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Kidney Transplants: Computer Display of Clinical and Laboratory Parameters

The First 100 Days

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OVER 1000 kidney transplantations have been reported from the Kidney Transplant Registry.[1] The results of these attempts to prolong life in patients with end-stage renal disease appear to be improving.[2, 3] The first 100 days following transplantation constitute the period of greatest hazard. Graphical representation of an idealized or average course over this period of many of the clinical and laboratory parameters applied in management could provide a useful basis for comparison of different treatment regimens, suggest certain relationships and contribute to the evaluation of parameters indicating rejection. Use of a computer to digest, arrange and display the large mass of data involved has permitted this type of presentation.

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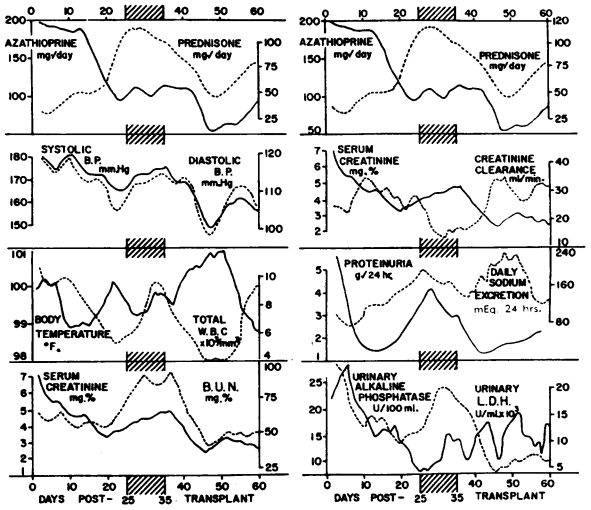
Subjects and Methods

Data were analyzed from 30 consecutive patients who received cadaver transplants which functioned for a period of at least two weeks after the immediate postoperative period. Values were recorded for weight, blood pressure, temperature, dosage of azathioprine (Imuran) and prednisone, leukocyte count and hematocrit, 24-hour urine volume and its specific gravity, concentrations of serum and urine creatinine, blood and urine urea nitrogen, urine sodium and protein, and activity of urine LDH and alkaline phosphatase. In many cases these parameters were measured daily for most of the first 100 days. Data were punched on cards and transferred to magnetic tape. Means of each parameter were calculated for each day, using available data from each patient, and a five-day moving average of the daily means was plotted for the 100-day period for each parameter. A similar plot was made of mathematically derived parameters including 24-hour clearances of creatinine and urea, 24-hour urinary excretion of urea, creatinine, sodium and protein, and of the concentration ratios of urine to serum creatinine and urea nitrogen. All calculations and plots were made by computer.*

*International Business Machines 7044 Computer and Calcomp 565 Plotter.

Canad. Med. Ass. J.
Feb. 22, 1969, vol. 100



Figs. 1 to 5 demonstrate five-day moving averages of daily means. Solid lines relate to ordinate scales on left and interrupted lines to those on the right.

Figs. 1 and 2.—Seven patients who had one or more rejection episodes during the first 60 days (Group I): several parameters suggest maximal rejection activity 25 to 35 days post-transplant.

In addition to the analysis covering all 30 patients, similar analyses and plots were made from data related to the 18 out of the 30 patients who survived 100 days, to the 12 who died during this period, to the 8 who died primarily from causes unrelated to rejection, to the 15

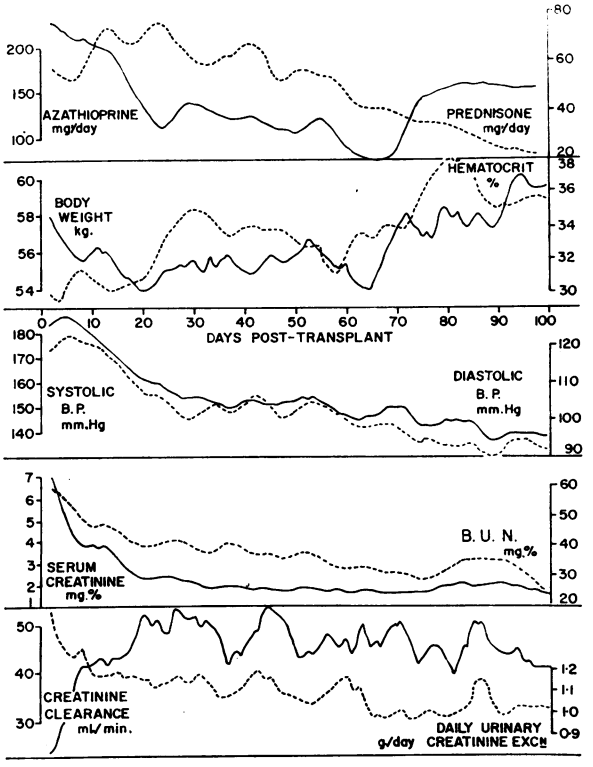


Fig. 3.—Fifteen patients who survived 100 days without evidence of a major rejection (Group II): improvement in renal function, blood pressure, body weight and hematocrit.

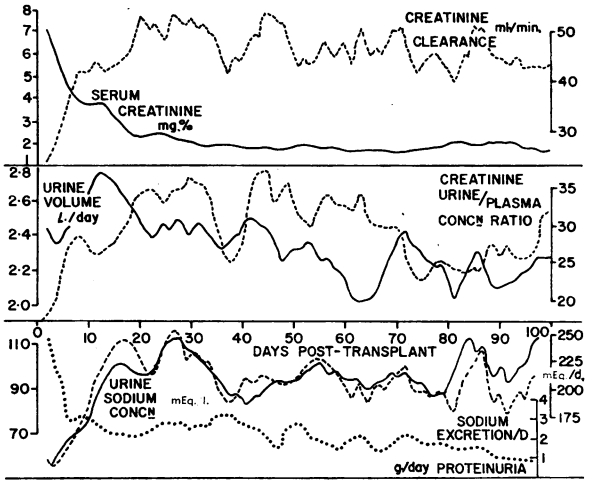


Fig. 4.—Fifteen patients who survived 100 days without evidence of a major rejection (Group II): several parameters suggest rejection tendency around the fifth week.

survivors who had no major rejection episodes, and to the 7 patients who had major rejections of the type associated with a four-fold increase in serum creatinine. Rejections were considered only during the first 100 days.

The immunosuppressive regimen and surgical and other methods used in management have previously been reported.[4, 5] Prevention and treatment of rejection included the use of prednisone, azathioprine and cactinomycin and irradiation of the transplanted kidney.

Some parameters are presented graphically for the group of seven patients who suffered one or more major rejection episodes (Group I, Figs. 1 and 2) and for the group of 15 survivors who had no major rejection episodes during the first 100 days (Group II, Figs. 3, 4 and 5). These two groups appear to offer the purest data with which to illustrate effects of the rejection process and of changing dosage of azathioprine and prednisone. The three patients whose deaths followed vascular occlusion of the graft and the five patients whose deaths were primarily due to infection were omitted. In all five of the latter cases a urinary fistula from the bladder or ureter led to infection, abscess formation and septicemia; the related changes in renal function were considered to be due to these processes or to obstruction and therefore, if included, would obscure the changes due to rejection.

All comments related to the parameters shown in Figs. 1 to 5 refer to five-day moving averages of daily means for the specific patient group under discussion.

Data for the seven patients who had major rejections (Group I) are presented for only 60 days because of insufficient data recorded after

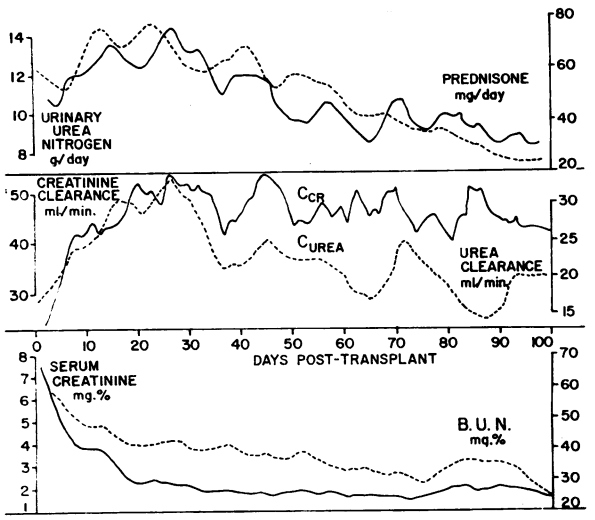


Fig. 5.—Fifteen patients who survived 100 days without evidence of a major rejection (Group II): relationship of prednisone dosage to excretion, blood levels and clearance of urea nitrogen.

this time. Interpretation should be made with reference to the fact that data were not included following the initiation of hemodialysis in two patients at 18 and 40 days post-transplant and before death primarily due to rejection, and that one patient died suddenly on day 43 from a cardiac arrest during a major rejection episode. A fourth patient in this group died on day 85. Data were collected less frequently during the last 40 days in Group II patients (Figs. 3, 4 and 5), particularly for those whose clinical course was satisfactory.

The use of a five-day moving average will have delayed for a short period the appearance of changing values and also will have decreased to some extent the amplitude of such changes.

Results and Discussion

The most striking of several features suggested by the almost simultaneous change in the value of several parameters was the possibility that a period of maximal rejection activity occurred around the fifth post-transplant week. Alterations indicating renal damage or impairment of function were largest in the seven patients who had major rejection episodes (Group I) and most are illustrated in Figs. 1 and 2. These changes include a rise in blood urea nitrogen and serum creatinine, a fall in clearances of creatinine and urea and of the urine to plasma ratio of creatinine, a decrease in excretion of urinary sodium, an increase in excretion of urinary protein and in activity of urine LDH, and a rise in blood pressure. The peak in prednisone dosage occurred at the beginning of this period.

As might be anticipated, the evidence for a corresponding period of increased rejection activity was less striking in those who were most successfully transplanted and survived 100 days without major rejection (Group II). In spite of the absence of a clear-cut rise in serum creatinine or blood urea nitrogen, there were appreciable declines in creatinine clearance, urine to plasma ratio of creatinine, urinary concentration and excretion rate of sodium and a slight increase in protein excretion during the same period (Figs. 3, 4 and 5). All but two of the 15 patients in Group II had one or more minor rejection episodes during the first 50 days, with a rise in serum creatinine of at least 50% and other evidence of rejection.[4] Also of interest in Group II patients are the lesser prednisone requirement (although they received somewhat more prednisone than the Group I patients during the second and third weeks) and the evidence of gradually improving health, as reflected by the improvement in blood pressure, hematocrit and body weight.

Another conclusion which could have been reached by observations on merely a few patients, yet is more convincingly illustrated by plotting the moving average of daily means for patient groups, relates to the dose of azathioprine during major rejection episodes (Group I, Fig. 1). The period of maximal rejection activity around the fifth week is the only interval during which the leukocyte count does not move in parallel with the azathioprine dosage and in the opposite direction to the temperature. The rising leukocyte count at this time may in part relate to the preceding decrease in the dose of azathioprine, but would seem predominantly to be due to the recently very high prednisone dosage, particularly as the associated decline in renal function might be expected to result in retention of azathioprine. This prednisone-induced rise in leukocytes interrupts a falling trend and may inspire a spurious confidence as leukopenia often appears in association with the subsequent reduction in prednisone dosage. We conclude that the dose of azathioprine should not be increased during severe rejection episodes; indeed, a reduction is usually necessary if the hazards of leukopenia are to be avoided.

Other conclusions became evident which were not anticipated, and although not of great importance do illustrate that analysis of this kind may bring to light relationships which lead to a better understanding of transplant physiopathology. They derive from Group II data.

The striking similarity in the patterns of prednisone dosage and rate of urea nitrogen excretion shown in Fig. 5 deserves comment. The

Canad. Med. Ass. J.
Feb. 22, 1969, vol. 100

decrease in urea excretion of about 30% between days 30 and 50 following the initial rising trend contrast with a much smaller decline of about 10% in creatinine excretion (shown at bottom of Fig. 3). This suggests a shift from negative to positive nitrogen balance which may also be reflected in a gradually increasing body weight (Fig. 3). The initial concurrent rise in clearances of urea and creatinine (Fig. 5) contrasts with the later relatively lower clearance of urea which is the more usual relationship between these two clearances; also, the decline in urea clearance despite a falling blood urea nitrogen and relatively stable creatinine clearance would seem to represent a combination of protein anabolism together with increased reabsorption of filtered urea, the former predominating.

The closeness with which the rate of urine sodium excretion follows the creatinine clearance (Fig. 4, Group II), particularly during the first 40 days, suggests that the glomerular filtration rate commonly plays a dominant role in the regulation of sodium excretion in transplanted kidneys during this period. The correlation, however, was less striking in the group of seven patients who had major rejections (Fig. 2). Group II patients were, in general, on a free diet within a few days of the transplantation; the exact intake of sodium was not recorded.

Comparing the results from all 30 patients with those from the 15 in Group II who did not sustain major rejections, important variations, with a few exceptions, were found to be similar in direction and time (although not necessarily in extent). Group II patients showed a lesser rise and an earlier decline in prednisone dosage, and an earlier decline in values for blood urea nitrogen, urine urea nitrogen and urine volume, compared with data for all 30 patients. Also, there was no significant increase in activity of either urinary lactic acid dehydrogenase or alkaline phosphatase during the period 25-35 days post-transplant in Group II, compared with a clear-cut increase of LDH and a questionable increase of alkaline phosphatase when all 30 patients were considered.

The relationships and conclusions suggested by this study of a relatively small group of patients require confirmation by a study of larger numbers. It is hoped that those working in this field will utilize the level II data sheets available from the Human Kidney Transplant Registry in Boston under the direction of Dr. Joseph E. Murray.[1] This data collection system has been extended to include daily clinical and laboratory data (Level II) as distinct from data referring only to periodic evaluation and survival (Level I data).

Summary Data concerning 16 clinical and laboratory parameters from 30 patients who received cadaver kidney transplants covering the first 100 days post transplant have been arranged and displayed by computer, for the group as a whole and as several subgroups. Representative examples of the plots of five-day moving averages of daily means made by computer are presented for seven patients who had major rejections during the first 100 days and for 15 who survived this period without a major rejection. Several relationships are discussed. Workers in the field of kidney transplantation are invited to use the Level II data sheets of the Human Kidney Transplant Registry.

Résumé Nous avons traité par ordinateur les données de 16 paramètres cliniques et de laboratoire obtenus de 30 malades qui avaient reçu une transplantation rénale. Ces paramètres couvraient la période de 100 jours post-opératoires pour l'ensemble du groupe et pour divers sous-groupes. Nous avons fait calculé les moyennes quotidiennes de chaque paramètre pour chaque malade et avons fait tracer par un traceur de courbes, la courbe des moyennes de cinq jours de chaque paramètre pour la période critique de 100 jours pour sept malades qui avaient présenté un rejet majeur et pour 15 autres qui avait survécu à cette période sans présenter de rejet majeur. Nous avons alors étudié diverses relations possibles entre les variations des paramètres et le traitement. Nous invitons les chercheurs dans ce domaine à utiliser les documents adoptés pour le niveau II (Level II) préconisés par le Human Kidney Transplant Registry.

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