grafts hyperacutely or between 1 to 3 months were found to have low second graft survival rates. Patients who rejected transplants after 3 months tended to have second transplant survival rates which were higher than their first graft survival rates.*

Second kidney transplants should be more rapidly rejected than the first according to the classical concept of transplantation immunity as established by Medawar. Human kidney transplants from cadaver donors appear to run counter to this rule. Survival of 257 second grafts almost exactly paralleled the survival of 1497 first grafts (*1*) (Fig. 1A). This confirms the findings of the Kidney Transplant Registry and those of Hume *et al.* (*2*). Of course, since the donors are not the same for the second graft, it could be argued that the diversity of HL-A antigens is so great that the chances for immunization to apply to a random second donor would be slight. Yet with cross-reaction it would be anticipated that, averaged over a large series of second transplants, second grafts should be rejected more rapidly than first grafts. Moreover, if immunologically responsive patients reject grafts, those who are selected out as rejectors by the first graft should more rapidly reject their second grafts. Yet most patients who are retransplanted have a *longer* survival time for their second than for their first graft. This study was undertaken to investigate this paradoxical effect.

Data of kidney transplant patients were kindly made available to us by 58 U.S. and Canadian transplant centers. Survival rates of 264 second grafts from cadaver donors transplanted between January 1967 and December 1971 were computed by actuarial methods (*3*) in different subsets as shown in Figs. 1 and 2. All patients had lost their first transplants either from related or cadaver donors. In none of the studied subsets could a significant difference be found in second graft survival after failures of first transplants from either related or cadaver donors.

Subdividing the patients into those who rejected their first grafts at different time periods, we found that three distinct types of second graft survival rates exist. As shown in Fig. 1B, patients who lose their first grafts within 1 month (hyperacute rejections excluded) have a second graft survival rate of 48 ± 6 percent (rate ± S.E.) at 1 year, a figure very similar to the

overall survival for first cadaver transplants (51 ± 1 percent at 1 year). These patients therefore can be assumed not to be affected adversely in any way by rejection of the first graft.

Patients who hyperacutely reject their first graft in the first month tend to more rapidly reject their second graft (27 ± 10 percent survival at 1 year) and seem to reflect the greater responsiveness and higher risk attendant with the presence of cytotoxins (*4*) (Fig. 1B). Of patients who had rejected their first transplants hyperacutely (including 9 recipients transplanted before 1967), 10 of 27 (37 percent) had hyperacute rejection again when retransplanted with a cadaver kidney and 9 other patients (total of 70 percent) rejected their second graft within 3 months. The prognosis for a second graft in a patient with hyperacute rejection is therefore poor. The suggestion that such recipients are strong immunologic responders is supported by the fact that those who hyperacutely rejected a second graft could be shown to have earlier violently rejected a first graft. Ten of 22 (40 percent) hyperacute failures of second cadaver transplants had rejected their first graft hyperacutely and 19 (86 percent) had lost their first transplants within 3 months.

A similar low rate of second graft survival in patients who reject their first graft in 1 to 3 months is found (31 ± 5 percent at 1 year) (Fig. 1C). These patients are adversely affected by their first transplants, for their second graft survival rates are lower than overall survival rates in patients receiving first grafts.

The most interesting group of patients are those who reject their first grafts after more than 3 months. These patients have a higher 1-year second graft survival rate (60 ± 5 percent) than the overall first graft rate in cadaver transplants (51 ± 1 percent, $P = .09$).

Although all the second grafts were from cadaver donors, 43 of the first grafts had come from related donors and 45 were from cadaver donors. The first graft survival was higher in transplants from related donors than in transplants from cadaver donors, as would be expected (Fig. 1D). The second graft survival rates were virtually identical and at 1 year were 60 ± 8 percent for both groups. Thus recipients of first grafts from related donors had a second graft survival of *cadaver* transplants which was almost as high at 1 year as their related donor graft survival. Recipients of first grafts from cadaver donors with a survival rate of 40 ± 7 percent at 1 year had a considerably improved second graft survival of 60 ± 8 percent at 1 year when retransplanted with cadaver kidneys ($P = .07$). A prolongation effect thus appears to have been induced by the rejection of the first graft.

A clearer separation of three groups can be made if the patients with preformed lymphocytotoxic antibodies are removed from the analysis (Fig. 2). As noted earlier, such patients are higher risks and more susceptible to direct effects of matching (*4, 5*). Among patients without cytotoxins, 1-year survival of second grafts in patients who rejected their first grafts more than 3 months after transplantation was remarkably higher (77 ± 7 percent) than the survival rate of first cadaver transplants in 664 cytotoxicity-negative recipients (*5*) (55 ± 2 percent, $P < .004$). Of the 36 first transplants, 18 were from related and 18 from cadaver donors, with 1-year graft survival rates of 82 ± 9 percent for related and 50 ± 11 percent for cadaver transplants. The improved second cadaver graft survival in recipients of first grafts from cadaver donors and the almost unchanged survival in patients who had a first graft from a related donor are again evident. The higher graft survival in second transplants could not be attributed to better matching for HL-A antigens. In contrast, the survival rate of second grafts in patients who rejected their first grafts between 1 and 3 months was 28 ± 8 percent ($P < .0005$). Again those who rejected grafts in less than 1 month had an intermediate second graft

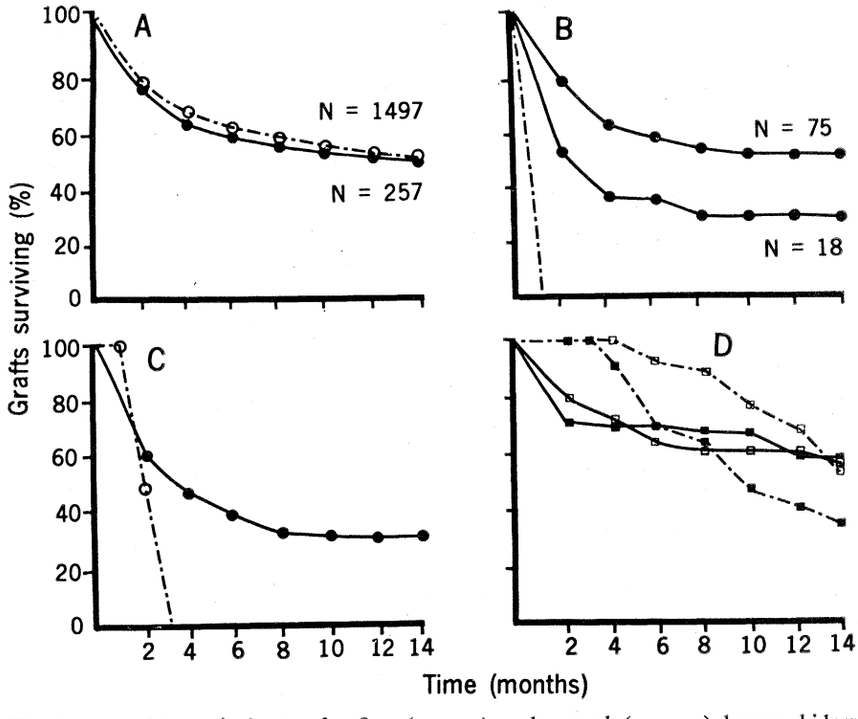

Fig. 1. Actuarial survival rates for first (— - —) and second (———) human kidney transplants; *N* gives the number of transplants in each of the studies. (A) The overall survival rates for first ($N = 1497$) and second ($N = 257$) grafts from cadaver donors are shown to be essentially the same. (B) Ninety-three patients who lost their first graft within 1 month were studied for survival of second grafts. Patients who rejected their first graft hyperacutely ($N = 18$) have a low second graft survival rate, whereas 75 other patients have almost the same graft survival as the overall rates in (A). (C) Eighty-three patients who rejected their first transplants between 1 and 3 months after transplantation have a second graft survival almost as low as patients with hyperacutely rejected first grafts. (D) The graft survival prolongation effect on second transplants from cadaver donors is shown in 88 patients who had a first graft duration of at least 3 months. Forty-three patients who have lost a first transplant from a related donor (□) have a second cadaver kidney graft survival which at 1 year is only slightly lower than the first graft survival and at 14 months posttransplantation even exceeds the survival rate of the first transplants. Forty-five second grafts from cadaver donors in recipients who had lost first grafts from cadaver donors (■) have a significantly higher survival rate than the first transplants.

survival rate of 52 ± 8 percent (*6*).

The fact that the survival rates of second grafts are varied, depending on the length of time that the first graft survived, suggests that the influence of the first graft can be of several kinds and that these are related to the cutoff periods of between 1 and 3 months. First grafts fail after more than 3 months almost solely as a result of a slow, relentless rejection process. These patients are generally a homogeneous group who if grafted again perhaps benefit from some enhancement or tolerance effect produced by the first graft. First grafts which fail between 1 and 3 months are often acutely rejected. This mode of rejection apparently leads to heightened sensitivity with lower second graft survival rates.

Patients who lose grafts in the first month constitute the most heterogeneous group. Some of the transplants are hyperacutely rejected. Second grafts into such patients have a low survival rate. Some grafts are removed because of surgical failure or of preservation failure. Technical failure apparently does not sensitize the host, confirming earlier data of Straffon *et al.* (*7*).

The basic problem which remains to be answered is whether the first kidney transplant actively influences the fate of second grafts by immunization or enhancement or both or whether it only serves to select out patients with different degrees of immunologic responsiveness. At first sight, since the overall second transplant survival rate is the same as the first transplant survival rate, it might be assumed that the first graft does not condition the host in any way. Closer examination of the time at which the first graft was rejected appears to show that rejection at 1 month is associated with no influence of the first graft, whereas hyperacute rejection and rejection between 1 and 3 months is associated with lower survival rates of the second grafts. Patients who hyperacutely reject grafts tend to acutely reject their second grafts. Of greatest interest is that patients who slowly reject their first graft tend to have a high second graft survival rate. Certain patients may be inherently "slow rejectors," and such patients with poor immunologic responsiveness (*8*) may also slowly reject second grafts. Immunologic responsiveness, on the other hand, cannot totally explain the clinical kidney transplant results, for patients who reject a first graft are not uniformly immunologic responders to second grafts, but often retain their second grafts longer than their first. Also, second grafts in patients who slowly rejected their first grafts survive *longer* than overall first grafts. We conclude, therefore, that the first graft may under certain conditions induce enhancement or tolerance.

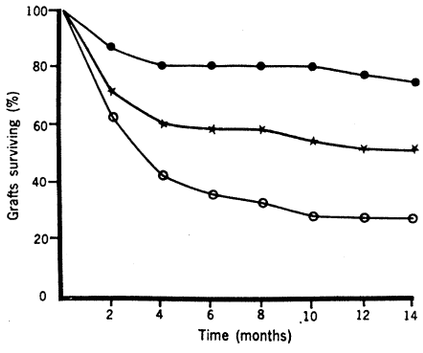

Fig. 2. Second graft survival rates in three subsets of cytotoxicity-negative recipients. Thirty-nine patients lost their first graft within 1 month (★), 35 patients in 1 to 3 months (○), and 36 patients after more than 3 months (●). It can be noted that transplant recipients who lost their first graft after more than 3 months have an unusually high second graft survival for cadaver kidney transplants.

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Silicon: An Essential Element for the Chick

Abstract. *Silicon is required for normal growth and development in the chick when a low silicon diet is fed in a trace element controlled environment. Day-old deutectomized cockerels fed a purified amino acid diet showed significantly retarded growth and development within 2 to 3 weeks. Chicks fed the same diet plus a silicon supplement showed 50 percent higher growth and normal development. Silicon meets the criteria for an essential trace element.*

Silicon is, next to oxygen, the most abundant element in the earth's crust, and at least trace amounts appear in most animal tissues (*1–3*). Although great importance has been attached to the study of the toxicity of the oxide, silica, and of certain fibrous silicates, mainly the involvement of silica in silicosis, there has been relatively little work concerned with the effect of silicon in normal metabolism, and until now there has been no proof that silicon plays any definite role in vital processes in animals or man. Silicon has generally been considered to be nonessential except in certain primitive organisms, notably diatoms, Radiolaria, and some sponges, which utilize silica as a component of body structure. I have now found that silicon is required for normal growth and development in the chick when a low silicon diet is fed in a trace element controlled environment, thus establishing silicon as an essential element (*4*).

Previous studies in this laboratory had suggested a possible role for silicon in bone formation. In vitro studies based upon electron microprobe analysis had shown the unique localization of silicon in active calcification sites in young bone (*5*). In the earliest stages