RENAL FUNCTION STUDIES OF SEVERELY BURNED PATIENTS

A PRELIMINARY REPORT*

B. W. HAYNES, JR., M.D., MICHAEL E. DEBAKEY, M.D.,
AND F. R. DENMAN, M.D.

HOUSTON, TEXAS

FROM THE DEPARTMENT OF SURGERY, BAYLOR UNIVERSITY COLLEGE OF MEDICINE, HOUSTON

IT IS A COMMON CLINICAL OBSERVATION that successful therapy of the early fluid translocational phase of severely burned patients is characterized by the maintenance of high levels of urinary flow. Maintenance of this function is perhaps the best clinical guide to the state of hydration of the patient. The threat to renal function is thought to arise from diminution in renal blood flow, resulting primarily from a decrease in circulating blood volume.[23] The renal complications of severe burns may vary from transient oliguria to anuria, and if severe, resemble the clinical picture of lower nephron nephrosis, seen in the crush syndrome, traumatic shock, and other conditions.[16]

In order to secure a fundamental knowledge of glomerular and tubular function, and renal hemodynamics in burned patients, the clearance technics developed by Smith were utilized.[22] It is believed that a better understanding of the alterations of function existing after burn injury would improve our ability to cope with the therapeutic problems presented.

METHODS

It was decided to survey a group of severely burned patients undergoing the treatment currently practiced in our hospital at varying periods post-burn to complete recovery. In addition to the usual clinical and laboratory studies, observations of the glomerular filtration rate, the effective renal plasma flow, the maximal tubular excretory capacity, the plasma volume, and the thiocyanate space were carried out. Inulin clearance[1] was used as a measure of glomerular filtration rate, and para-amino hippurate clearance,[2] at low plasma levels of this agent, determined the effective renal plasma flow. All clearance values were corrected to 1.73 sq. meters body surface area. Para-amino hippurate at high plasma levels in saturation quantity was used to determine the maximal excretory capacity of the tubules. The plasma volume was measured by T-1824, Evans blue dye, using multiple samples,[3] and the total blood volume calculated from the hematocrit. The thiocyanate space was measured by the method of Crandall and Anderson.[4] Two urine collection periods were used for each determination, one for inulin and low-level PAH clearance, and one for high level PAH clearance. Urine collection periods averaged 20 minutes with satisfactory urine flows, usually above 2 cc. per minute, and relatively constant plasma levels of the agents used were regularly obtained. The fraction of the plasma filtered at the glomerulus (filtration fraction, per cent) was obtained by dividing the glomerular filtration rate (cc./min.) x 100 by the renal plasma flow (cc./min.). Normal ranges depicted on the figures include both sexes, the uppermost line representing the upper limit of normal for males and the lower line

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representing the lower limit of normal for females.[12]

RESULTS

Sixteen renal functional observations on eight severely burned patients with 15 to 80 per cent body surface area involvement have been carried out (Table I). With regard to fluid intake, the treatment of this group of patients was quite adequate, in that urinary outputs above 100 cc./hour were regularly seen and nitrogen retention did not occur. As might be expected, blood pressure determinations were within normal range and clinical shock was not observed. There was one death in the group due to severe uncontrolled infection plus gangrene of an extremity occurring 25 days after burn. Renal failure was not a factor in this patient's death. In addition to adequate fluid and electrolyte therapy, adequate amounts of plasma and whole blood were used to counteract for the most part the early plasma loss, and correct or prevent the subsequent anemia. Hematocrit determinations at all stages of therapy were kept above 40 per cent so that anemia as a factor in the production of abnormal kidney function can be eliminated.[17] A rather severe hypoproteinemia (3.7 Gm. per 100 cc.) was observed in one case (R. R.) at the time of his initial renal functional evaluation. The possible importance of this factor with relation to the abnormalities seen will be commented upon.

It may be observed that during the first two and a half week post-burn, a majority of the glomerular filtration rate determinations fall above or in the upper limits of the normal range (Fig. 1). As emphasized by the trend lines, there appears to be a tendency for the filtration rate to descend to normal levels during this period (Fig. 1).

The determinations of renal plasma flow show no such change, the values falling well within normal range (Fig. 2). In view of the somewhat unusual relationship of renal plasma flow to filtration rate, it is well to point out that the absolute validity of the plasma flow data under abnormal conditions such as were met here cannot be assured without measurement of the extraction ratio of para amino hippurate by the kidney. These measurements involve analysis of arterial blood and renal venous blood (obtained by renal vein catheterization) for PAH, and were not practicable in this series. However, the observance of normal values for PAH clearance at low levels (renal plasma flow) and at high levels (tubular excretory capacity) as well, would strongly suggest that the tubular cell is extracting PAH normally and that the determinations are valid.

Since the renal plasma flow studies are within normal limits, and the glomerular filtration rate data are considerably increased, this increase must be accomplished by an increase in the quantity of plasma filtered.

Filtration fractions closely parallel the trend noted in the glomerular filtration rate (Fig. 3). The majority of values fall well above normal range shortly after the burn is received, and tend toward normal, reaching this level coincident with the glomerular filtration rate.

In summary, the burn patients studied show an unusual pattern of response, which is characterized by an increased glomerular filtration rate, a normal renal plasma flow, and an increased filtration fraction. These values trend downward to reach normal at approximately two and a half weeks post-burn. The directional arrows to be seen in Figure 4 graphically summarize these trends.

Determinations of the maximal tubular excretory capacity reveal two points of interest. Shortly after injury, all determinations of tubular function are within normal limits, but as time progresses, the excretory capacity appears to increase (Fig. 5). After two and a half weeks, three determinations performed on one patient (C.C.) show continued tubular hyperactivity. Continuation

TABLE I.—*Renal Function Data on Severely Burned Patients.*

Patient / Sex	C.C. M	L.J. Fe	H.M. Fe	P.L. Fe	R.R. M	C.C. M	M.A. Fe	L.J. Fe	C.C. M	C.C. M	I.G. Fe	R.R. M	B.L. M	C.C. M	C.C. M	C.C. M
Body weight—Kg.	100	79.5	73	48	73		50				50		79.5			
Days post-burn	2	4	4	5	5	6	6	8	10	13	15	16	17	27	42	92
Glomerular filtration rate* (cc./min.)	160.1	111.2	197.4	130.0	213.3	140.6	207.5	102.4	163.9	227.8	154.4	158.2	128.3	150.3	114.5	80.7
Renal plasma flow* (cc./min.)	521.0	562.1	694.9	606.5	835.7	528.6	668.3	640.4	672.3	954.6	518.1	715.4	763.1	793.6	535.5	407.0
Filtration fraction (%)	30.7	19.8	28.4	21.4	25.5	26.6	31.0	15.9	24.4	23.8	29.8	22.1	16.8	18.9	21.4	19.8
Maximal tubular excretory capacity* (mg./min.)	72.6	48.9	85.3	69.8	66.9	119.2	76.9	77.5	87.8	77.7	91.1	112.4	87.3	102.0	103.1	107.8
Plasma volume (cc.)		2,551	2,551	2,475	4,630			2,732		3,906	3,425	4,237				4,630
Blood volume (cc.)		4,368	6,031	4,098	9,666			4,635		7,193	6,041	8,864				7,396
Thiocyanate space (cc.)		16,000	26,316	13,477	27,777		14,085	16,949				29,154				32,260
Temperature (0) F°	102°	98^{6}	101°	99°	98^{6}	101^{6}	101^{6}	98^{6}	98	98^{6}	102^{6}	100°	98^{6}	100°	98^{6}	98^{6}
% B.S.A. burned 2°	8	15	15	30	80		12				40	80	15			
3°	12		25				8				25		5			
Total	20	15	40	30	80		20				65	80	20			
Intake	7650		6928	4013	6000		3770				3,535		7,060			
(Average first week) (cc. per 24 hrs)							2885				1,634		4,800			
Urinary output	5366		5813	800 (?)	2816											
(Average first week) (cc. per 24 hrs)																

* Corrected to 1.73 sq. m. body surface area.

of increased tubular activity for as long as three months is perhaps open to question. The laboratory determinations were satisfactory in that saturation levels of PAH above 60 mg. per 100 cc. were obtained as well as relatively constant blood levels and an adequate urine flow. It is possible that the values noted represent a normal range for that individual which have risen from a previously depressed level. Obviously further studies are needed to elucidate these points.

DISCUSSION

Although there is a large volume of work in the literature concerning the various functional facets of the kidney, there is a paucity of data concerning the effects of burns upon these functions. A search of the literature for the past ten years reveals one reference to similar work in man. Lawson, Bradley, Cournand[5] reported studies on two patients, carried out in the immediate post-burn period, one of which showed a relatively normal glomerular filtration rate, a reduced renal blood flow and, thus, an elevated filtration fraction (36.9 per cent). This determination of the glomerular filtration rate was considered to be technically questionable, however, and in the second patient, insufficient data were recorded to permit calculation of the filtration fraction. Reference was made to a third patient with severe burns, who, though not in shock at the time, as evidenced by a mean blood pressure of 75 mm. Hg., exhibited a low filtration rate, an extremely low renal plasma flow, and an elevated filtration fraction (41 per cent). It was their conclusion that the increase in filtration fraction probably represented a fundamental pattern, and since the first and second patients were examined after having received 600 and 300 cc. of plasma respectively, it was further concluded that this pattern was probably not altered by plasma therapy. No subsequent studies were re-

FIG. 1

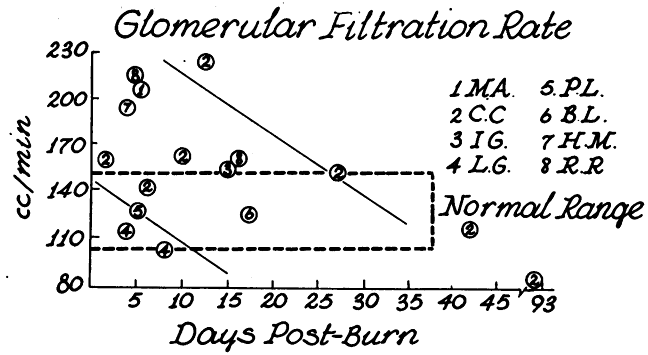
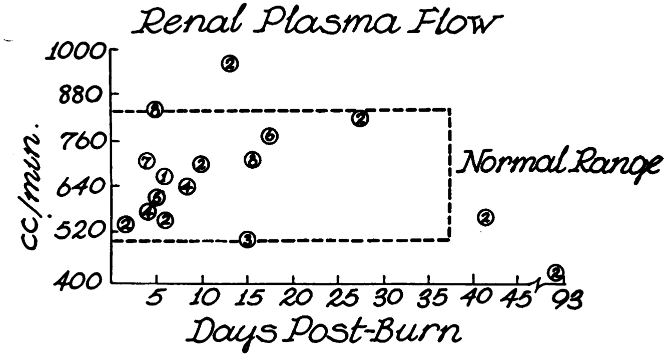


FIG. 2



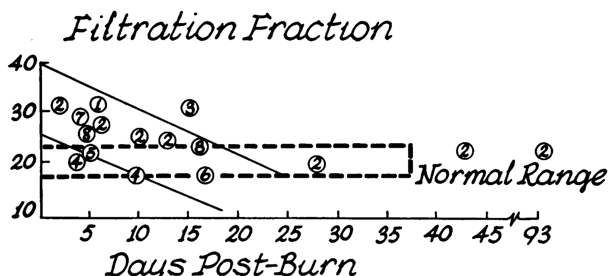


FIG. 3

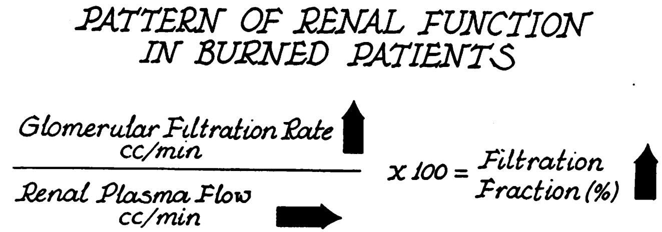


FIG. 4

FIG. 1.—During the first two and a half weeks after burn injury, a majority of the glomerular filtration rate determinations fall above or in the upper limits of the normal range. There appears to be a tendency for these values to descend to normal levels during this period.

FIG. 2.—The determinations of the effective renal plasma flow show no abnormal change.

FIG. 3.—The filtration fraction values parallel the change noted in the glomerular filtration rate, indicating that the increase in filtration rate was accomplished by an increase in the quantity of plasma filtered.

FIG. 4.—Summarizing the trends noted in the renal function data, an increased filtration rate divided by a normal renal plasma flow equals an elevated filtration fraction.

ported. Dziemian noted a depression in all renal functions in goats with 50 per cent surface area third degree burn.[24] In a similar group treated with blood and plasma no significant renal change from the control was noted.

He observed, however, that the glomerular filtration rate was maintained more effectively than the renal plasma flow, thus producing a rise in filtration fraction. Efferent glomerular constriction was considered to be the hemodynamic alteration producing this change. These observations are similar to our own to the extent that an increased filtration fraction was noted in both series, suggesting that there may be a common factor in operation.

Any explanation of the changes noted in the burn patient must take into account functional variations produced by such factors as water load, blood pressure, blood volume and interstitial volume, plasma protein concentration, and adrenal activity, to mention a few. It obviously becomes extremely difficult to attribute any change to a specific variable, when many variables may affect that change, and are operating simultaneously. It is also true that the physiologic limits of variation are quite wide, so that extreme caution must be used in interpreting any apparent abnormality. It is of value, however, to compare the functional pattern seen in these burn patients with that seen under various conditions, so that the field of probable explanation can be narrowed.

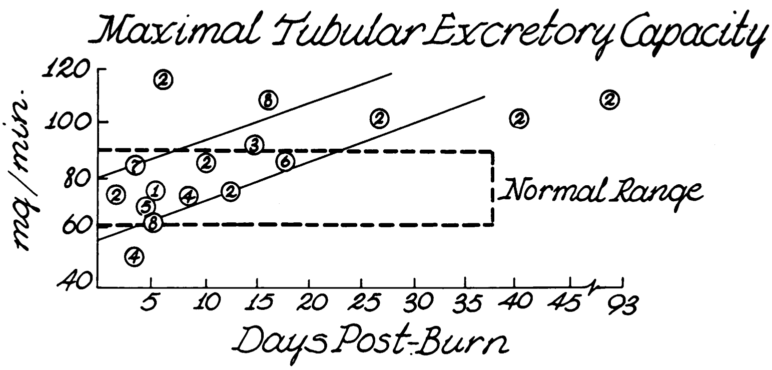
As has been indicated, successful therapy of the severely burned patient demands a large intake of fluid to diminish the dehydrating effect of fluid loss into and from the burn wound. A characteristic of this group of burned patients and others[6] was a varying degree of expansion of the extracellular space, as measured by sodium thiocyanate. Though in these cases no direct correlation between surface area damage and space expansion could be drawn, the larger increases of volume (up to 98 per cent) tended to be associated with the larger burns. Under normal conditions the kidney will respond to overhydration with saline solution by a relatively constant alteration of functional pattern, *i.e.*, an increased glomerular filtration rate, an increased renal plasma flow, and a maintenance of their normal relationships so that the filtration fraction remains relatively constant.[7] Figure 6 presents this pattern of response and others compared to that seen in burned patients. It is apparent that the absence of a rise in renal plasma flow in the burned group suggests that the observed alteration is not due to increased hydration, *per se*. With regard to the excretory capacity of the tubules, Handley[7] notes a direct relationship between the glomerular filtration rate and the tubular excretory capacity in that increase in the filtration rate by normal saline injection is followed by increased tubular function. This is deduced as evidence to indicate that in the dog an increased number of functioning nephrons occur in response to this stimulus. The question of whether the kidney can increase the number of functioning nephrons in response to overhydration or other stimulus has never been satisfactorily answered. Our data would indicate that there may not be a direct relationship between filtration rate and excretory tubular mass (Figs. 1 and 5).

Studies on the effect of thyroxin on renal function[8-18] indicate that the pattern produced is one of increased glomerular filtration rate, increased renal plasma flow and a relatively normal filtration fraction (Fig. 6). Though it may be reasonable to assume an increased thyroxin production in severe burns, especially those showing evidence of increased metabolism such as fever, the functional pattern seen under these conditions is essentially dissimilar to that seen in burns.

The group of patients studied were normotensive, as evidenced by direct measurement, and by adequate urinary function. Hypotension produces a characteristic pattern of renal function essentially dissimilar to the one observed, *i.e.*, a lowered glomerular filtration rate, a lowered renal plasma flow and a normal filtration fraction, which later tends to fall as the hypotension persists[5, 21] (Fig. 6).

DOCA (desoxycorticosterone acetate) and cortisone appear to be most fundamental. DOCA produces an interesting pattern.[9, 19] The glomerular filtration rate is increased, as is the renal plasma flow, but to a greater extent, thus giving a rise in filtration fraction

FIG. 5



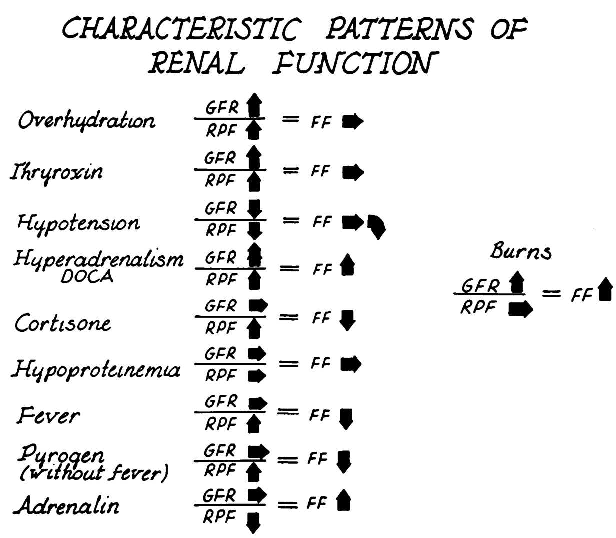


FIG. 6

FIG. 5.—The determinations of the maximal tubular excretory capacity are within normal range during the first two and a half weeks post-burn. Three observations on one patient after three weeks are considerably above normal range.

FIG. 6.—The functional pattern seen in burned patients is compared here to the pattern of several physiologic variables.

Under conditions of severe thermal injury, the adrenal cortex receives perhaps a maximal stimulus for outpouring of corticoid hormones (the alarm reaction of Selye[14]). Of these substances, studies on tion (Fig. 6). This pattern resembles that seen in burns, with the exception of the increased renal plasma flow. Though the mechanism of this alteration is not known, it may serve as a possible explanation for the changes seen. One group of observers found cortisone to produce a constant glomerular filtration rate, an increased renal plasma flow, and a diminished filtration fraction.[10] We have carried out similar observations on five uneventful postoperative cases. Each received 100 mg. of cortisone daily for three days and showed no significant change in renal function. It is possible that this difference in result is due to difference in dosage of the drug, since the investigation referred to used up 500 mg. daily. In any event, the pattern noted is essentially different from that seen in burns.

The concentration of plasma protein is of considerable importance in the maintenance of fluid within the glomerular capillary by virtue of the oncotic pressure produced. Reduction of this concentration must tend to increase the amount of fluid lost through the capillary and thus produce an increase in glomerular filtration rate. Burned patients are commonly hypoproteinemic after two to three weeks, especially those with extensive burns. During the first two days when hemoconcentration is maximal, the plasma protein is usually increased in concentration, though the total circulating protein may be decreased. Plasma and whole blood used in therapy tend to diminish the protein loss. On theoretical grounds plasma protein deficiency might seem to be a most reasonable explanation of increased glomerular filtration without increased renal plasma flow. However, hypoproteinemia usually does not occur at the time when the increased filtration rate is at its peak. The adequate plasma and whole blood therapy which these patients received would make this possibility less likely. Studies of hypoproteinemia[11] with cirrhosis of the liver do not indicate an alteration of functional pattern from the normal, in spite of severe degrees of hypoalbuminemia (3 Gm. per 100 cc.) (Fig. 6). It was noted, however, that immediately following treatment with human serum albumin, the filtration rate and renal plasma flow rose, the plasma flow rising to a greater extent, thus producing a fall in filtration fraction. It was further noted that this alteration in filtration fraction had returned to its approximate pre-injection value by 24 hours. These data suggest that the effects of diminished serum protein produce a definite but relatively short-lived effect. One patient in this series (R.R.) noted to have a severe hypoproteinemia (3.7 Gm. per 100 cc.) at the time of his first observation, revealed a moderate increase in filtration fraction (25.5 per cent). On his second determination, at which time his total protein was 5.7 Gm. per 100 cc., an increase of 54 per cent over the previous value, a filtration fraction of 22.1 per cent was obtained. Though the importance of this factor in determining the observed changes must await further study, it is probable that other forces are more important.

Fever will produce a maintained glomerular filtration rate, an increased effective renal plasma flow and a reduction of the filtration fraction (Fig. 6). This change is considered to reflect the kidneys' participation in the generalized vasodilatation and specifically efferent glomerular vasodilatation.[22] In an attempt to separate the effect of pyrogens and the fever they produce, Coldring and Chasis[12] gave pyrogenic inulin and prevented the fever rise by the use of amidopyrine. Following this, they noted a pattern of response, characterized by a maintenance of glomerular filtration rate, an increase in renal plasma flow, and a fall in the filtration fraction (Fig. 6) identical with the previous response.

Since the oral temperature was frequently elevated preceding the function study in our series (Table I) the effects of fever and pyrogen must be considered. Comparison of the functional pattern of this response with that of the burn patient reveals little similarity. Significant elevations of the renal plasma flow are produced in both conditions, which are not seen in the burn series.

In an attempt to evaluate the renal functional changes seen in the hypertensive nephropathies, the effect of adrenaline has been studied.[12] It was noted that this substance maintains the glomerular filtration rate in the face of a reduction in renal plasma flow by increasing the filtration fraction (Fig. 6). Other investigators have confirmed this pattern of response.[20] This alteration is thought to be accomplished by efferent glomerular vasoconstriction, which raises filtration pressure, and reduces renal plasma flow.[22] This pattern of response was found to be characteristic of early hypertension, and was considered to be a compensatory mechanism for maintenance of adequate glomerular filtration in the face of reduction of blood flow.

Though the data reported here do not closely follow the adrenaline response, it is conceivable that under conditions of increased filtration rate and renal plasma flow, associated with a normal filtered fraction, as might be expected from the increased extracellular space determinations noted on Table I, the addition of adrenaline or some similar pressor substance might produce enough diminution of renal plasma flow to assume a relatively normal level, maintain an already elevated filtration rate, and thus produce an increased filtration fraction. The fact that this type of pattern persisted for two and a half weeks strongly suggests that, granting the above assumptions, adrenaline is not the effector agent, since the maintenance of any considerable output of this drug for this period of time seems unlikely. With regard to the possible effect of absorption from the burn wound of split protein products or bacterial toxins, one would anticipate that the effect on the kidney would be a pyrogenic response and would not serve as an explanation of the observed changes.

To summarize, certain known physiologic variables produce relatively characteristic renal functional changes which resemble, to a greater or lesser degree, the observed pattern in burned patients. Of these variables, the ones which seem most applicable are (1) overhydration, (2) increased thyroxin output, (3) hyperadrenalism, especially desoxycorticosterone acetate, (4) pyrogenic response, (5) hypoproteinemia and (6) increased adrenaline activity. Ariel and Miller[13] observed a pattern of functional changes in a group of major surgical cases in the immediate postoperative period which are similar to those observed in our burn patients. It was their conclusion that the change noted was most likely humoral in etiology, specifically adrenaline and adrenocorticotropin. A slight depression in the tubular excretory mass was also observed.

To choose one or a combination of the above variables to explain the observed changes is unjustified in view of the evidence. Further studies are in progress to attempt to clarify these relationships.

CONCLUSIONS

1. Severely burned subjects adequately treated exhibit a degree of renal functional compensation which is compatible with complete recovery.

2. Sixteen renal clearance studies, carried out on eight severely burned patients, reveal a relatively constant pattern of response, which may be characteristic of this type of injury. It is characterized by an increased glomerular filtration rate, a normal effective renal plasma flow, and an increased filtration fraction. This pattern is noted within the second day post-burn, and the filtration rate and filtration fraction decline to reach and maintain normal values at two and a half to three weeks after injury.

3. Physiologic variables which might conceivably produce the observed alteration, *i.e.*, over-hydration, increased thyroxin, desoxycorticosterone acetate, pyrogenic response, hypoproteinemia and adrenaline are discussed. On the basis of the available evi-

dence the mechanism of the observed alteration must for the present remain unexplained.

4. Tubular function, as measured by the maximal tubular excretory capacity was within normal limits after injury in a group of severely burned but adequately treated patients. There appears to be a tendency toward increasing excretory ability of the tubule with the passage of time. The majority of the observations made before three weeks post-burn were within normal range, and the observations made after this time on one patient appear to be significantly high.

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