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Fractional excretion of sodium after renal transplantation

CHANGGI D. HONG, BHARAT S. KAPOOR, M. ROY FIRST, VICTOR E. POLLAK, and J. WESLEY ALEXANDER

Departments of Medicine and Surgery, University of Cincinnati Medical Center, Cincinnati, Ohio

Fractional excretion of sodium after renal transplantation. After renal transplantation low urinary sodium concentration (U_{Na}) has been used to diagnose acute rejection (AR), for the early phase of AR is often associated with reduced renal perfusion. Early postoperative graft failure without low U_{Na} favors the diagnosis of ischemic tubular damage (ATN). As fractional excretion of filtered sodium (FE_{Na}) better reflects glomerulotubular balance in renal sodium handling, FE_{Na} was analyzed during the first 2 weeks in 118 renal allografts. From data on 41 transplants with good early renal function (GEF), a temporal profile of FE_{Na} was obtained and used to evaluate the behavior of FE_{Na} by means of standardized FE_{Na} (z score). Individual subjects followed their own profile with a small deviation ($\Delta z < 1.4$ for 2 days). In 31 instances, acute rejection was diagnosed. In 14 with AR, the z score deviated little; 2 responded to methylprednisolone given intravenously. In 17 with AR, the z score fell significantly ($\Delta z > 1.5$ for 2 days), an average of 2.6 days before the first rise in serum creatinine concentration; 15 responded to treatment. The difference between these two groups was significant ($P < 0.001$). This functional heterogeneity and different responses to treatment may indicate different immunologic mechanisms which damage different target cells in the graft in AR. In 46 patients with acute tubular necrosis after cadaver kidney transplantation FE_{Na} was significantly higher than it was in the GEF group as early as the first posttransplantation day and approached normal as the renal function recovered. This behavior of FE_{Na} was clearly different from that in AR.

Excrétion fractionnelle du sodium après transplantation rénale. Après transplantation rénale une concentration urinaire de sodium (U_{Na}) faible est considérée comme un signe de rejet aigu (AR), du fait que la phase précoce du rejet est souvent associée à une diminution du débit rénal. L'échec précoce d'une greffe sans abaissement de U_{Na} est en faveur d'une tubulopathie ischémique (ATN). Puisque l'excrétion fractionnelle du sodium filtré (FE_{Na}) est le meilleur reflet de l'équilibre glomérulo-tubulaire concernant le sodium, FE_{Na} a été étudiée pendant les 2 premières semaines d'évolution de 118 allogreffes rénales. A partir de l'observation de 41 transplants ayant eu un bon fonctionnement précoce (GEF) un profil de FE_{Na} en fonction du temps a été obtenu et utilisé pour évaluer le comportement de FE_{Na} au moyen d'une FE_{Na} standardisée (test z). Les sujets ont suivi leur propre profil avec une déviation faible ($\Delta z < 1{,}4$ par 2 jours). Le rejet aigu a été diagnostiqué dans 31 cas. Quatorze d'entre eux avaient une déviation minime de z; deux ont répondu à la méthylprednisolone i.v. Dix sept sujets avaient une déviation significative de z ($\Delta z > 1{,}5$ par 2 jours), 2,6 jours en moyenne avant la première augmentation de la créatinine; quinze ont répondu au traitement. La différence entre ces deux groupes est significative ($P < 0{,}001$). Cette hétérogénéité fonctionnelle et cette différence de réponse au traitement peuvent être la traduction de mécanismes immunologiques différents qui atteignent des cellules cibles de la greffe différentes au cours du rejet aigu. Chez 46 malades ayant des lésions ischémiques après transplantation de reins de cadavre, FE_{Na} était significativement plus élevée que dans le groupe GEF dès le premier jour après la transplantation et revenait vers la normale au fur et à mesure que la fonction rénale s'améliorait. Ce comportement de FE_{Na} est nettement différent de celui observé dans les rejets aigus.

The clinical diagnosis of acute rejection after renal transplantation is made from a constellation of clinical and laboratory clues, for there is yet no single clear-cut method of making the diagnosis [1–7]. None of these findings is individually pathognomonic for acute rejection of the kidney allograft. In clinical practice, early diagnosis and therapy of acute rejection are assumed to be important to prevent and minimize irreversible injury to the graft kidney from the rejection process. Thus, the clinical picture of acute rejection is usually not allowed to develop fully, and treatment presumably limits the clinical manifestations of acute rejection, thereby making the diagnosis of acute rejection even more difficult.

From the premise that any significant episode of acute rejection is associated with a measurable change in renal function, the initial basis for suspecting acute rejection has been an impairment of renal function, usually a rise in serum creatinine concentration. In practice, any increasing degree of azotemia that is not attributable to other easily definable causes is considered as probable acute rejection.

Physiologic and radiologic studies indicate that acute rejection of the kidney allograft is frequently associated with decreased renal perfusion [8–13], evidenced by decreased urine volume with low sodium and high urinary osmolality [14], increased

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plasma renin activity [15], poor peripheral filling on arteriogram [16], and abnormal ^{131}I-orthoiodohippurate scintiphotographic findings [17]. All of these changes develop in the absence of systemic hemodynamic alterations, such as hypovolemia, or hypotension, or both, which also may result in reduced renal perfusion. This "inappropriate" intrarenal ischemia is further suggested by histologic changes in small blood vessels, for example, microthrombosis, intimal swelling, fibrinoid necrosis, hyperplasia of the juxtaglomerular apparatus, and, occasionally, "ischemic" collapse of the glomeruli [18–22].

It is reasonable, therefore, to suspect that a physiologic stage in which a glomerulotubular imbalance with tubular preponderance might develop early in acute rejection before subsequent tubulointerstitial inflammation impairs tubular epithelial function. With intact tubular function, decreased renal perfusion would be manifested as an altered handling of filtered sodium even before a decrease in glomerular filtration can be detected [23]. In fact, low urinary sodium concentration is a useful clinical clue for the diagnosis of acute rejection [1–7, 13]. Physiologic considerations, however, suggest that the appropriate way to evaluate the renal handling of sodium would be the analysis of the fractional excretion of filtered sodium (FE_{Na}), for this term takes into account the actual amount of sodium filtered at the glomeruli and the fraction reabsorbed by the tubules. There are no data on the normal concentration of urinary sodium after renal transplantation to allow one to determine what is abnormally low. If there is indeed a significant intrarenal ischemia indicative of glomerulotubular imbalance in the early stage of acute rejection, monitoring the fractional excretion of filtered sodium should provide a clinical clue to the diagnosis of acute rejection prior to the rise in serum creatinine concentration.

Early postoperative graft failure presents a diagnostic problem, especially when oliguria develops after a period of up to 24 hours of apparent normal diuresis. It is important to distinguish reversible graft failure secondary to ischemic tubular necrosis from other possible causes of early anuria or oliguria such as acute rejection, vascular thrombosis, and mechanical obstruction of the urinary tract. Hyperacute rejection usually becomes apparent on the operating table immediately after vascular anastomosis. Acute rejection is an ever present threat, but is seen more commonly after the first few days of an apparently normal course. The entire constellation of clinical findings including a variety of laboratory data, urograms, arteriograms, and radioisotopic studies usually provide diagnostic clues. Even with renal biopsy, however, it may at times be impossible to differentiate with certainty between acute tubular necrosis and an acute rejection crisis. The presence of graft swelling with tenderness, unexplained fever, relatively low urinary excretion of sodium (U_{Na}) and high urinary urea concentration associated with worsening of renal function favor the diagnosis of acute rejection rather than acute tubular necrosis [24]. The diagnosis of ischemic renal injury is usually one of exclusion. If all other causes of graft failures in the very early posttransplant period have been excluded with reasonable certainty, one usually assumes that the diagnosis is acute tubular necrosis and that the kidney is likely to recover [25].

One hundred eighteen cases who had received a renal allograft were analyzed retrospectively to establish the temporal profile of normal FE_{Na} after renal transplantation, to develop a technique to determine abnormal values of FE_{Na}, and to evaluate the diagnostic significance of FE_{Na} for acute rejection and acute tubular necrosis. We report two subgroups of acute rejection identified by different behavior of FE_{Na} and their different responses to conventional treatment for acute rejection.

Methods

The data analyzed, retrospectively, were from 118 renal allografts done between September 1972 to July 1977 at the University of Cincinnati Medical Center; all allografts with appropriate data for the calculation of sequential daily FE_{Na} were included. One hundred were cadaver kidneys, and 18 were from living related donors. In 70 patients, both kidneys had been removed prior to transplantation; 48 kept their own kidneys throughout the observation period.

Twenty-four hour urine samples were collected through indwelling Foley catheters during postoperative days 1 and 2, and thereafter by voiding from 6:00 A.M. to 6:00 A.M. The volume was recorded to the nearest milliliter. Serum samples were obtained by venipuncture at about 7:00 A.M.[1] Serum and urine creatinine concentrations were measured

[1] During periods of rapid change immediately after transplantation, the use of the morning P_{Cr} for the calculation of GFR with subsequently collected 24-hour urine would underestimate GFR and thereby overestimate FE_{Na}. This problem can be avoided if one uses spot urine specimens for U_{Na} and U_{Cr} obtained concurrently with blood specimens for P_{Cr} and P_{Na}.

by Technicon Autoanalyzer with appropriate dilution of specimen in the case of urine. Sodium concentration was measured by flame photometry (IL-443).

Calculation of FE_{Na}. The calculation of FE_{Na} was done by:

$$\%FE_{Na} = \frac{\text{Na excreted}}{\text{Na filtered}} \times 100 = \frac{U_{Na} \cdot V}{P_{Na} \cdot GFR} \times 100$$

$$= \frac{U_{Na} \cdot V}{P_{Na} \cdot \frac{U_{Cr}V}{P_{Cr}}} \times 100 = \frac{(U/P)_{Na}}{(U/P)_{Cr}} \times 100$$

The patients were maintained on a regular hospital diet containing about 200 mmoles of sodium per day as soon as the postoperative clinical condition allowed oral intake.[2] Before this, they received intravenous fluid infusion, replacing two thirds of the hourly output plus 50 ml/hr with alternating bottles of normal saline and half-normal saline. When a significant weight gain, or rise in blood pressure, or both occurred during rejection episodes, suggesting salt and water retention, the dietary salt and water were restricted moderately. When patients received diuretics, the subsequent data on FE_{Na} could not be interpreted and were not analyzed.

Definitions. The initial 2-week course of the renal allografts was classified into one of the following three categories: *Good early function (41 grafts).* This diagnosis was made when there was a continuing fall in serum creatinine concentration to < 2 mg/dl by day 7 posttransplantation. *Acute tubular necrosis (46 grafts).* This clinical diagnosis was made by convention when the graft function deviated from "good early function" following transplantation *and* when the graft perfusion was judged by the surgeon to be good postanastomosis, and later in the first week by renal scan (in most cases) performed with 15 mCi of ^{99m}Tc in the form of Renotech® (Squibb), and mechanical obstruction of the urinary tract was ruled out. *Acute rejection (31 grafts).* This diagnosis was made when there was an increase, or failure of expected decline, in serum creatinine concentration occurring after an initial period conforming with good early function *and* two or more of the following: *(a)* fever, otherwise unexplained, *(b)* reduction in urine output, *(c)* graft tenderness with or without enlargement of the graft, *(d)* $U_{Na} < 20$ mEq/liter.

Response to therapy for acute rejection was defined as a return of serum creatinine concentration towards the prerejection level within 10 days after the initiation of treatment for rejection. This treatment consisted of 250 to 500 mg i.v. of methylprednisolone daily, with or without local irradiation (150 rads) of the graft every other day by ^{60}Co. This treatment was continued until: *(a)* there was an arbitrary maximal cumulative dose of methylprednisolone of up to 3 g, with or without a local irradiation dose of 900 rads, *(b)* the serum creatinine concentration declined on 2 or 3 consecutive days, *(c)* other clinical contraindications (such as bacterial pneumonia or urinary tract infection) developed.

The *standard immunosuppressive treatment* at the University of Cincinnati Medical Center consisted of azathioprine, prednisone, and goat antilymphocyte globulin (ALG). Azathioprine was given in a dose of 2 mg/kg/day from the day of transplantation. This dose was reduced to 1.5 mg/kg/day while serum creatinine was > 2 mg/dl to prevent bone marrow suppression. Prednisone was reduced from the initial preoperative dose of 400 mg/day, step by step until patients were sent home with a maintenance dose of about 1 mg/kg/day by the end of week 3 or 4. ALG was used in low dose (2 mg/kg/day, i.m.) for 3 weeks until 1977, thereafter in a larger dose (15 mg/kg) intravenously 15 times over 4 weeks.

Results

Patients with good early function

Distribution of FE_{Na}. To determine the appropriate mathematic methods for the analysis, we analyzed data on FE_{Na} on postoperative day 7 from 29 previously nephrectomized patients with good early graft function. The data showed clearly that the distribution of FE_{Na} was log-normal. All subsequent statistical analyses of FE_{Na} were done after logarithmic transformation and were expressed on a logarithmic scale [27].

Effect of native kidneys on FE_{Na}. Because FE_{Na} is very high in chronic renal failure [28–31], it was important to assess whether there were any effects of the presence of the diseased kidneys on FE_{Na} after renal transplantation. The data on 29 nephrectomized and 12 nonnephrectomized patients with good early function were compared (Fig. 1) and did not differ significantly. There was also no significant

[2] The amount of sodium actually taken varied widely among patients, and from day to day in individuals. This important variable was not and could not have been controlled in this retrospective study; as shall be seen later in this paper, it was possible to make clinical use of FE_{Na} even under such inadequately controlled conditions.

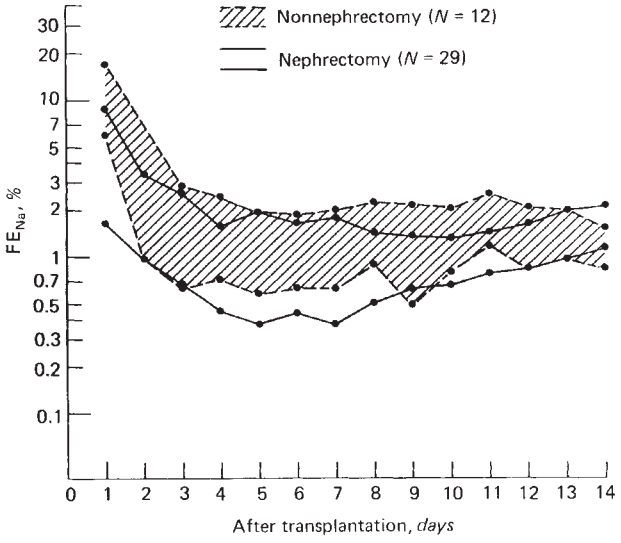

Fig. 1. *%FE$_{Na}$ after renal transplantation with good early function in a group with* (cross-hatched band) *and a group without* (open band) *nephrectomy of native diseased kidneys.* The bands cover mean ± 1 SD. There is no significant effect of the presence of native diseased kidneys on FE_{Na} as long as graft function is good.

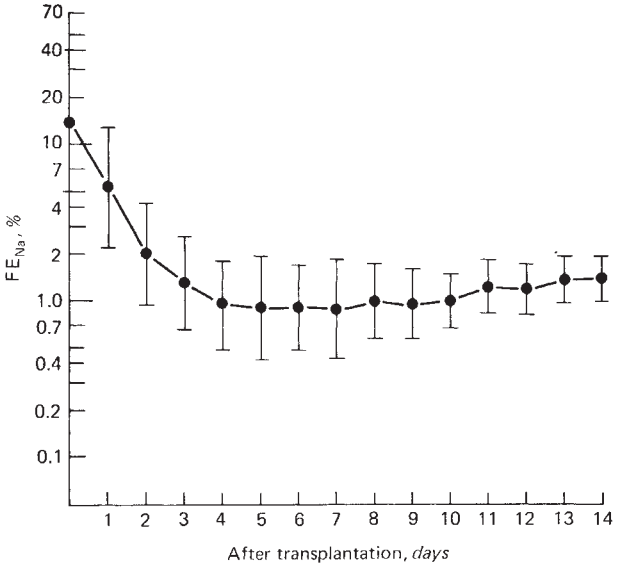

Fig. 2. *%FE$_{NA}$ (mean ± 1 SD) after renal transplantation with good early function (N = 41).*

difference in FE_{Na} between cadaver kidney recipients and related donor kidney recipients with good early graft function.

Establishment of the norm for FE$_{Na}$. FE_{Na} values from all 41 patients with good early function were pooled, regardless of nephrectomy status or source of the graft, to establish a norm that would be used

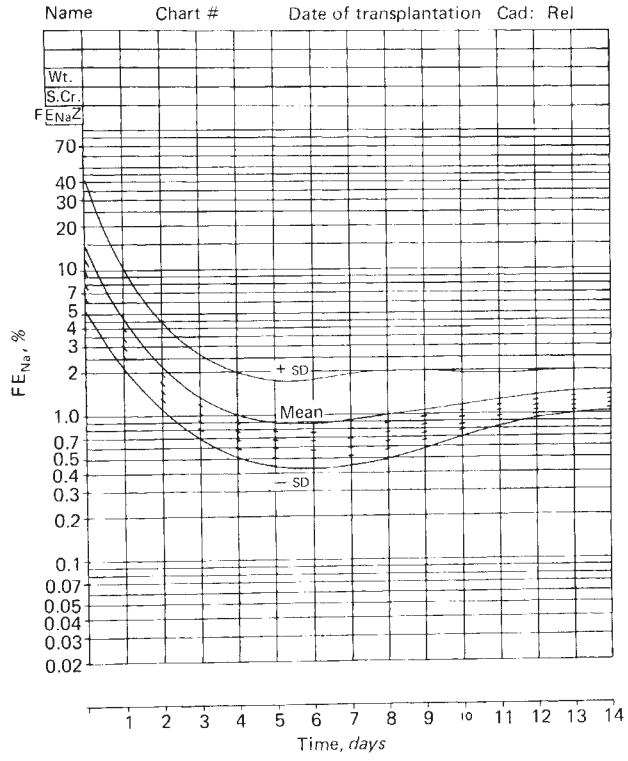

Fig. 3. *Nomogram used to obtain z score graphically at bedside.*

to evaluate the individual case (Fig. 2). The mean FE_{Na} (+ 1 SD, − 1 SD) on the day of renal transplantation was 14.5% (41.0%, 5.10%); on postoperative day 1, 5.41% (13.0%, 2.25%); on day 2, 2.03% (4.30%, 0.97%); and rapidly decreased to reach the lowest value, 0.91% (1.91%, 0.44%) on postoperative day 7; thereafter FE_{Na} gradually rose to 1.47% (2.05%, 1.05%) by postoperative day 14 and stayed about the same level thereafter (Fig. 2).

Calculation of z score. Because absolute values of FE_{Na} change rapidly during an uncomplicated course after renal transplantation, FE_{Na} values from an individual should be evaluated in the same context. For this purpose, a modification of growth-curve techniques was used [32].

Individual FE_{Na} was standardized by means of z transformation, that is,

$$z = (\text{individual } FE_{Na} - \text{mean } FE_{Na})/SD$$

where mean and SD represent the mean and standard deviation of FE_{Na} of 41 patients with good early function, calculated daily.

Figure 3 can be used at the bedside to obtain a z score simply and graphically without having to use the above equation. The curve corresponding to the mean represents a z score of zero, + 1 SD repre-

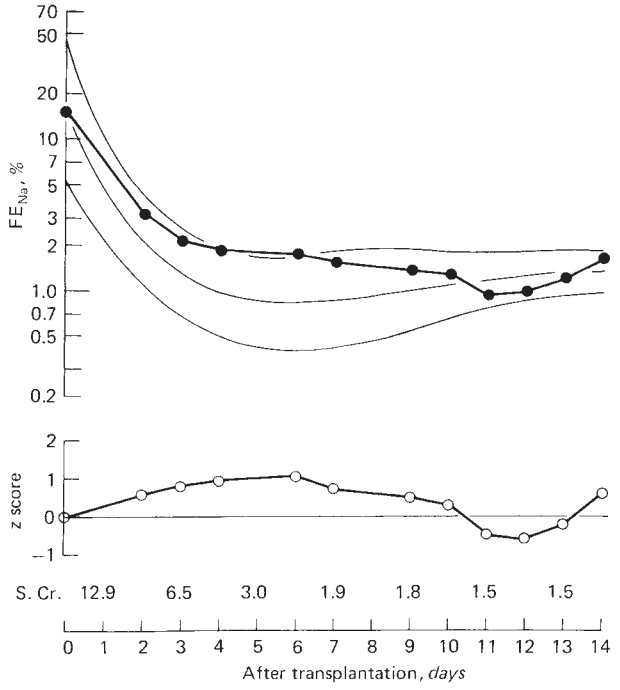

Fig. 4. *Representative case of good early renal function.* The widest fluctuation of z score is 1.2 from day 12 to day 14.

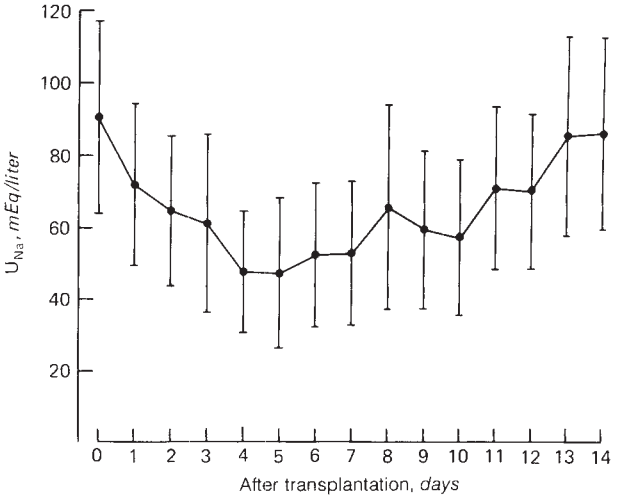

Fig. 5. U_{Na} *(mean ± 1* SD*) after renal transplantation with good early function (mean ±* SD*;* $N = 41$*).*

sents a z score of + 1.0, − 1 SD represents z score of − 1.0, and so on. The intervals between mean and − 1 SD are partitioned into five equal divisions to facilitate estimation of z score graphically to the nearest tenth.

Range of z score in patients with good early renal function. In this group of patients, FE_{Na} fluctuated within a very narrow range of z score during the postoperative course, despite a marked reduction in absolute values of FE_{Na} from the immediate postoperative period to the second postoperative week. A representative case, whose postoperative course was uneventful and who was judged to have had good early function, is illustrated in Fig. 4. The FE_{Na} was 15.0% on the day of transplantation and 1.0% on postoperative day 11. The corresponding z score showed only a small change from 0.0 on day 1 to + 1.0 on day 6 with a slow decline to − 0.5 on day 12.

In this group, the z score rarely changed by more than 1.4 over a 2-day period, and there was much less fluctuation from day to day.

Criteria of "abnormal" change in z score. From the above observations in patients with good early function, we used an arbitrary set of criteria to determine an abnormal value of FE_{Na} or abnormal behavior of FE_{Na} during the postoperative course: *(a)* FE_{Na} with z score of > 2.0 or < -2.0 was assumed to be abnormally high or abnormally low, respectively, for that day; *(b)* changes of FE_{Na} by Δz of > 1.4 over a period of 1 or 2 days. This behavior was considered to be abnormal, that is, abnormal drop or abnormal rise.

Urine sodium concentration in patients with good early function. For comparison with the data on FE_{Na}, the time course of U_{Na}—a frequently used diagnostic parameter—is plotted in Fig. 5. U_{Na} changed along this time course with a wide range of "normal." On days 4 to 6, about 8% of "normals" had $U_{Na} < 20$ mEq/liter.

Patients with acute rejection

Behavior of FE_{Na} at the time of acute rejection. In the 118 transplantations analyzed, 31 episodes of acute rejection were diagnosed before the end of postoperative week 2, and treatment was initiated.

Of the 31 episodes of acute rejection, 17 were associated with an abnormally low or with an abnormal drop in z score for FE_{Na} immediately preceding the first rise in serum creatinine concentration (Figs. 6 and 7). These changes in z score for FE_{Na} were not associated with loss of body weight or decrease in blood pressure, except in two patients whose body weight decreased by 2 and 1 kg, respectively. Most acute rejection episodes were accompanied by weight gain and rise in blood pressure. The first appearance of an abnormally low FE_{Na} z score preceded the first rise in serum creatinine concentration by 2.6 ± (SD) 1.6 days; in every instance the change in z score occurred prior to the clinical diagnosis of acute rejection. In no case was

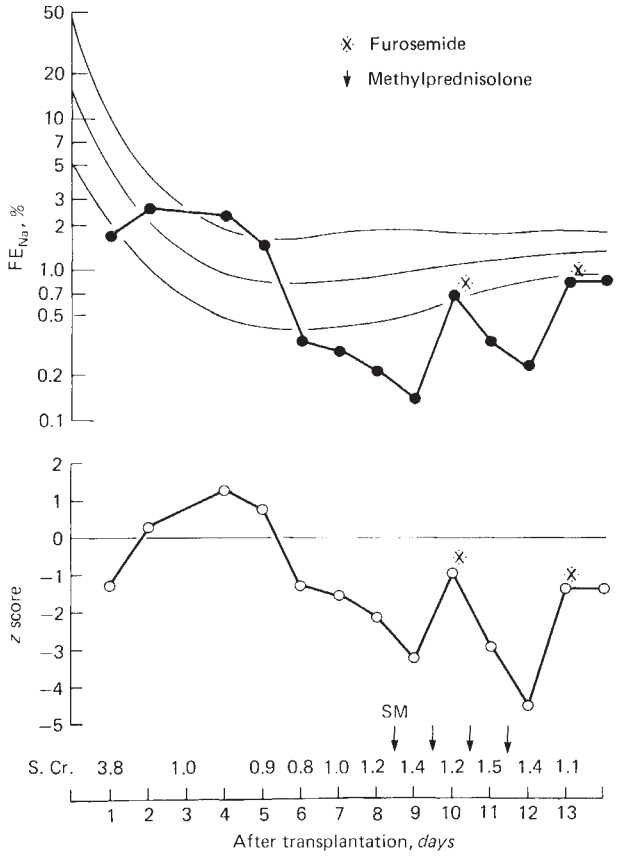

Fig. 6. *Representative case of acute rejection associated with a significant decrease in FE_{Na}.* The z score decreased by 2.1 from day 5 to day 6, 1 day before the first rise in serum creatinine concentration. SM indicates methylprednisolone pulse.

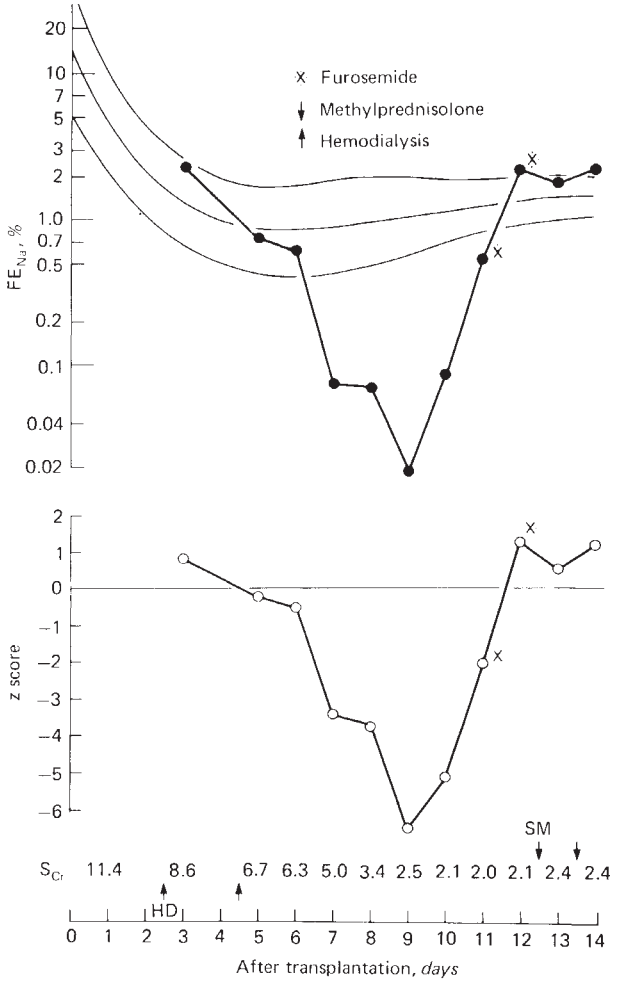

Fig. 7. *Another example of acute rejection associated with a significant decrease in FE_{Na}.* The z score decreased by 2.9 from day 6 to day 7, 6 days prior to the first rise in serum creatinine concentration. HD indicates hemodialysis; SM is methylprednisolone pulse.

an abnormal drop in z score not followed within a week by a rise in serum creatinine concentration.

Fourteen acute rejection episodes were not associated with any significant change in z score for FE_{Na} before or at the time of diagnosis (Fig. 8). Six of these had an abnormally high FE_{Na} z score soon after rejection was diagnosed (Fig. 9).

Because one criterion for the clinical diagnosis of acute rejection was $U_{Na} < 20$ mEq/liter, we compared the appearance of an abnormally low U_{Na} and abnormal drop in z score for FE_{Na}. Of 17 grafts with an abnormal drop in z score, only 8 had abnormally low U_{Na}; only 1 out of 14 without a significant drop in z score showed abnormally low U_{Na}. Although the association is statistically significant ($\chi^2 = 4.16$, $P < 0.05$), the data indicates that U_{Na} was a poor predictor of a fall in z score for FE_{Na}; half of the grafts with acute rejection and a significant drop in FE_{Na} z score did not have $U_{Na} < 20$ mEq/liter.

Response of acute rejection to treatment according to the behavior of FE_{NA}. Table 1 shows the response to treatment in the 31 episodes of acute rejection. Of 17 patients with an abnormally low FE_{Na} z score, 15 responded, and renal function was restored to previous levels. In contrast, only 2 of 14 patients whose FE_{Na} z score did not change significantly ($\Delta z < 1.4$ for 2 days) responded to treatment. This difference in response rate is highly significant ($\chi^2 = 14.1$; $P < 0.001$). The 17 responders and 14 nonresponders did not differ significantly in terms of their age, sex, history of previous transplantation, nephrectomy status, and type of donor. Of 17 patients whose FE_{Na} decreased significantly and who did not respond to treatment, 2 lost weight (2 kg and 1 kg, respectively) just prior to the first rise in serum creatinine concentration.

In contrast, low U_{Na} did not predict therapeutic response. Of 9 patients with rejection episodes and

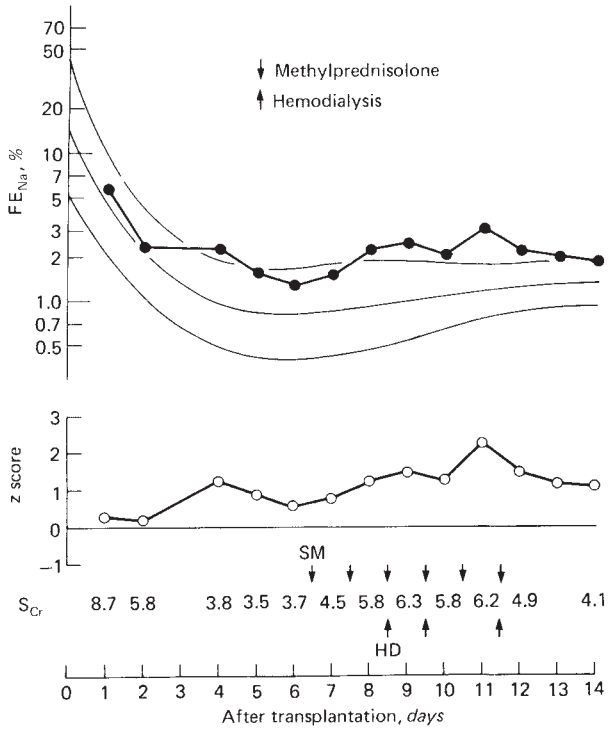

Fig. 8. *Representative case of acute rejection associated with no significant change in FE_{Na}.* SM and HD are defined in Fig. 7.

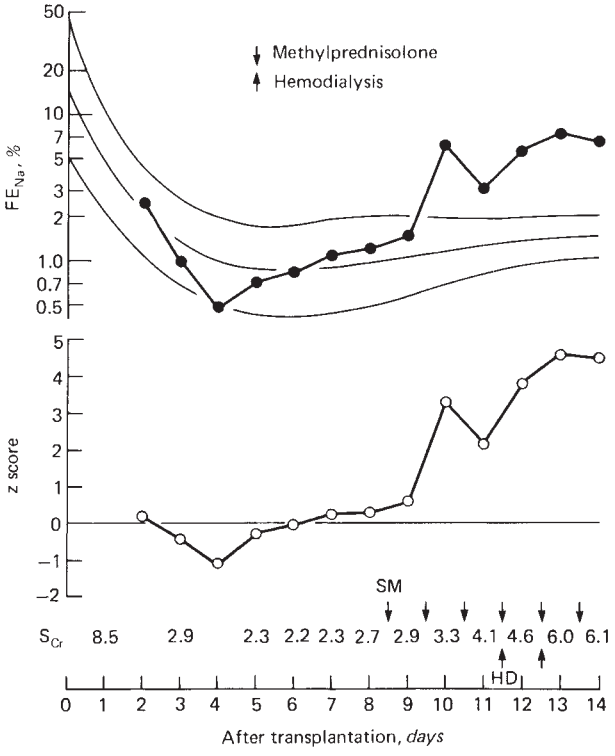

Fig. 9. *Representative case of acute rejection associated with a significant rise in FE_{Na}.* The z score rose by 1.7 from day 9 to day 11, 4 days after the initial rise in serum creatinine concentration: SM and HD are defined in Fig. 7.

Table 1. Response to treatment for acute rejection according to the behaviour of FE_{Na}

	FE_{Na} z score during acute rejection[a]	
	Low	Not low
Response	15	2
No response	2	12

[a] $\chi^2 = 14.1$; $P < 0.001$.

Table 2. Graft status at 4 months according to the behavior of FE_{Na} during initial acute rejection

	FE_{Na} z score during acute rejection[a]	
	Low	Not low
Functioning	16	7
Lost from renal failure	1	7[b]

[a] $\chi^2 = 5.67$; $P < 0.002$.

[b] There were three incorrectly diagnosed acute rejection episodes (see Discussion). If they are excluded from the analysis the differences between the two groups are greater ($\chi^2 = 10.9$; $P < 0.001$).

low U_{Na}, 3 did not respond to treatment, whereas 11 of 22 patients with rejection episodes without low U_{Na} responded ($\chi^2 = 0.20$, $P > 0.5$).

Graft status at 4 months posttransplantation. Because there was such a striking difference in response to treatment according to their different behavior in terms of FE_{Na}, we analyzed the later outcome of the 31 transplantations with early (within 2 weeks) rejection episodes at the end of postoperative month 4 (Table 2). Of the 17 patients who showed abnormally low FE_{Na} z scores during the early rejection episode, 16 maintained functioning grafts, as compared to only 7 of 14 patients whose FE_{Na} z score did not change significantly at that time. This difference is significant ($\chi^2 = 5.67$; $P < 0.02$). The other 7 grafts were lost from progressive deterioration of graft function within 4 months. Pathologic examination of nephrectomized grafts in all 7 cases showed findings consistent with severe rejection with or without infarction.

Patients with acute tubular necrosis

In the 118 transplantations analyzed, 46 episodes of acute tubular necrosis were diagnosed and were treated with hemodialysis as needed in addition to the standard immunosuppressive treatment. All episodes of acute tubular necrosis were seen after cadaver kidney transplantation with variable ischemia times. As a group, on the first day after

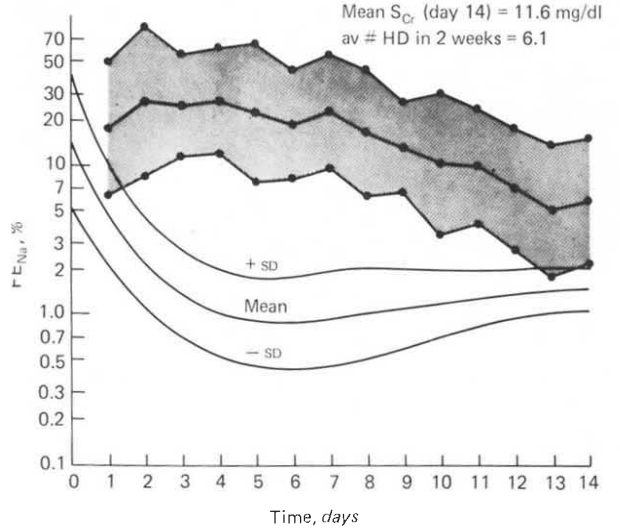

Fig. 10. *FE_{NA} in acute tubular necrosis with prolonged oliguria ($N = 10$).* The background statistical norm is from Fig. 3. HD is hemodialysis.

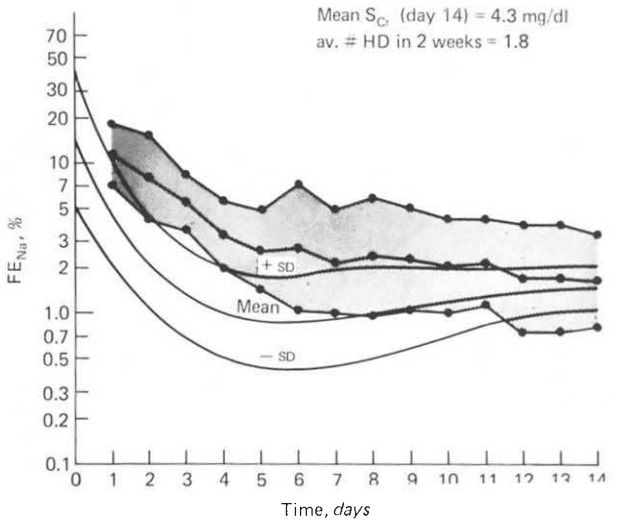

Fig. 12. *FE_{Na} in nonoliguric acute tubular necrosis.* HD is hemodialysis.

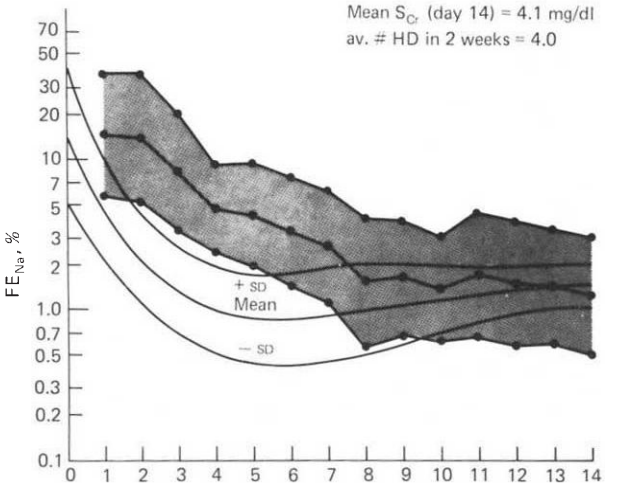

Fig. 11. *FE_{Na} in acute tubular necrosis with oliguric period shorter than 11 days.* HD is hemodialysis.

transplantation, the subjects thus diagnosed showed significantly higher FE_{Na} (mean, 14.2% ± [SD] 33.2, 6.04%) than did the group with good early function (mean, 5.41% ± [SD] 13.0, 2.25%), and FE_{Na} remained elevated for varying lengths of time until renal function improved. Because of the variable severity of necrosis, this group was subdivided into three groups according to the length of oliguria, defined as urine volume less than 500 ml/24 hr, that is, acute tubular necrosis with prolonged oliguria (oliguric period > 10 days, 10 subjects), acute tubular necrosis with brief oliguria (oliguric period < 10 days, 24 subjects), and nonoliguric acute tubular necrosis (12 subjects). The FE_{Na} data of these three subgroups are shown in Figs. 10 to 12. In patients with necrosis and prolonged oliguria, FE_{Na} remained very high throughout the observation period of 2 weeks posttransplantation; the mean serum creatinine concentration on day 14 was 11.6 mg/dl. In patients with relatively brief oliguria (average, 5.5 days), FE_{Na} was high as early as the day after transplantation, and gradually came down towards normal by day 12 and remained normal; the mean serum creatinine concentration on day 14 was 4.1 mg/dl. In patients without oliguria, the course of the FE_{Na} was similar to that in the group with a brief oliguric phase; the mean serum creatinine concentration on day 14 was 4.3 mg/dl.

In this group of 46 grafts with acute tubular necrosis, a significant drop in z score for FE_{Na} ($\Delta z >$ 1.4/2 days) was seen on 12 occasions. Seven were clearly associated with acute weight loss. The mean weight loss was 2.3 ± (SD) 1.0 kg over 2 days; all lost > 1.5 kg. This loss of body weight, which implies a sudden change in salt and water balance, was seen invariably in the early diuretic phase. On the other five occasions, a significant drop in z score for FE_{Na} was associated with either no change in body weight or mild weight gain.

Discussion

The pathogenesis of the rejection reaction following renal transplantation is still not well understood. Both cell-mediated and humoral immune mechanisms may be involved [33], and this may be reflect-

ed histologically in the finding of predominant cellular rejection or predominant microvascular rejection [21]. The bimodal nature of acute rejection is also evident when other immunologic parameters such as circulating immune complexes [34] or antibodies to donor B-lymphocytes [35] are examined. Whether there is a functional difference between these two morphologically and possibly immunologically distinct types of rejection episodes is not known.

Low U_{Na} is reported in association with acute rejection of the allograft kidney and has been used as a clue for the diagnosis of acute rejection [1–7]. Low U_{Na} has been interpreted as a reflection of decreased renal perfusion during acute rejection [8–10, 16, 17]. The studies on which this interpretation was based were done in well established acute rejection, and only a few observations have been made in longitudinal repetitive fashion in the same subject [12, 13, 16]. This longitudinal study showed reversibility of the decreased renal perfusion on treatment of acute rejection, usually with an increased dose of steroid. Morphologic observations showed vascular changes which potentially compromise blood flow in untreated dog [9, 11] and immunosuppressed man [18, 21, 22]. A reduction in renal perfusion was therefore considered to be an essential feature of the early phase of acute rejection and to be reversible if treated early enough.

Ability to excrete urine with a very low sodium concentration when renal blood flow is reduced requires intact tubular function to reabsorb filtered sodium. When tubular function is impaired, while RBF and GFR are decreased, U_{Na} is not lowered. This fact has been applied in differentiating prerenal azotemia from acute tubular necrosis [36]. Physiologic considerations would dictate that the better way to evaluate renal handling of sodium as a clue to change in renal perfusion and glomerulotubular balance is to measure FE_{Na}, for this term takes into account the actual amount of sodium filtered and the fraction reabsorbed by the tubule. FE_{Na} differentiated prerenal azotemia from acute tubular necrosis better than did U_{Na} [37]. FE_{Na} was very low in prerenal azotemia, whereas it was significantly elevated in acute tubular necrosis.

There are few observations on sodium handling by the allograft kidney, especially in early postoperative period when the risk of acute rejection is high. Ogden and Holmes [14] classified their 53 patients according to the course of renal function during the first 3 to 6 weeks after transplantation. The group with acute rejection developed a late reduction in creatinine clearance after initial good function. During the rejection episodes, mean U_{Na} decreased from 107 to 16 mEq/liter, and mean $U_{Na}V$ decreased from 173 to 8.2 μEq/min. These changes were considered to reflect decreased renal perfusion during acute rejection. No attempt was made to study the time course of these changes. Their normal group, with no reduction in creatinine clearance, was subdivided into two: one with "no pattern of urinary solute change" and the other with a fall in U_{Na} and $U_{Na}V$. The last subgroup was considered to be dehydrated. Therefore, a fall in U_{Na} and $U_{Na}V$ was of diagnostic value for acute rejection only in the presence of an unchanged creatinine clearance.

Chisholm et al [38] reported that 13 of 20 rejection episodes, which developed within 4 months, were associated with a fall in 24-hour $U_{Na}V$. They reported that this was not an early change in the course of acute rejection and that it was not diagnostically significant. As 24-hour $U_{Na}V$ was not correlated with GFR nor with total urine volume, change in $U_{Na}V$ could not give any insight into the renal perfusion status or glomerulotubular relationship in sodium handling. Seven rejection episodes occurred which were not associated with a fall in 24-hour urine sodium, and were not discussed further.

We have examined carefully, in longitudinal fashions, the rejection episodes developing within the first 2 posttransplantation weeks. Two distinct groups of acute rejection were identified according to the behavior of the FE_{Na}. One showed a significant decrease in FE_{Na}; the other showed no such change. In the first group, the rapid decrease in FE_{Na} prior to the first rise in serum creatinine concentration is consistent with decreased renal perfusion from local mechanisms, for there was no systemic factor, such as volume contraction and/or hypotension, which might have affected the renal circulation. The result of treatment for acute rejection in this group (response in 15/17) was significantly better than in the other group which did not show any such change in FE_{Na} at the time of onset of acute rejection (response in 2/14). The same criteria were used for the clinical diagnosis of acute rejection, and no clinical distinction could be made between these two groups of acute rejection, except for the FE_{Na} and response to treatment. The second group may not, of course, have had a true acute rejection episode. If indeed this group did not, it indicates the nonspecificity of the conventional clinical criteria for the diagnosis of acute rejection. On the other hand, the unresponsiveness to conven-

tional treatment cannot exclude the diagnosis of acute rejection, for it presumes without grounds that all acute rejections are responsive.

Failure to drop the FE_{Na} in the second group may be simply a reflection of more severe damage to tubules, and this could be the real reason why the therapeutic response is so poor in this group. It may, however, be postulated that the second group did not have a decreased renal perfusion at the beginning of acute rejection and that some other physiologic or perhaps immunologic mechanism was involved in the acute deterioration of renal function, conceivably direct tubular damage without initial vascular involvement. Although no histologic study was performed at the time of onset, the subsequent histologic findings in all 7 nephrectomized grafts from the second group within a 4-month period showed the changes consistent with advanced rejection. Because of advanced pathologic changes in these kidneys, it was not possible to determine the predominant pattern of histologic changes. The subsequent hospital course of several patients in the second group revealed possible factors other than acute rejection which might have contributed, at least in part, to deterioration of renal function: unnoticed partial ureteric obstruction by a blood clot (1 patient), partial obstruction suggested by a dilated ureter (1 patient), urinary tract infection (1 patient), and perinephric wound infection (1 patient). Three of these eventually recovered graft function and were functioning well by the fourth month. The fourth patient, with perinephric infection, underwent graft nephrectomy on day 79; severe rejection was found. One may argue that the 3 patients whose renal functions recovered eventually were erroneously included into the group of acute rejection. If these three patients were excluded from the analysis (Table 2), it would make the notion stronger that acute rejection without a drop in FE_{Na} z score had a poor prognosis ($\chi^2 = 10.9$, $P < 0.001$).

Whether these two groups of acute rejection were mediated by different immunologic mechanisms cannot be known from this study. Whatever the pathogenetic mechanisms, the different responses to conventional treatment are striking. Furthermore the functional pattern during the early acute rejection episodes has prognostic value for graft survival. A prospective study on early acute rejection, correlating the pathophysiology of sodium handling, predominant histologic pattern, various immunologic parameters, and hopefully measurement of RBF would be very rewarding.

Although $U_{Na} < 20$ mEq/liter has often been used as one criterion for the clinical diagnosis of acute rejection after renal transplantation, there are no data to show the range of U_{Na} in normal (or uneventful) allografts. It was found that U_{Na} also changed along the course posttransplantation with a rather wide range of "normal" (Fig. 5). Thus, on the posttransplantation day 4 to 6, about 8% of "normals" had $U_{Na} < 20$ mEq/liter. The data clearly demonstrate that a low U_{Na} (< 20 mEq/liter) was less helpful than was change in FE_{Na} in diagnosis of acute rejection episodes, and was of no value in predicting the response to treatment.

Standardized FE_{Na} score (z) is useful for early diagnosis of acute rejection. A significant decrease in FE_{Na} z score ($\Delta z > 1.4$) without a decrease in body weight predicts a good response to conventional treatment, whereas a rise in serum creatinine concentration without a preceding decrease in FE_{Na} z score makes the diagnosis of acute rejection responsive to conventional treatment unlikely. With the latter combination of laboratory data, factors other than acute rejection should be sought, and graft biopsy is probably indicated for diagnostic purposes. This type of acute rejection (no decrease in FE_{Na} z score) is usually not responsive to conventional treatment and carries a poor prognosis for graft survival.

The data clearly showed that the presence of the native diseased kidney did not alter the temporal profile of FE_{Na} after uneventful transplantation (Fig. 1). To what extent the native kidney obliterates the salt retention by the allograft undergoing acute rejection and thereby prevents a decrease in z FE_{Na} is not known and cannot be evaluated unless a separate collection of urine from both old and new kidneys is made. If the old kidney masks the drop in z FE_{Na} during acute rejection, however, one might expect such episodes of acute rejection, without nephrectomy of the native kidneys (possibly high FE_{Na}), to respond to treatment in the same way as those who showed a decreased FE_{Na} with the native kidneys removed previously. This was not the case, and the proportion of nephrectomized patients in the responders and nonresponders was not significantly different.

There is always a difficult practical problem in differentiating acute rejection from acute tubular necrosis in immediate postoperative graft failure. Some workers use antirejection therapy routinely when graft function deteriorates after good initial diuresis [39]. The problem is further complicated by the heterogeneity in the severity of ischemic tubular damage as shown in this paper. Some practitioners,

therefore, half-heartedly initiate antirejection therapy when they think the recovery from acute tubular necrosis to be "unusually" slow, suspecting acute rejection might have been superimposed upon acute tubular necrosis. Of the 46 patients with acute tubular necrosis in this series, 12 received antirejection treatments starting anywhere between day 7 to day 13 for the suspected acute rejection superimposing upon tubular necrosis. It was difficult to judge the results of these treatments. There was no secondary rise in the serum creatinine concentration prior to the treatment, no biopsy was done before the start of anti-rejection treatment, and the subsequent course was not different from that in the rest of the group. There were 12 patients who showed a significant drop in z score for FE_{Na} during the course of acute tubular necrosis; 7 of these 12 were associated with a significant acute weight loss in the early diuretic phase, probably due to dehydration.

It is shown in this paper that FE_{Na} in acute tubular necrosis is clearly higher than it is in good early function or acute rejection, providing a useful diagnostic clue especially in early graft failure in cadaver kidney transplantation. Drops in FE_{Na} should be interpreted in conjunction with state of fluid balance, particularly in the early diuretic phase.

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Reprint requests to Dr. C. D. Hong, Department of Internal Medicine, Division of Nephrology, University of Cincinnati Medical Center, 5363 Medical Sciences Building, 231 Bethesda Avenue, Cincinnati, Ohio 45267, USA

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